Protocol Title: Phase I-II Study of MEK162 for Children with Low Grade Gliomas and Other Ras/Raf/ERK Pathway Activated Tumors

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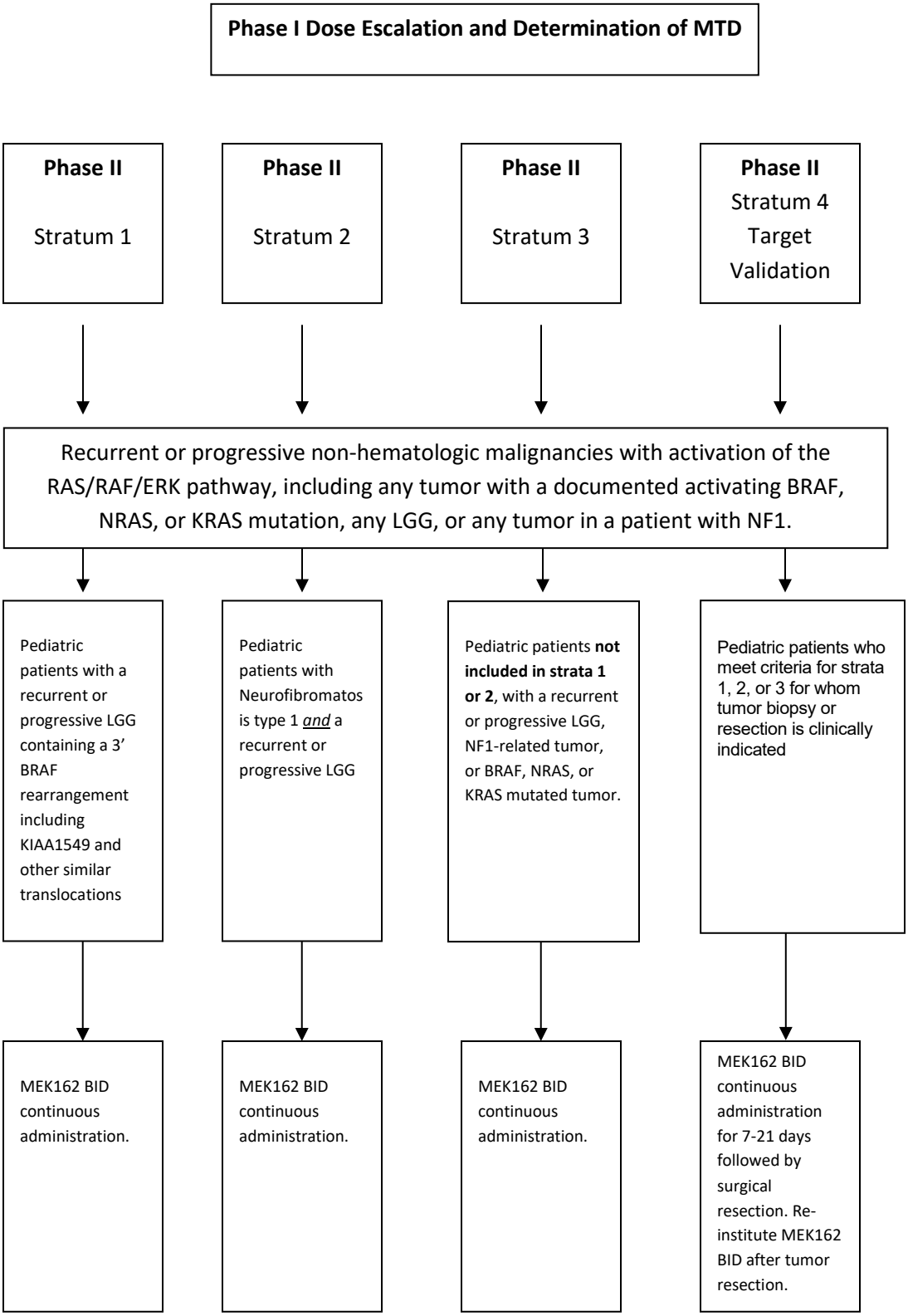
Phase I Dose Escalation and Determination of MTD
Phase II
Stratum 1
Phase II
Stratum 2
Phase II
Stratum 3
Phase II
Stratum 4
Target
Validation
Recurrent or progressive non-hematologic malignancies with activation of the RAS/RAF/ERK pathway, including any tumor with a documented activating BRAF, NRAS, or KRAS mutation, any LGG, or any tumor in a patient with NF1.
Pediatric patients with a recurrent or progressive LGG containing a 3' BRAF rearrangement including KIAA1549 and other similar translocations
Pediatric patients with Neurofibromatosis type 1 and a recurrent or progressive LGG
Pediatric patients not included in strata 1 or 2, with a recurrent or progressive LGG, NF1-related tumor, or BRAF, NRAS, or KRAS mutated tumor.
Pediatric patients who meet criteria for strata 1, 2, or 3 for whom tumor biopsy or resection is clinically indicated
MEK162 BID continuous administration.
MEK162 BID continuous administration.
MEK162 BID continuous administration.
MEK162 BID continuous administration for 7-21 days followed by surgical resection. Re-institute MEK162 BID after tumor resection.

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase/SGPT
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase/SGOT
AUC	Area under the plasma concentration-time curve
AUC0-24	Area under the plasma concentration-time curve from 0 to 24 hours
BID	*bis in diem*/twice a day
CK	Creatine kinase
Cmax	Maximum (peak) concentration of drug
CNS	Central nervous system
CRO	Contract Research Organization
CSF	Cerebral spinal fluid
CSR	Central serous retinopathy
CTO	Clinical Trials Office
DLT	Dose limiting toxicity
DSMC	Drug Safety Monitoring Committee
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
HFSR	Hand-foot skin reaction
Hr	Hour
IHC	Immunohistochemical
IRB	Institutional Review Board
LGG	Low-grade glioma
LLOQ	Lower limit of quantification
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTD	Maximum tolerated dose
NF1	Neurofibromatosis type 1
PBL	Peripheral blood lymphocytes
PD	Pharmacodynamics
PK	Pharmacokinetics
QD	Once daily
RVO	Retinal vein occlusion
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event

Glossary of Terms

Assessment	A procedure used to generate data required by the study
Cycle	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Enrollment/Enrolled	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package that is linked to one of the treatment groups of a study.
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient who enrolls in the study.
Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.

1. PROTOCOL SUMMARY

1.1 Phase I

Patients with non-hematologic malignancies that are recurrent, progressive, or refractory after standard up-front therapy receiving MEK162 will define the MTD, DLT, and toxicity profile.

1.2 Phase II

Patients with recurrent or progressive tumors signaling through the Ras/Raf pathway after standard up-front therapy will be treated in three strata to define the activity of MEK162.

Stratum 1: Pediatric patients with recurrent or progressive low-grade glioma (LGG) characterized by a 3' BRAF rearrangement (KIAA1549 fusion and similar translocations).

Stratum 2: Pediatric patients with neurofibromatosis type 1 (NF1) *and* recurrent or progressive LGG.

Stratum 3: Pediatric patients with recurrent or progressive tumors thought to involve the Ras/Raf/ERK pathway but not included in strata 1 or 2. This includes any LGG not included in strata 1 or 2 (i.e., any LGG without a BRAF rearrangement in a patient without NF1), any tumor other than LGG in a patient with NF1, and any other tumor with a known activating BRAF, NRAS or KRAS mutation.

Stratum 4 (Surgical Arm, Target validation): Patient with eligible histology for whom tumor biopsy or resection is clinically indicated. Patients will receive MEK162 for 7 to 21 days prior to their surgery. Samples will be analyzed for concentration of drug and target inhibition.

1.3 Length of Therapy

Protocol treatment will last approximately 48 weeks (12 cycles) from the start of MEK162 in the absence of disease progression or significant toxicity. Patients deriving benefit may continue therapy for 12 additional cycles (up to 24 cycles total). A cycle will consist of 28 days (+/- 3 days) and MEK162 will be given continuously. See Section 6.6.

1.4 Response Assessment

Imaging to assess response will be performed at the end of cycle 1 (+/- 1 week; optional in phase II), at the end of cycle 3 (+/- 2 weeks) and after every three cycles thereafter (+/- 2 weeks).

2. OBJECTIVES AND ENDPOINTS

2.1 Phase I

Primary Objectives

- To determine the MTD (or proposed phase II dose) of MEK162 suspension administered on a continuous, twice daily dosing schedule, in children with tumors that are recurrent, progressive, or refractory after standard therapy.

Secondary Objectives

- To characterize the safety and tolerability of MEK162 suspension in children with advanced solid tumors.
- To assess the pharmacokinetic profile of MEK162 and its metabolite (AR00426032) when administered as an oral suspension in children and adolescents with recurrent, refractory or progressive tumors
- To assess any preliminary antitumor activity of MEK162 in children with advanced solid tumors.

Exploratory Objectives

- To explore the PD effects of MEK162 on biomarkers of the Ras/Raf/MEK/ERK signaling pathway activity in PBL and tumor tissue (if available).

Primary Endpoints

- Frequency of DLTs associated with twice-daily administration of MEK162 suspension.

Secondary Endpoints

- Frequency of AEs and SAEs; changes in laboratory values
- Plasma PK parameters
- Tumor response

Exploratory Endpoints

- Post treatment changes in expression of biomarkers of Ras/Raf/MEK/ERK pathway activity (e.g. pERK) in peripheral blood and tumor tissue (if available)

2.2 Phase II

Primary Objectives

- To assess preliminary efficacy of MEK162 in pediatric LGG characterized by a BRAF truncated fusion lesion.
- To assess preliminary efficacy of MEK162 in LGG in children with NF1.

Secondary Objectives

- To determine the 12-month progression-free and overall survival in pediatric patients with a recurrent or progressive LGG characterized by a BRAF truncated fusion lesion (KIAA1549 and similar translocations) (Stratum 1).
- To determine the 12-month progression-free and overall survival in pediatric patients with NF1 and recurrent or progressive LGG (Stratum 2).

Exploratory Objectives

- To assess response rate and 12-month progression free and overall survival in pediatric patients with a recurrent or progressive tumor with known or presumed signaling through the Ras/Raf/ERK pathway not included in strata 1 or 2, including tumors positive for BRAF V600E or activating NRAS or KRAS mutations, any LGG not eligible for strata 1 or 2 (i.e., any LGG without a BRAF truncated fusion in a patient without NF1), and any tumor other than LGG in a patient with NF1 (Stratum 3).
- To correlate treatment response with molecular phenotype.
- To quantify the intra-tumoral concentration of MEK162 after 7-21 days of twice-daily administration, and correlate with plasma PK assessment.
- To assess downstream Ras/Raf/MEK/ERK pathway inhibition, as measured by ERK phosphorylation, after treatment with MEK162 for 7-21 days, and correlate with blood PD assessment.
- To describe patient and parent-reported quality of life outcomes in children with LGG and other Ras/Raf/ERK pathway-activated tumors undergoing treatment with MEK162.

Primary Endpoints

- Response rate (strata 1 and 2).

Secondary Endpoints

- 12-month progression-free and overall survival (strata 1 and 2).

Exploratory Endpoints

- Response rate, OS, and PFS in patients in stratum 3 (other tumors with known or presumed activation of the Ras/Raf/MEK/ERK pathway, not included in strata 1 or 2).
- Tumor response as a function of BRAF tumoral genotype.
- Target Validation (Surgical Arm): Intra-tumoral MEK162 concentration, and intra-tumoral inhibition of downstream mediators of the Ras/Raf/MEK/ERK pathway (e.g., pERK).
- Patient and parent-reported outcomes as assessed using the PedsQL^{TM} Brain Tumor Module.

3. BACKGROUND

3.1 Significance

The Ras pathway is implicated in a large number of tumors in adult patients and is activated in NF1-associated tumors (1). Low-grade gliomas (LGG) are the most common brain tumor in children (2) and the majority have abnormal signaling through the Ras/Raf pathway (3). Complete resection is not feasible in many patients and incompletely resected LGG have a high rate of progression and recurrence (3,4)Best currently available therapies have limited efficacy, and the long-term burden of disease and treatment-related morbidity is significant. Results from the largest randomized phase III trial to date for children with LGG showed a 5-year event free survival of only 47% (5) There is clearly a need for more effective therapies using novel mechanisms of action. A variety of other tumor types are also known to have abnormal expression of the Ras/Raf and include high-grade glioma, pleomorphic xanthoastrocytoma, and ganglioglioma (6); melanoma(7); thyroid carcinoma (8); and Langerhans cell histiocytosis (9). A number of other tumor types have abnormal signaling through this pathway because of upstream activation of tyrosine kinase receptors (10).

Mitogen activated ERK kinase 1 and 2 (MEK1/2), a dual specific kinase, is a critical component of the Ras/Raf/MEK/ERK pathway, an important regulator of cellular survival, growth, and proliferation. Oncogenic dysregulation of this pathway has been described in diverse malignancies, including pancreatic cancer, colon cancer, lung cancer, melanoma, thyroid malignancies, histiocytosis, and glioneuronal tumors. Aberrant constitutive activation of this pathway via a unique BRAF tandem duplication has been demonstrated in 77-84% of juvenile pilocytic astrocytomas, the most common subtype of pediatric LGG (3,11,12).(13) Positive immunostaining for pERK in tumors harboring the duplication confirms aberrant activation of this pathway (3,12). These findings suggest that the Ras/Raf/MEK/ERK pathway may play a critical role in the genesis of this disease and may be a promising therapeutic target.

3.2 Study Agent Background and Associated Known Toxicities

Preclinical data (please refer to the most recent Investigator's Brochure for most recent data): MEK162 (ARRY-162 / ARRY-143162) is an oral, highly selective, ATP non-competitive MEK1/2 inhibitor. The biological activity of MEK162 has been evaluated in vitro (both enzymatic and cell culture assays) and in vivo in mouse xenograft studies. MEK162 potently inhibits MEK 1/2 in both biochemical assays using purified protein, and in cells. MEK162 has demonstrated robust, but selective, growth inhibitory activity in a wide variety of cancer cell lines. In a collection of ~500 genetically annotated cell lines, MEK162 showed anti-proliferative activity preferentially in cells harboring activating mutations of the ERK pathway (e.g. BRAF, NRAS and KRAS), and in particular, activating mutations in BRAF and NRAS. In vivo, MEK162 has demonstrated dose dependent tumor growth inhibition in various subcutaneous tumor transplants harboring BRAFV600E mutations (HT29, COLO205, A-375) as well as activating mutations in both NRAS (Hs 944.T) and KRAS (MiaPaCa2, A549, LoVo, Calu6). These data suggest that MEK162 may provide a potential therapeutic benefit in cancer indications harboring these mutations. In animals, exposure (AUC) and Cmax generally increased in a dose proportional manner. The plasma clearance is low (range: ~2 to 8 mL/min/kg) and the mean plasma half-life values ranges from 2 to 9 hours. MEK162 has moderate membrane permeability and is a substrate of P-gp and BCRP. MEK162 exhibited high plasma protein binding in vitro (> 96%, except dog 84%) and is predicted to have good stability with respect to hepatic metabolism. Nonclinical in vitro and in vivo data indicated that

MEK162 is metabolized by multiple routes but primarily by glucuronidation pathways (mainly via UGT1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via CYP1A2 and 2C19). The formation of active metabolite AR00426032 is mediated primarily by CYP1A2 with minor contributions from other cytochrome P450 enzymes (CYPs). MEK162 potently inhibits CYP2B6 and weakly inhibits CYP1A2 and 2C9. It is not considered a time dependent inhibitor of CYP1A2, CYP2C9, CYP2D6, and CYP3A. In vitro evidence also suggests that MEK162 could induce CYP3A. Acute, subchronic, and chronic reproductive toxicity, genotoxicity and phototoxicity studies were completed to support the chronic administration of MEK162 in adult and pediatric cancer patients. The clinical toxicity of MEK inhibitors has been more similar to that of monkeys than rats and include gastro-intestinal intolerance and diarrhea, rash, central serous retinopathy (only seen in humans) and retinal vein occlusion (rarely seen in humans). In vitro and in vivo phototoxicity studies conducted in mice indicate that MEK162 has a very low risk of weak phototoxic potential at therapeutic doses. This is supported by human safety data: as of January 7, 2015, of 1945 patients who have received at least one dose of MEK162, there has been one reported grade I photosensitivity reaction. Given the embryo-lethal effects seen in rats and rabbits and the teratogenic effects seen in rabbits, MEK162 should not be used in pregnant women and women of childbearing potential must be advised to use highly effective contraception methods.

Clinical data (please refer to the most recent Investigator's Brochure for most recent data): As of January 7, 2015, a total of 1945 subjects/patients have received at least one dose of MEK162, either as a single agent or in combination with PKC, CDK4/6, PI3K, RAF, EGFR or IGF-1R inhibitors or paclitaxel, and have been evaluated for safety, including 204 healthy subjects, 164 patients with rheumatoid arthritis, 6 patients with hepatic dysfunction, and 1571 patients with advanced cancer. The experience with MEK162 as a single agent in oncology patients includes six studies with 705 patients enrolled as of January 7, 2015. These include two Phase I, two Phase II, and two Phase III studies:

- [ARRAY-162-111]: A phase I dose escalation study in patients with solid tumors with an expansion phase in biliary and colorectal cancer. A total of 93 patients received at least 1 dose of binimetinib. Four dose levels were evaluated: 30 mg BID, 45 mg BID, 60 mg BID and 80 mg BID. Two of 4 patients receiving 80 mg BID experienced ocular dose-limiting toxicities (DLTs), thus the 80 mg BID dose was declared non-tolerable. Seven patients were enrolled at 60 mg BID and no DLTs were observed, therefore, 60 mg BID was declared the MTD. Following completion of the Dose-escalation Phase, a total of 74 patients were enrolled in the Expansion Phase. The dose of 45 mg BID was determined as the recommended phase II dose (RP2D) due to the higher-than-expected frequency of ocular AEs at the 60 mg dose level.
- [CMEK162X1101]: a phase I dose escalation study in Japanese patients with solid tumors and an expansion in patients with Ras or BRAF mutations
- [CMEK162X2201]: a phase II study in patients with advanced melanoma.
- [CMEK162AUS11]: a phase II study in patients with Ras/Raf/MEK activated tumors.
- [CMEK162A2301]: a phase III, two-arm, randomized study in patients with advanced unresectable or metastatic NRAS Q61 mutation-positive melanoma.
- [ARRAY-162-311]: a phase III, two-arm, randomized study in patients with recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube or primary peritoneum.

The most frequently reported AEs suspected to be related to binimetinib, regardless of grade and binimetinib dose were skin toxicity (rash, dermatitis acneiform), GI events (nausea, vomiting, diarrhea), edema peripheral, fatigue and blood creatine phosphokinase (CK) increased. The majority of these AEs were Grade 1 or 2 with less than 5% of cases Grade 3 or 4, with the exception of elevation of blood CK, reported as Grade 3 or 4 in 24% in [CMEK162X2201] and 17% in [CMEK162X1101] studies.

The experience with MEK162 in cancer patients in combination studies comprises 13 ongoing studies with 866 patients as of 07-January-2015.

- Five studies with RAF inhibitors encorafenib and RAF265: [CMEK162X2102], phase II study of sequential single-agent encorafenib followed by a rational combination with targeted agents (including binimetinib) after progression in adults with locally advanced or metastatic BRAF V600 melanoma; [CMEK162X2110], phase Ib dose finding, dose escalation study of binimetinib in combination with encorafenib, in selected advanced solid tumors; [CLGX818X2102], phase II study of binimetinib in combination with encorafenib in patients with locally advanced or metastatic BRAF V600 melanoma; [CMEK162B2301], phase III , randomized, 3-arm study in patients with BRAF V600 mutant locally advanced unresectable or metastatic melanoma; [CLGX818X2109], phase II study of open-label study of encorafenib and binimetinib, followed by a rational combination with targeted agents after progression, in adults with advanced/metastatic BRAF V600 melanoma.
- Three studies with PIK3C/AKT pathway inhibitors BEZ235 (pan-PI3K/mTOR) buparlisib (pan-PI3K) and BYL719 (PIK3CA): [CMEK162X2103], [CMEK162X2101] and [CMEK162X2109], all three are phase Ib, dose escalation and expansion studies in selected advanced solid tumors.
- One study with PKC-selective inhibitor sotrastaurin: [CMEK162X2203]: phase Ib/II study in patients with metastatic uveal melanoma.
- One study with CDK4/6 inhibitor LEE011: [CMEK162X2114], phase Ib/II study, in patients with NRAS mutant melanoma.
- One study with IGF-1R monoclonal inhibitor ganitumab: [CMEK162X2111], phase Ib/II dose escalation and expansion study in patients with selected advanced solid tumors.
- One study with EGFR inhibitor panitumumab: [CMEK162X2116], phase Ib/II, dose-escalation study in patients with mutant RAS or wild-type RAS metastatic colorectal cancer.
- One study with standard chemotherapy agent paclitaxel: [ARRAY-162-112], phase Ib, dose-escalation and expansion study in women with platinum-resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal cancer.

Overall, the frequently reported AEs suspected to be related to binimetinib in combination studies were found to be similar to those found in single-agent studies, which include GI events (diarrhea, nausea, vomiting), skin toxicities (dermatitis acneiform, rash) CK elevation and retinal events. The percentage of patients that discontinued study drug due to AEs regardless of relationship to binimetinib ranged from 2.6% [CMEK162X2203] to 36% [CMEK162X2101]. Fifty two DLTs were

observed in all combination studies, 13 (out of 52) in the [CMEK162X2101] study combining binimetinib with the PI3K inhibitor buparlisib. The most frequents DLTs reported were GI disorders, ocular disorders and skin toxicities.

A total of 128 deaths were reported during the study or within 30 days of last dose of study drug in cancer patients, either in single agent or combination studies (45 and 46 respectively). The most frequent cause of treatment discontinuation was disease progression and other events not related to study drug. Fatal SAEs suspected to be related to study drug include the following: (single agent) acute hepatic failure; (in combination with BYL719) pneumonitis; (in combination with LEE001) intracranial hemorrhage.

Based on the experience from 13 completed phase I studies and 1 completed phase II study, binimetinib has demonstrated an acceptable and manageable safety profile with the majority of AEs Grades 1 or 2 of intensity and reversible.

Pharmacokinetics: In healthy subjects, MEK162 exposure (as indicated by C_{max} and AUC) appeared to increase in a dose-proportional manner following single and multiple doses over a dose range of 5 to 80 mg QD for single dose and 5 to 60 mg QD and 20mg BID for multiple doses. The median apparent terminal elimination half-life was 5.98 hours (single dose) and 7.11 hours (multiple doses), and the median time of maximum plasma concentration (T_{max}) was 1 hour post dose. These initial PK data supported a BID dosing-regimen of MEK162. The AR00426032 metabolite represented < 13% of the parent drug in plasma and < 5% of the parent drug was excreted renally. Accumulation of MEK162 was < 40% following QD dosing and < 75% following BID dosing.

Pre-clinical studies in mice support that >50% inhibition in pERK in HT-29 tumors for 24 hours is optimal for significant tumor growth inhibition. This degree of sustained pERK inhibition was best achieved with BID dosing at lower doses ($\leq$ 10 mg/kg/dose) or QD dosing at higher doses ($\geq$ 30 mg/kg/dose). Given that little to no drug was apparent in plasma at 24 hours post-dose (at low doses) in the pre-clinical xenograft studies, a BID dosing regimen was considered to be the most reliable murine schedule to maintain plasma concentrations for optimal efficacy. Therefore, a BID dosing-regimen (e.g., 45 mg) should provide sufficient exposure with acceptable safety and adequate continuous pharmacological inhibition of the primary target.

The initial evaluation of the PK data of MEK162 in patients with advanced cancer (ARRAY-162-111 and CMEK162X2201) at the doses evaluated to date (30 to 80 mg BID) indicated that both the plasma concentration-time profiles and PK parameters were similar to those in healthy subjects, as well as in patients with rheumatoid arthritis. The inter-subject variability for AUC and Cmax was ~40%. The mean active metabolite-to-parent ratio was less than 25% across all study days and dose levels tested. Steady state is reached by Day 15 and accumulation of MEK162, as estimated using non-compartmental methods, is around 50% (or 1.5 fold).

To integrate all the available PK information, a preliminary population PK model describing the PK of MEK162 was built using data from 68 subjects from the Array and Novartis studies. The model suggests that the PK can be adequately described using linear kinetics (2-compartmental open model with first order absorption and a lag time). There was extensive tissue distribution and clearance of MEK162 estimated as 17 L/h. For the typical individual, steady state is reached by Day 15 and accumulation of MEK162 is around 70% (or 1.7 fold). For further information, refer to the Investigator's Brochure.

3.3 Rationale for the Current Study

Rationale for the Current Study Population:
Low-grade gliomas (LGG) are the most common brain tumor in children (2). Complete resection is not feasible in the majority of patients (3). Incompletely resected LGG have a high rate of progression and recurrence (3). Best currently available therapies have limited efficacy, and the long-term burden of disease and treatment-related morbidity is significant. Results from the largest randomized phase III trial to date for children with LGG showed a 5-year event free survival of only 47% (5). There is clearly a need for more effective therapies using novel mechanisms of action.

Rationale for the Current Study Design:
Mitogen activated ERK kinase 1 and 2 (MEK1/2), a dual specific kinase, is a critical component of the Ras/Raf/MEK/ERK pathway, an important regulator of cellular survival, growth, and proliferation. Oncogenic dysregulation of this pathway has been described in diverse malignancies, including pancreatic cancer, colon cancer, lung cancer, melanoma, thyroid malignancies, histiocytosis, and glioneuronal tumors. Aberrant constitutive activation of this pathway via a unique BRAF tandem duplication has been demonstrated in 77-84% of sporadic pilocytic astrocytomas, the most common subtype of pediatric LGG (3,11,12). Positive immunostaining for pERK in tumors harboring the duplication confirms aberrant activation of this pathway (3,12). Similarly, in mouse models of NF1-associated optic pathway glioma, MEK inhibition led both to decreased tumor volume, and to a reduction in tumor-associated retinal nerve-fiber loss and ganglion cell reduction(14). These findings suggest that the Ras/Raf/MEK/ERK pathway may play a critical role in the genesis of both sporadic and NF1-associated low-grade glioma, and may be a promising therapeutic target.

Rationale for the Study Dosing/Treatment Plan:
MEK162 (ARRY-162 / ARRY-143162) is an oral, highly selective, ATP non-competitive MEK1/2 inhibitor. CNS penetration of MEK162 was assessed using a novel scanning MALDI-TOF technique developed at the pediatric LGG program at DFCI, which assesses extravascular and intra-vascular drug concentration by evaluation co-localization with heme (13). By this technique, MEK162 was found to have diffuse CNS extravascular penetration in the CNS. A phase I study in adults with advanced solid tumors suggests that it is well tolerated. The RP2D in adults is 45 mg twice daily (15). Phase II and phase III studies are underway. Preliminary results from one phase II study revealed partial responses in 20% of patients with advanced melanoma and either a V600 BRAF or an NRAS mutation treated with MEK162 at 45mg twice daily (16).

Rationale for the Pediatric Phase II Dose:

Preliminary findings from the phase I component of this protocol are as follows: 19 children were enrolled on the phase I study, 18 of whom were DLT-evaluable. Three DLT-evaluable participants were enrolled and treated at each dose level from 1 through 4, and 6 DLT-evaluable participants at dose level 5 (32mg/m2/dose bid). No DLTs were observed during the DLT evaluation period in any participant. Preliminary analysis of initial pharmacokinetic data showed that the pediatric AUC and Cmax values at 32mg/m2/dose were similar to corresponding values in adult patients at the adult RP2D of 45 mg/dose bid. Based on these findings, the convened study committee determined 32mg/m2/dose bid to be the pediatric RP2D for this study.

Rationale for Correlative/Exploratory Studies:

The target validation component of the study will allow us to determine the ability of MEK162 to penetrate into the tumor as well as assess the ability of MEK162 to affect its target. A short course pharmacokinetics and pharmacodynamic evaluation on these patients for correlation is also planned.

4. ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

Phase I

Patients with recurrent, refractory, or progressive non-hematologic malignancies (CNS or solid tumors) associated with activation of the RAS/RAF/ERK pathway, including any LGG, any tumor in a patient with NF1, or any tumor with a documented activating BRAF, NRAS, or KRAS mutation, will be eligible. LGG is defined as any WHO grade I or II (or equivalent) astrocytic, oligodendroglial, and/or glioneuronal tumor.

Phase II

Patients with recurrent or progressive disease, as defined in the following three strata below, will be eligible. For eligibility determination, tumor imaging from at least two time-points must be available to document radiographic progression or recurrence. Patients with non-progressive refractory tumors will not be eligible.

- Stratum 1: patients with LGG with a BRAF truncated fusion that is measurable in at least two dimensions on imaging.
- Stratum 2: patients with NF1 *and* LGG that is measurable in at least two dimensions on imaging.
- Stratum 3: Pediatric patients with a recurrent or progressive tumor thought to involve the Ras/Raf/ERK pathway but not included in strata 1 or 2 that is measurable in at least two dimensions on imaging. This includes any LGG not included in strata 1 or 2 (i.e., any LGG without a BRAF truncated fusion in a patient without NF1), any tumor other than LGG in a patient with NF1, and any other tumor with a documented activating BRAF, NRAS, or KRAS mutation.
- Stratum 4 (surgical arm, target validation): Patients who meet criteria for stratum 1, 2, or 3 for whom tumor biopsy and/or resection is clinically indicated.

- Tumor tissue for correlative studies must be available for all patients except those with NF1 and LGG (stratum 2) or any patient with optic pathway glioma (stratum 2 or 3), for whom tumor tissue is optional.

- Patients must have received at least one prior chemotherapy or radiation regimen prior to progression.

- At the time of enrollment, at least 6 weeks must have elapsed since the last dose of any nitrosourea, and the longer of 2 weeks or 3 half-lives must have elapsed since the last dose of any other tumor-directed medication. or biologic therapy.

- At least 3 months must have elapsed since the last dose of irradiation to the target tumor(s) at the time of enrollment.

Phase I + II

The remaining criteria apply for both phases:

- Patients must be $\geq$1 year and <18 years old.

- Performance Score using the Karnofsky Performance Scale (patients > 12 years old) or Lansky Play - Performance Scale (patients ≤ 12 years old) must be $\geq$ 60 assessed within two weeks prior to enrollment.

- Participants must have normal organ and marrow function as defined below within two weeks prior to enrollment:
    - Absolute neutrophil count $\geq$ 1,000/mcL
    - Platelets $\geq$ 75,000/mcL and > 7 days since last platelet transfusion. Hemoglobin $\geq$ 9 gm/dL and > 7 days since last red blood cell transfusion
    - Not refractory to red cell or platelet transfusions
    - Hepatic: Total bilirubin $\leq$ 1.5 times the upper limit of normal; SGPT (ALT) and SGOT (AST) $\leq$ 3 times the institutional upper limit of normal
    - Renal: Serum creatinine which is less than 1.5 time the upper limit of institutional normal for age or GFR > 70 ml/min/1.73m^2
    - QTc interval $\leq$ 450ms
    - Left ventricular ejection fraction (LVEF) $\geq$ 50% as determined by an echocardiogram

- Female patients of childbearing potential must have negative serum or urine pregnancy test within 72 hours of the first dose of MEK162. Patient must not be pregnant or breast-feeding. Patients of childbearing or child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study and for 30 days following cessation of treatment.
- Patient must be able to take oral/enteral medication.

- Patient, parent, or legal guardian must be able to understand and willing to provide informed consent.

- Patients must have recovered from the effects of prior therapy.

4.2 Exclusion Criteria

Patients with any of the following characteristics will not be eligible:

- Patients for whom other curative or established standard-of-care therapeutic options with acceptable morbidity exist.
- Patients with any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.
- History of Gilbert's syndrome
- Patients receiving any other anticancer or experimental drug therapy.
- Use of hematopoietic growth factors within 2 weeks prior to initiation of therapy.
- Any other investigational agents within 2 weeks or ≤ 3 half-lives (whichever is longer) before start of study therapy.
- Patients who have undergone surgery ≤ 3 weeks or who have not recovered from side effects of this procedure prior to receiving study drug.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, impaired gastrointestinal function, or psychiatric illness/social situations that would limit compliance with study requirements.
- History or current evidence of retinal vein occlusion (RVO) or predisposing factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).
- History of retinal degenerative disease
- Prior therapy with a MEK inhibitor
- Impairment of gastrointestinal function (e.g., active ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
- Patients who have a neuromuscular disorder that is associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

- Patients with uncontrolled hypertension

4.3 Inclusion of Women, Minorities, and Other Underrepresented Populations

This protocol is open to males and females of all races. See Inclusion Criteria above regarding specific eligibility requirements for female and male patients of child-bearing or child-fathering potential, respectively.

5. ENROLLMENT PROCEDURES

5.1 Reservation

Before enrolling a patient on study, a reservation must be made with the Children's Hospital Los Angeles (CHLA) Operations Center. In order to make a reservation you may call the Operations Center at 323-361-7673 during the business hours of **8:30am- 5pm Pacific Time Monday through Friday**, excluding holidays, and send an email to mek162@chla.usc.edu with the following information (when sending an email, please include "Reservation Request" in the subject line):

Name of requesting institution with contact information
Patient Initials (First, Last)
Patient date of birth

If an enrollment slot is available, you will receive an email from the CHLA study operations center to confirm your reservation. All reservations are active for 5 full calendar days beginning the next full day after the day the reservation is created.

5.2 Enrollment

In order to enroll a patient onto study, the following must be done:

- Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
- Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration and enrollment, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.** A protocol-specific Eligibility Checklist will be provided to each Participating Institution by CHLA. It is the responsibility of the local investigator to confirm eligibility criteria and to complete the eligibility checklist. A copy of the completed and MD signed eligibility checklist must be submitted to the CHLA operations center on the day of enrollment.
- Patients must be enrolled prior to beginning treatment on this study. Patients will be enrolled by contacting the CHLA operations center at 323-361-7673 during the business hours of **8am- 5pm Pacific Time Monday through Friday**, excluding holidays. Sites will be asked to complete the eligibility form on the designated web-based DataLabs electronic data capture system prior to making this call. In addition, the supporting documentation, which confirms eligibility, should be emailed to the CHLA study operations office at mek162@chla.usc.edu.
- Each patient will be assigned a unique registration and study subject number. An email confirming eligibility and assigned dose level (if applicable) will be sent to the treating facility, Study chair, and Study co-chair(s).

- Following confirmation of registration and enrollment, participants may begin protocol treatment. For any issues that would cause treatment delays, please contact the Study Chair. If a participant does not receive protocol therapy following registration, the participant's registration protocol status must be changed and the study registration may be canceled.
- Any patient who begins study therapy before confirmation of enrollment will be deemed ineligible.

6. TREATMENT PLAN

6.1 Overview

Phase I

The phase I component will follow a 3+3 design. MEK162 will be administered as a suspension prepared by the on-site pharmacy. The starting dose will be 16 mg/m^2/dose twice daily (BID) which is approximately 67% of the current adult RP2D (Recommended Phase II dose, 45mg bid in a 1.9m^2 adult). Doses will then be escalated in an inter-patient stepwise fashion until dose-limiting toxicities (DLTs) are observed (see 6.4.1). Pharmacokinetic studies will be performed on all patients in the phase I component of the trial. Pharmacodynamic studies, including measurement of phosphorylated ERK in peripheral blood mononuclear cells, will also be performed on all patients in the phase I component of the trial. Tissue-based pharmacodynamic studies will be performed on patients where tumor tissue is available.

Phase II

The primary goal of the phase II component is to determine the therapeutic efficacy, as measured by response rate, of MEK162 in pediatric patients. Three groups of patients will be evaluated.

- Stratum 1 will include pediatric patients with the BRAF truncated fusion with progressive or recurrent LGG.
- Stratum 2 will include pediatric patients with NF1 and LGG. The separation of NF1 patients with LGG into a separate stratum is based on the observation that LGG in this population have distinct biological features compared to LGG in non-NF1 patients, and follow a distinct clinical course.
- Stratum 3 will include pediatric patients with recurrent or progressive tumors thought to involve the Ras/Raf/ERK pathway but not included in strata 1 or 2. This includes any LGG not included in strata 1 or 2 (i.e., any LGG without a BRAF truncated fusion in a patient without NF1), any tumor other than LGG in a patient with NF1, and any other tumor with a known activating BRAF, NRAS or KRAS mutation.
- Stratum 4 (Target Validation) The primary goal of the target validation stratum will be to assess the on-target biologic effects of MEK162, and to assess the degree of tumor penetration by active drug. This phase will proceed concurrently with the phase II portion of the trial and will be open to patients with recurrent or progressive tumors for whom re-resection is clinically indicated. Patients who meet eligibility criteria for phase II and for whom a debulking surgery is planned will be eligible. Patients who elect to enroll in the target validation stratum will initially receive the phase II dose of MEK162 for 7-21 days pre-operatively. At the time of surgery, both peripheral blood and tumor sample will be obtained. Tumor tissue will be assessed for drug concentration and for on-target effects of MEK162, with additional correlative studies.

Once patient is sufficiently recovered post-operatively to resume study drug (determined by local investigator, less than 21 days in most cases), the screening evaluations (Table 9), including tumor imaging, will be repeated. Study calendar will be reset at the time of screening evaluation, and the first day that study drug is administered postoperatively will be considered cycle 1 day 1 of treatment. If repeat imaging shows no measurable residual disease, patient may resume treatment at the discretion of the local investigatory, and will be followed for toxicity but will be considered non-evaluable for response. Patients enrolled in the target validation stratum with measurable postoperative disease will be evaluated for response in an exploratory fashion (see Section 14).

Target accrual for both Stratum 1 and Stratum 2 is 20 response-evaluable patients, using a single cohort design (see Statistical Considerations, Section 14).

MEK162 will be given orally twice daily, as a suspension prepared by the on-site pharmacy, or as a tablet. Four weeks of treatment will constitute one cycle. Patients will remain on treatment for 48 weeks in the absence of tumor progression or development of unacceptable toxicities (see section 6.6). Patients deriving benefit may continue treatment for an additional 48 weeks (96 weeks or 24 cycles total). Responses will be determined using the Response Assessment in Neuro-Oncology (RANO) imaging criteria (17,18).

6.2 Treatment Schema

Phase I

Treatment began at 67% of the adult RP2D (16mg/m^2/dose taken twice daily). This was based on the following calculation:

An adult RP2D of 45mg bid and an average adult m^2 of 1.9m^2 = 45/1.9 = 23.7mg/m^2
67% of 23.7mg/m^2 = 15.9mg/m2 starting dose (which was rounded to 16mg/m^2)

Doses were increased as detailed below:

Dose level -1:	12 mg/m^2/dose BID
Dose level 1:	16 mg/m^2/ dose BID (starting dose)
Dose level 2:	20 mg/m^2/dose BID
Dose level 3:	24 mg/m^2/dose BID
Dose level 4:	28 mg/m^2 /dose BID
Dose level 5:	32 mg/m^2 /dose BID

Phase II

All patients in the phase II component (including those in the target validation stratum), will be treated at a starting dose of 32mg/ m^2 /dose BID (dose level 5). This is the RP2D determined by the study committee (chair and co-chairs) taking into consideration the MTD defined in the phase I component, any significant adverse events identified after cycle 1, and PK/PD results.

Continuation Treatment
After the completion of 12 cycles of study therapy, patients deriving benefit may continue study drug for up to 12 additional cycles at the discretion of the investigator. See section 6.6 (Duration of Therapy).

6.3 Agent Properties and Administration

Chemical Name: 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1Hbenzimidazole-6-carboxamide

Mechanism of Action: MEK162, generic name binimetinib, previously named ARRY 438162, is a potent and selective allosteric, ATP non-competitive inhibitor of MEK1/2 that is active in inhibiting pERK and growth of BRAF mutant cancer cells in the low nanomolar range.

Classification: Small molecule inhibitor

Mode of Action: Selective allosteric, ATP un--competitive inhibitor of MEK1 and MEK2

Formula: $C_{17}H_{15}BrF_2N_4O_3$

Relative Molecular Mass: 441.23

Appearance: White to light tan powder or white to slightly beige powder. Tablets are yellow to dark yellow capsule shaped

Packaging and labeling: MEK162 will be provided by Array BioPharma as film-coated tablets for oral use of dosage strength 15 mg. The film-coated tablets consist of MEK162 drug substance, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and a commercial film coating.

Dosing (see Appendix II and Appendix XII): The study drug will be administered based on body surface area and should be calculated approximately monthly.

Route of Administration: MEK162 will be administered orally BID, as a suspension prepared by the on-site pharmacy (Appendix XVI), or as a tablet. See Appendix II.

Supplier: Investigational supply from Array BioPharma

Supply and Receipt: Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, MEK162 should be stored according to the

instructions specified on the drug labels. Study medication will be dispensed by an authorized person at the investigator's site.

Storage: The storage conditions of the MEK162 film coated tablets are "Do not store above 25°C, protect from light." Packaging is in plastic bottles acceptable for pharmaceutical use.

Stability: Will be provided on the Certificate of Analysis (COA) for each lot of MEK162 distributed by Array BioPharma.

Drug Accountability: Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation. At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will either destroy (with permission from Array BioPharma) or return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Array BioPharma.

Disposal and Destruction: The drug supply may be destroyed at the investigational site according to site standard operating procedure. If site procedures do not allow for destruction, the drug supply will be destroyed at a facility designated by Array BioPharma.

6.4 Toxicities and Dose Reductions

Definitions of dose limiting toxicities (DLTs): Toxicity will be assessed using the NCI CTCAE, version 4.03, unless otherwise specified. A DLT is defined as an AE or abnormal laboratory value assessed as at least possibly related to the study medication, which occurs ≤ 28 days following the first dose of MEK162 (Cycle 1, and cycle 2 day 1), and meets any of the criteria listed in the table below. Required cycle 2 day 1 evaluations that are delayed for any reason should be included as part of the DLT assessment. Whenever a patient experiences a toxicity that fulfills the criteria for a DLT, *treatment with the study drug will be interrupted* and the toxicity will be followed up. Any dose reduction within the DLT period will be considered a DLT. The DLT must be reported to the Study PI, Dr. Robison, and the CTO Operations Center Coordinator, Jasmine Pauly, within 48 hours of the event. Please see section 12.2 for the reporting timeline.

Table 6-1: Toxicity Table for Phase I/II DLT Period Assessment

TOXICITY	DLT CRITERIA
Hematologic	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE Grade 3 or 4 neutropenia with fever (temperature ≥ 38.5°C)
Skin and subcutaneous tissue disorders	Rash, hand-foot skin reaction (HFSR) or photosensitivity CTCAE Grade 3 > 7 consecutive days despite skin toxicity treatment (as per local practice)*
	Rash, HFSR or photosensitivity CTCAE Grade 4

Eye disorders	CSR (Retinopathy) CTCAE Grade 2 for > 14 consecutive days confirmed by ophthalmologic examination*
	CSR (Retinopathy) CTCAE Grade ≥ 3, confirmed by ophthalmologic examination
	Retinal disorder other than CSR (retinal detachment/tear, retinal vascular disorder, retinopathy other) CTCAE Grade ≥ 2 confirmed by ophthalmologic examination
	Visual disturbances without ocular (retinal) changes: blurred vision, flashing lights, floaters CTCAE Grade ≥ 3
Gastro-intestinal	≥ CTCAE grade 3 nausea or vomiting ≥ 48 hrs. despite optimal anti-emetic therapy*
	≥ CTCAE grade 3 diarrhea ≥ 48 hrs. despite optimal anti-diarrhea treatment Pancreatitis Grade ≥ 3
Hepato-biliary	≥ CTCAE grade 3 total bilirubin
	≥ CTCAE grade 3 ALT, or ≥ CTCAE grade 2 ALT with total bilirubin > 2x ULN (Isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting)
	Serum alkaline phosphatase CTCAE Grade 4 > 7 consecutive days*
ECG QT Interval	QTc interval > 500 msec on at least two separate ECGs
Cardiac disorders	Decrease of LVEF > 10% (absolute value) † compared to baseline and the LVEF is below the institution's LLN Left ventricular systolic dysfunction Grade ≥ 3 Other cardiac disorders Grade ≥ 3
Renal	Serum creatinine > 2x ULN
Other non-hematologic events	≥ CTCAE grade 3, except for the exclusions noted below
Exceptions to DLT criteria	Asymptomatic CTCAE grade 3 CK elevation < 5 days of CTCAE grade 3 fatigue < 5 days of CTCAE grade 3 edema Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based on institutional guidelines with consideration of the prohibited medications listed in this protocol. *Will be considered a DLT if toxicity begins within the DLT period and does not resolve within the specified time frame. †Changes in LVEF % refer to absolute value: e.g., a 10% decrease from 60% would be 50% (not 54%).	

Follow-Up for Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed up at least once a week (or more frequently if

clinically indicated) for 4 weeks, and subsequently at approximately 4 week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, cardiologist, dermatologist, etc., should be consulted as deemed necessary. All patients must be followed up for AEs and SAEs for 30 days following the last dose of MEK162.

Patients exhibiting hypomagnesaemia, hypocalcaemia, and/or hypokalemia, should receive electrolyte replacement as indicated by national and institutional guidelines and be followed until laboratory values have normalized or as clinically indicated.

Follow up evaluations for appearance of central serous retinopathy (CSR): Patients on the study will be examined regularly to monitor for the possible development of CSR, as the appearance of CSR has been associated with MEK162 treatment. Ophthalmologic examinations will be performed periodically as outlined in Tables 9-1 and 9-3. For patients developing a CSR of any grade, in addition to the ophthalmologic evaluations detailed in section 6.4 below, it is recommended to follow up the CSR with an ophthalmological exam every two weeks for 8 weeks, and subsequently at approximately a 4-week interval. Dose modification guidelines are outlined below.

Dose Modification and Dose Delay

Any dose reduction within the DLT period will be considered a DLT. Dose reductions within the DLT period should be undertaken in concordance with the sections below.

Dose interruptions of more than 7 days per cycle must be discussed with and approved by the study chair.

Missed/skipped doses will *not* be made up (i.e. the patient should not double their dose if the previous dose was missed).

No intra-patient dose re-escalation is allowed after dose reduction due to any adverse event.

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below. In general, doses should not be reduced or interrupted for Grade 1 toxicities, but treatment to control symptoms should be provided as appropriate. All adverse events (AE) should be followed weekly or as clinically appropriate until stabilization or resolution.

Skin toxicity (such as macular popular rash, acne, rash, dermatitis acneiform, etc.), visual changes (related to CSR), nausea, diarrhea, and asymptomatic reversible elevation of CK have been associated with MEK162 administration. Please refer to the table below for the study-drug dose-adjustment recommendations for MEK162 induced toxicities. Please refer to Appendix XIII and Appendix XIV for additional supportive care guidelines for the management of MEK162-induced skin toxicity and diarrhea, respectively.

All dose reductions must be by 2 dose levels (e.g., from dose level 5 to dose level 3), except for patients at dose level 1 requiring dose reduction, who may be reduced to dose level -1. Patients at dose level -1 meeting dose reduction criteria must be removed from protocol therapy.

Table 6-2: Recommended Dose Modifications Associated with Treatment-Related Adverse Events

CTCAE v4.0.3 Grade (unless otherwise specified)	**Dose Adjustment for Study Drug MEK162**
Eye disorder – CSR like events	
Grade 1	Maintain dose level of MEK162 and increase frequency of ophthalmologic monitoring to at least every 14 days.†
Grade 2	Maintain dose level of MEK162 and repeat ophthalmologic evaluation within one week: - If resolved to Grade ≤ 1 in ≤ 21 days, maintain dose of MEK162. - If not resolved to Grade ≤ 1 in ≤ 21 days, reduce dose of MEK162 or maintain dose of MEK162 based upon the Investigator's discretion after consultation with the ophthalmologist.
Grade 3	Interrupt MEK162 and repeat ophthalmologic evaluation within one week: - If resolved to Grade ≤ 1 in ≤ 21 days, reduce dose of MEK162 - If not resolved to Grade ≤ 1 in ≤ 21 days, discontinue patient from study drug treatment.
Grade 4	Permanently discontinue MEK162, continue close ophthalmologic monitoring.
Eye disorders – RVO	
Any grade	Permanently discontinue MEK162.
Eye disorder – Other retinal events (grading based on CTCAE grading for retinal detachment)	
Grade 1	Repeat ophthalmologic exam including OCT and visual acuity assessment within 10 days. If OCT findings are worse on follow-up exam (even if asymptomatic), interrupt MEK162. Decision to resume therapy will be made on a case-by-case basis in discussion with the sponsor, investigator, and treating ophthalmologist.
Grade 2	Interrupt MEK162 and repeat ophthalmologic monitoring (including OCT and visual acuity assessment) within 10 days. -If retinal event returns to baseline or resolves ≤ Grade 1 severity, MEK162 resume

CTCAE v4.0.3 Grade (unless otherwise specified)	**Dose Adjustment for Study Drug MEK162**
	at the same dose level. -If not improved but not definitively worse, resume MEK162 at a reduced dose. Otherwise, continue to interrupt treatment and discuss the case with the investigator, ophthalmologist and Sponsor prior to resuming treatment.
Grade 3	Interrupt MEK162 and repeat ophthalmologic monitoring (including OCT and visual acuity assessment) within 10 days. -If retinal event returns to baseline or resolves to ≤ Grade 1 severity, MEK162 may be resumed at a reduced dose. Otherwise, continue to interrupt treatment and repeat the complete ophthalmologic assessment in 10 days. - If retinal event returns to baseline or resolves to ≤ Grade 1 severity after a second 10-day period, MEK162 may be resumed at a reduced dose; otherwise, permanently discontinue study therapy.
Grade 4	Permanently discontinue MEK162. Continue close ophthalmologic monitoring.
Other eye disorders	
Grade 1 – 2	Maintain dose level of MEK162 and increase frequency of ophthalmologic monitoring to at least every 14 days.†
Grade 3	Interrupt MEK162 and refer patient to ophthalmologist within one week: -If resolved to Grade ≤ 1 in ≤ 21 days, reduce dose† of MEK162 - If not resolved to Grade ≤ 1 in ≤ 21 days, discontinue patient from study drug treatment.
Grade 4	Permanently discontinue MEK162.
Liver related adverse events*	
Grade 1 AST or ALT Grade 1 (> ULN – 3 x ULN)	Maintain dose level of MEK162.
Grade 2 AST or ALT (> 3 – 5.0 x ULN) **AND blood bilirubin ‡ ≤ 2.0 x ULN**	Interrupt dose of MEK162 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: - If resolved in ≤ 14 days, maintain dose level of MEK162. - If resolved in > 14 days, reduce dose level of MEK162.
AST or ALT (> 3.0 – 5.0 x ULN) **AND blood bilirubin ‡ > 2.0 x ULN**	Interrupt dose of MEK162 until resolved to Grade ≤ 1, then: - If resolved in ≤ 7 days, reduce dose level of MEK162. - If resolved in > 7 days, discontinue patient from study drug

CTCAE v4.0.3 Grade (unless otherwise specified)	**Dose Adjustment for Study Drug MEK162**
	treatment.
Grade 3 AST or ALT (> 5.0 – 8.0 x ULN) **AND blood bilirubin ‡ ≤ 2.0 x ULN** AST or ALT (>8 x ULN) **AND blood bilirubin ‡ ≤ 2.0 x ULN** AST or ALT (> 5.0 x ULN) **AND blood bilirubin ‡ > 2.0 x ULN**	Interrupt dose of MEK162 until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: - If resolved in ≤ 14 days, maintain dose level of MEK162. - If resolved in > 14 days, reduce dose level of MEK162. Permanently discontinue MEK162. Permanently discontinue MEK162.
AST or ALT Grade 4 (> 20.0 x ULN)	Permanently discontinue MEK162.
Cardiac disorders	
Left ventricular systolic dysfunction/ejection fraction decreased* Asymptomatic decrease of >10% (absolute value) in LVEF compared to baseline and the LVEF is below the institution's lower limit of normal. ‡‡	Interrupt dose of MEK162 and repeat evaluation of LVEF within 2 weeks If the LVEF recovers (defined as ≥ LLN and absolute value decrease ≤ 10% compared to baseline) ‡‡ in ≤ 4 weeks, reduce dose after approval of the Study Chair. Monitor LVEF 2 weeks after restarting on MEK162, every 4 weeks for 12 weeks and subsequently as per protocol. If the LVEF does not recover within 4 weeks, permanently discontinue patient from study treatment. Closely monitor LVEF until resolution (or for 16 weeks).
Grade 3 – 4	Permanently discontinue patient from MEK162. Closely monitor LVEF for 16 weeks or until resolution. Note: Copies of ECHOs could be requested for patients with absolute value decrease of >10% in LVEF compared to baseline and LVEF < LLN.
CK elevation	
Any grade	- Assess hydration status. Consider supplemental hydration if oral intake inadequate.

CTCAE v4.0.3 Grade (unless otherwise specified)	**Dose Adjustment for Study Drug MEK162**
	- Measure serum creatinine, with interval reevaluation as clinically appropriate. - If total CK ≥ 3X ULN, measure isoenzymes and myoglobin in blood or urine.
Grade 1-2	Continue treatment on same dose level.
Grade 3 (> 5X ULN- 10X ULN)	If asymptomatic with normal creatinine: Maintain dose of MEK162 and monitor closely. If symptomatic (muscle pain/spasms) or serum creatinine >ULN: Interrupt dose of MEK162 until resolved to CTCAE Grade ≤ 1 and monitor closely (Section 6.4), then: - If resolved in ≤ 21 days, reduce dose of MEK162. - If resolved in > 21 days, discontinue patient from study drug treatment.
Grade 4	If asymptomatic: interrupt and monitor closely . - If resolved in ≤ 21 days, reduce dose of MEK162. - If resolved in > 21 days, discontinue patient from study drug treatment. If symptomatic : permanently discontinue treatment.
QTc Prolongation	
QTc > 500 msec (Grade 3) (confirmed)	1st occurrence: Treatment with MEK162 should be temporarily suspended. Electrolyte abnormalities, if any, should be corrected and any concomitant medication that may potentially prolong QT should be discontinued. Patient monitoring until resolution of the adverse event should be implemented in the hospital including a consultation with a cardiologist. Once the QTc prolongation has resolved (CTC Grade < 1), MEK162 may be restarted at a reduced dose. 2nd occurrence: If a second episode occurs that is attributed to MEK162, study drug must be permanently discontinued.
Rash	
Grade 1	Treatment with MEK162 should be maintained at the current dose.

CTCAE v4.0.3 Grade (unless otherwise specified)	**Dose Adjustment for Study Drug MEK162**
	Initiate prophylactic regimen if it was not already started and monitor closely.
Grade 2	1st occurrence: Treatment with MEK162 should be maintained at the current dose and the rash should be closely monitored. *Initiate prophylactic regimen if it was not already started* Reassess within a maximum of two weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade < 1. Resume treatment at the same dose level. Subsequent occurrences: Reassess within a maximum of 2 weeks. If rash worsens or does not improve, interrupt dosing until improvement to Grade < 1. Resume treatment at a reduced dose level.
Grade 3	1st occurrence: Treatment with MEK162 should be interrupted. Reassess the patient weekly. Consider referral to dermatologist and manage rash per dermatologist's recommendation - Interrupt treatment until improvement to Grade ≤ 1. Resume treatment with MEK162 at the same dose level Subsequent occurrences: Interrupt treatment until improvement to Grade ≤1. Resume treatment with MEK162 at a reduced dose level *Consider referral to dermatologist and manage rash per dermatologist's recommendation*
Grade 4	Permanently discontinue MEK162
Diarrhea	
Uncomplicated§ Grade 1-2	Consider temporary interruption of MEK162 until resolved to Grade ≤ 1. Treatment may then be resumed at current dose level.
Complicated§ Grade 1-2	Temporarily interrupt MEK162 treatment until resolved to Grade ≤ 1. Restart MEK162 at a reduced dose level.
Grade 3	Temporarily interrupt MEK162 treatment until resolved to Grade ≤ 1. Restart MEK162 at a reduced dose level.
Grade 4	Temporarily interrupt MEK162 treatment until resolved to Grade ≤ 1. Restart

CTCAE v4.0.3 Grade (unless otherwise specified)	**Dose Adjustment for Study Drug MEK162**
	MEK162 at a reduced dose level
All other adverse events (suspected to be related)	
Grade 1-2	In the event is a persistent Grade 2 AE, not responsive to a specific therapy, consider study drug interruption or reduction.
Grade 3	Interrupt study drug until resolution to Grade ≤1 or to pre-treatment/ baseline level. If the event resolves within 21 days then study drug may be restarted at a lower dose, (two levels below that previously received) based upon the Investigator's discretion.
Grade 4	Permanently discontinue MEK162 §§

* Not according to CTCAE.

† Ophthalmologic monitoring should include ocular coherence tomography (OCT) and slit lamp examination if feasible, in addition to visual acuity testing, visual field assessment, and indirect fundoscopy. Further evaluation with specialized retinal imaging (e.g. angiography) should be performed as indicated.

‡ Refers to total bilirubin.

‡‡ Change in LVEF % refers to absolute value: e.g., a 10% decrease from 60% would be 50% (not 54%).

§ The determination of whether grade 1-2 diarrhea is uncomplicated or complicated will be made by the investigator. Complicated diarrhea will typically be characterized by one or more of the following: moderate to severe cramping, fever, neutropenia, sepsis, bleeding, dehydration, decrease in performance status, or nausea and vomiting.

§§ A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤1 within 21 days of discontinuing drug and, if in the opinion of the Investigator and Study Chair, the event is not life-threatening, and the patient can be managed and monitored for recurrence of AE. Any patients requiring a treatment interruption of longer than 21 days must discontinue study drug permanently.

6.5 Concomitant Medications

All medications (other than the study drugs) taken within 4 weeks of study treatment initiation and all concomitant therapy and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study, with reasons for use, should be recorded. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications and nutritional or vitamin supplements.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after starting study drug.

Patients taking medication chronically should be maintained on the same dose and schedule throughout the study period, as medically feasible. The days of full pharmacokinetic blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of full pharmacokinetic sampling, if medically feasible.

Permitted Concomitant Therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted. Please refer to MEK162 IB for possible interactions with other drugs. Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents, such as PRBCs, pain medications, anti-emetics, short courses of steroids, and anti-diarrheals are allowed. Oral contraceptive pills are permitted. The use of any other potential new concomitant medications may be discussed between the investigator and the sponsor on a case-by-case basis. Please refer to Table 6-3 and Appendix I for a list of drugs to be used with caution.

Transfusions or growth factor support for white cell counts, platelets, or red blood cells are not permitted during Cycle 1, unless the patient has already experienced a DLT. Transfusions and growth factor support should not be used prophylactically during Cycle 1.

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible.

The investigator should instruct the patient to notify the study site about any new medications including vitamins, supplements, and herbal supplements he/she takes after the start of the study drug. All medications (other than study drug) including vitamins, supplements and herbal supplements and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be noted.

Permitted concomitant therapy requiring caution and/or action

The solubility of MEK162 is pH dependent and a 10-fold decrease in solubility is observed between pH 1 and 2. Patients receiving concomitant treatments that could potentially modify the gastric pH (i.e. PPI) should be instructed to take them at least two hours after the administration of MEK162. In vitro data showed that MEK162 is a substrate of P-gp and BCRP and thus the use of drugs that are known to inhibit these transporters should be used with caution. Please refer to Table below for a list of these drugs.

Table 6-3: List of inhibitors of human transporters to be used with caution

Transporters	Category	Substrate
P-gp	Calcium Channel Blockers	felopidine, verapamil, diltiazem, mibefradil, nifedipine, nitrendipine
	Protease inhibitors	indinavir, ritonavir, lopinavir, telaprevir, saquinavir, nelfinavir
	Antibiotics	Fexofenadine, clarithromycin, azithromycin, erythromycin, rifampin
	Antiarrhythmics	quinidine, dronedarone, amiodarone
	Adrenergic Antagonist	carvedilol, talinolol
	Herbal Medications	Schisandra chinensis, St. John's wort, milk thistle (silybum marianum), ginkgo biloba
	Others	valspodar (PSC 833), elacridar (GF120918), ranolazine, fluvoxamine, itraconazole, quercetin, captopril, conivaptan, paroxetine, ticagrelor, telmisartan, tolvaptan
BCRP	Others	elacridar (GF120918)

***** This table was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies"; and from the University of Washington's Drug Interaction Database.
For further information, please see the FDA's website:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093606.htm

MEK162 showed relatively potent inhibitory potency for CYP2B6 (unbound K_i of 1.67 µM). Based on these *in vitro* findings, MEK162 may inhibit the metabolic clearance of co-medications metabolized by CYP2B6, if sufficiently high concentrations are achieved *in vivo.* Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of this enzyme. Please refer to Appendix I for a list of CYP2B6 substrates.

Drugs with a known, a conditional or a possible risk to induce Torsade de Pointes (TdP) should be used with caution. Patients receiving such medications must be carefully monitored for potentiating of toxicity due to any individual concomitant medication, and may require dose titration of the drug substance. For further information, please visit the website of the QTdrugs.org Advisory Board of the Arizona CERT.

The impact of UGT1A1 inhibitors or inducers on PK of MEK162 *in vivo* is unknown; therefore, inhibitors or inducers of UGT1A1 should be co-administered with caution.

The effect of inhibitors or inducers of CYP1A2 or CYP2C19 *in vivo* is unknown; therefore, strong inhibitors or inducers of CYP1A2 or CYP2C19 should be used with caution. Please refer to Appendix I.

Prohibited concomitant therapy

- Medications that carry a strong risk for QT prolongation are prohibited
- Concurrent anti-neoplastic therapy, including radiotherapy are prohibited

Growth Factors: Routine use of growth factors (i.e. G-CSF, GM-CSF, erythropoietin) is not permitted. However, therapeutic use of G-CSF or GM-CSF in patients with serious neutropenic conditions, such as sepsis, may be considered at the investigator's discretion.

Anti-emetics: The use of anti-emetics will be at the investigator's discretion. Use of anti-emetics should be recorded in the concomitant medication diary.

Febrile neutropenia: Febrile neutropenia should be managed according to the local institutional guidelines. Measures include laboratory testing, blood and urine cultures, and institution of broad-spectrum antibiotics.

Pneumocystis carinii pneumonia (PCP) prophylaxis: The use of medication (i.e., trimethoprim/sulfamethoxazole, dapsone, atovaquone, or pentamidine) for PCP prophylaxis in patients on chronic steroids is recommended, but is at the investigator's discretion.

Surgical Procedures: If a surgical procedure is required for a reason other than tumor progression (i.e. the onset of hydrocephalus), these procedures should be documented, but will not constitute criteria for declaring the patient "off therapy."

Central Venous Catheters: Treatment via central venous catheters is not needed.

6.6 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue for approximately 48 weeks or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

After the completion of 12 cycles, patients deriving benefit may continue investigational drug for up to 12 additional cycles (up to 24 cycles or 96 weeks total) at the investigator's discretion.

6.7 Duration of Follow-Up

Participants will be followed for AEs for 30 days after discontinuation of study therapy or until death, whichever occurs first. Participants who discontinue study therapy due to unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For all patients that complete therapy or come off therapy for any other reason, toxicity assessment (for new SAEs and unresolved prior AEs) will continue for 30 days or until the events return to baseline. Patients

that start new therapy will not be evaluated for new SAEs. After the 30 days, survival data and MRI scans (if available) will be requested for all patients.

Recommended follow-up for patients that complete therapy will occur every 3 months (+/- 2 weeks) for the first year (can be more or less frequent) and then approximately annually until progression or change of therapy. Frequency of disease assessment in patients receiving continuation therapy is at the discretion of the investigator.

6.8 Criteria for Removal from Study

Participants will be removed from treatment when any of the criteria listed in Section 6.6 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant. Reasons for study removal include: death, patient lost to follow-up, or patient withdrawal of consent.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Dr. Nathan Robison at (323) 361-8147 or Dr. Mark Kieran at (617) 632-4907.

7. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dose Delays and Modifications

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4, which is identified and located on the CTEP website at: http//ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, appropriate supportive and symptomatic care should be provided, include anti-emetics, antidiarrheals, etc., as indicated. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, antidiarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

7.2 Expected Toxicities for MEK162

Please refer to the most recent Investigators Brochure for a list of the current known and suspected MEK162 toxicities.

7.3 Management of Treatment-Related Events

For rash-like events, institutional standard of care treatment should be initiated promptly upon occurrence of such events. Treatment of rash may include, but is not limited to, topical or oral antibiotics, topical or oral anti-inflammatory, topical or oral corticosteroids, and oral antihistamines. Sun avoidance or careful use of sunscreen is recommended. Emollients may be used prophylactically or as treatment for rash (see Appendix XIII).

For elevated CK levels, patients may remain on MEK162 per investigator discretion if asymptomatic.

Patients may be treated symptomatically for nausea, vomiting, and diarrhea with standard anti-emetic and anti-diarrheal medications (see appendix XIV). Prophylactic treatment for nausea should be considered. Prophylactic treatment for diarrhea is not required.

Patients with edema may be treated with diuretic medications if indicated.

For stomatitis/mucositis-like events, institutional standard of care treatment should be initiated promptly upon occurrence of such events.

Patients with a history or current evidence of CSR, RVO or ophthalmopathy present at baseline that would be considered a risk factor for CSR or RVO should not be treated with MEK162 (see exclusion criteria).

The decrease of cardiac ejection fraction has been reported with other MEK inhibitors in clinical development. The review of all cardiac SAEs across all studies administering MEK162, either as a single agent or in combination with other antineoplastic drugs, suggests that these side effects are also observed with the Array/Novartis compound MEK162. Therefore, in order to ensure patient safety in all ongoing clinical studies with MEK162, monitoring of cardiac function and stringent inclusion/exclusion criteria are included and followed.

Although there was one fatal case of liver failure in study MEK2201 at 60 mg BID, thorough review of liver abnormalities observed across the different studies, revealed that most of the changes in liver parameters (transaminases, bilirubin) have been Grade 1-2. To ensure an adequate and prospective monitoring of liver toxicities stringent guidelines for inclusion criteria and dose modifications were included in the protocols.

8. CORRELATIVE STUDIES

8.1 Pharmacokinetic Studies

The blood sampling regimens for determining the pharmacokinetics of MEK162 and its primary active metabolite AR00426032 are given in Table 8-1. Blood samples for MEK162/AR00426032 concentration measurements will be collected on all patients in the study from both the phase I and phase II component. Exact dates and clock times of drug administration and actual PK blood draw should be recorded on the appropriate eCRF. If a patient experiences an AE that results in an unscheduled visit or fits the criteria of a SAE as determined by the Investigator, a blood sample should be collected for measurement of drug concentrations at or around that time. Additionally, if a patient experiences an ocular event of any grade, a blood sample should be collected.

If vomiting occurs within 4 hours following study-drug administration on the day of PK blood sampling (Cycle 1 Day 1 and Day 15), the time (using the 24-h clock) of vomiting should be recorded on the transmittal forms, which accompanies the sample. No additional trial medication should be taken that day in an effort to replace the material that has been vomited.
If a patient withdraws prematurely from the study, a PK blood sample for MEK162 analysis (2 mL of sample) should be obtained whenever possible. Sample should be collected as soon as possible after the last dose of MEK162, and the date and time of last dose should be recorded.
Whenever an ECG with a QTc change from baseline > 60 msec or a new absolute QTc ≥ 500 msec result is known, a blood sample to assess the concentrations of MEK162/AR00426032 should be obtained and the time of sample collection noted.

A detailed description of the planned pharmacokinetic analyses is given below.

Pharmacokinetic blood sample collection and handling

All blood samples will be taken either by direct venipuncture or from an indwelling venous cannula. Blood should be collected in accordance with institutional guidelines. All samples must be carefully packed in suitable material containing sufficient dry ice to keep them frozen during shipment. A list of samples, including the date, subject number, and the time of sampling should be included in the shipment. Any missing samples should be notified on the list.

Complete instructions for sample processing, handling and shipment is provided in Appendix IV. Any sampling problems should be noted on the eCRF and on appropriate source documentation.

Table 8-1: Schedule of blood sample collections for MEK162 Pharmacokinetics (Dose Escalation Phase I and Phase II)

Cycle	Day	PK
1	1	Pre-dose

1	1	0.5hr
1	1	1hr
1	1	2hr
1	1	4hr
1	1	6hr
1	2	Pre-dose
1	15	Pre-dose
1	15	0.5hr
1	15	1hr
1	15	2hr
1	15	4hr
1	15	6hr
Phase I: Cycles 2-12 Phase II: Cycles 2-4	1	Pre-dose
At the time off study or associated with toxicity		

Take pre-dose sample immediately prior to the start of study drug (MEK162) administration.
In the event of difficulty scheduling sampling for PK, the samples may be obtained ± 3 day from the scheduled date (except for Day 1 of Cycle 1). There is a +/- 15 minute window for any samples taken from 0.5 hr – 2hr and +/- 30 minute window for >2hr. For Cycle 2+ pre-dose samples the previous dose time must be recorded.

At the specified time points, 2.0 mL of blood will be collected in tubes containing EDTA (purple top). The tubes will be kept in an ice water bath after blood collection. Within 30 minutes, the tubes will be centrifuged at between 3°C and 5°C for 10 minutes at approximately 1500g to separate plasma. Immediately after centrifugation, transfer at least 0.5 mL of plasma into 2-mL polypropylene screw-cap tube (MEK162/AR00426032). The tubes will be placed in a freezer set at < -70ºC until shipment.

Assay for Plasma MEK162: Plasma concentrations of MEK162 and its metabolite, ARR00426032, will be measured at QPS, LLC using a validated liquid chromatography-tandem mass spectrometry assay with an LLOQ of 5.0 ng/mL for both analytes.

All plasma pharmacokinetic samples should be shipped Monday through Wednesday to the following address:

QPS Sample Coordination
3 Innovation Way
Suite 240
Newark, DE 19711
Phone: 302-369-5120
Fax: 302-369-5602
Email: sample@qps.com

8.2 Pharmacodynamic Studies

As outlined in the Table 8-2 below, tumor, blood, and urine (Phase II) samples will be collected in cryovials, in BD 367863 Vacutainer EDTA tubes, and sterile urine collection containers, respectively before and during treatment with the MEK162 to investigate the effect of the drug at the molecular and cellular level as well as to determine how baseline values/levels and changes from baseline in the markers may relate to exposure, clinical outcomes, and resistance. Details are outlined in Appendices III, IV, V, VI, VII, VIII, and IX.

Table 8-2: Schedule of Samples

Sample Type	Time Point	Format	Collection Tube	Shipment Tube	Shipment Conditions/ Temperature	Label
Tumor	**Pre-treatment**	**FFPE**	**N/A**	**Block or H&E slide, 20-40 unstained slides**	**Ambient (room temperature)**	**Subject ID, CTO registration ID, patient initials, date sample obtained**
	Pre-treatment	**Frozen (not fixed)**	**1.5 ml Cryovial**	**1.5 mL Cryovial**	**Dry Ice or -80°C**	**Subject ID, CTO registration ID, patient initials, date sample obtained**
	Post-treatment	**Frozen (not fixed)**	**1.5 ml Cryovial**	**1.5 mL Cryovial**	**Dry Ice or -80°C**	**Subject ID, CTO registration ID, patient initials, date sample obtained**
Pharmacodynamic Blood (6mL)	**Tube 1: Pre-treatment**	**Whole Blood, Frozen**	**BD 367863 Vacutainer EDTA**	**1.5 mL Cryovials (aliquoted from Vacutainer)**	**Dry Ice or -80°C**	**Subject ID, CTO registration ID, subject initials, date & time sample obtained, PD #1**
	Tube 2: Phase I Cycle 3 Phase II Cycle 4 Day 1, 4-6 hours after dose	**Whole Blood, Frozen**	**BD 367863 Vacutainer EDTA**	**1.5 mL Cryovials (aliquoted from Vacutainer)**	**Dry Ice or -80°C**	**Subject ID, CTO registration ID, subject initials, date & time sample obtained, PD #2**
	Tube 3: Time of progression, end of treatment, or end of cycle 12	**Whole Blood, Frozen**	**BD 367863 Vacutainer EDTA**	**1.5 mL Cryovials (aliquoted from Vacutainer)**	**Dry Ice or -80°C**	**Subject ID, CTO registration ID, subject initials, date & time sample obtained, PD #3**

Streck BiomarkerBlood (9mL-10mL)	**Phase I: Any time (Pre-treatment preferred)** **Phase II: Pretreatment, and day 1 of cycles 2, 4, 7, and at end of treatment or end of cycle 12.**	**Whole blood at room temperature**	**9mL or 10mL Cell-Free DNA BCT Streck tube**	**9mL or 10mL Cell-Free DNA BCT Streck tube**	**Ambient (room temperature)**	**Subject ID, CTO registration ID, subject initials, date sample obtained, PD and time point**
Urine (10mL-45mL)	**Phase II: Pretreatment and day 1 of cycles 2, 4, 7 and at end of treatment or end of cycle 12**	**Urine with urine preserve at room temperature added**	**Sterile, screw top urine collection cup**	**50 mL sterile conical tube (transferred from collection cup)**	**Ambient (room temperature)**	**Subject ID, CTO registration ID, subject initials, Date & Time Obtained, Urine and time point**
CSF (1mL-10mL	**When clinically indicated**	**CSF at room temperature**	**10mL Cell-Free DNA BCT Streck tube**	**10mL Cell-Free DNA BCT Streck tube**	**Ambient (room temperature)**	**Subject ID, CTO registration ID, subject initials, date sample obtained, CSF and time point**

Before shipment, please confirm with Sarah Becker via email (pnotissuebanking@partners.org) that proper materials are sent.

All materials from Table 8-2 should be sent to:
Keith Ligon C/O Sarah Becker
450 Brookline Ave JFB215A
Boston, MA 02215

Table 8-3: Stratum 4 Target Validation Sample Schedule Cycles 0-1

Sample Type	Cycle 0	Day of Surgery	Cycle 1
PK	**None**	**Single Collection**	**Full Panel**
6mL Blood PD	**Pre-treatment**	**Single Collection**	**None**
9-10 mL Streck Blood PD	**Pre-treatment**	**Single Collection**	**None**
Urine PD	**Pre-treatment**	**None**	**None**

Biomarker Assessments in Tumor Samples

A representative baseline tumor tissue sample (archival or fresh) will be requested from all patients to perform the assessments as described in Tables 8-4 and 8-5.

Table 8-4: Summary of Assessments in Tumor Tissue for Participants in Strata 1, 2, and 3

Tumor markers	Archival tissue	Frozen tissue (if available)

pS6(Ser240/244, 235/236)	**X**	**X**
pERK (T202/Y204) CST #4370	**X**	**X**
pMEK1/2 (S221) CST #2338	**X**	**X**
BRAF V600E Roche #790-4855	**X**	**X**
Duplication/fusion BRAF FISH	**X**	**X**

Table 8-4: Summary of Assessments in Tumor Tissue for Participants in Stratum 4

Tumor markers	Pre-Treatment Tissue	Post- Treatment Tissue
Cleaved Caspase 3 IHC	**X**	**X**
pS6(Ser240/244, 235/236) IHC	**X**	**X**
pERK(T202/Y204) CST #4370 IHC	**X**	**X**
pMEK1/2 (S221) CST #2338 IHC	**X**	**X**
Oncopanel (which assesses BRAF V600E)	**X**	**X**
Array CGH (which assesses duplicated/fusion BRAF)	**X**	**X**
KI67 IHC	**X**	**X**

Fresh Frozen Post-Dose Tumor Biopsies

These will be requested if tissue acquisition is clinically indicated. Tumor tissue samples are important to investigate the effects of MEK162 on molecular signaling and may aid identification of markers predictive of efficacy, of pharmacodynamics markers, or of markers related to resistance/early resistance to treatment.

- One “green pea sized” specimen from previously banked snap frozen primary tumor material, regardless of time from surgery, should be rapidly transferred (without thawing) from long term frozen storage to a Styrofoam box (minimum suggested internal dimensions of 30cm x 30cm x 30cm) filled with as much dry ice as possible. Samples should be submitted in 1.5ml standard size Cryovials containing the tumor material and labeled with the MEK162 Subject ID, site name, and subject initials.

Collection of Archival Tumor Samples

Archival tumor samples representing current disease status are required at baseline for all patients for whom an archival sample is available. If tissue is available from several surgeries, the most recent tissue should be sent.

- The local pathologist should select the “best block” which contains viable tumor with greater than 50% tumor nuclei, less than 30% necrosis, and the tissue fragment size in total ~0.5cm in diameter for advanced studies. The block should contain sufficient tissue to provide 20-40 standard 5-micron FFPE slides for the planned advanced studies. If you are unable to send a block, please send an H&E slide and 20-

- 40 unstained slides (no heat treatment, “plus” type charged slides).

Pharmacodynamic and Biomarker Assessments in Blood

Pharmacodynamic: The pharmacodynamic effects of MEK162 on MEK signaling will be assessed by measuring pMEK and pERK in serum. Other methods of pathway signaling quantitation may also be used. **A** whole blood sample (approximately 6 mL in an EDTA tube) will be obtained Cycle 1 Day 1 pre-dose and at Cycle 3 (Phase I) or Cycle 4 (Phase II) Day 1 4-6 hours post-dose in order to provide a normal (non-tumor) control tissue sample for DNA sequencing as a normal genomic control. This sample will be used to identify tumor-specific gene alterations by comparing DNA from tumor samples with DNA from normal-non-tumor cells.

Biomarker: Samples of blood will be requested at the time of venipuncture for additional biomarker studies (see Appendices III, IV, V, VI, VII, VIII, and IX). These samples may be used to support analyses of potential tumor mutations versus polymorphisms. These samples will be drawn into a purple top EDTA tube with anticoagulant/preservative, inverted a few times to mix, and placed on wet ice temporarily Whole blood must be aliquoted into as many 1.5mL standard cryovials (~1mL per tube) as needed. Blood should not be processed further and placed in a freezer -80°C until shipment. Samples should be shipped in a Styrofoam box with 7-10lbs of dry ice to Dr. Keith Ligon's laboratory at the address above.

Processing for the ambient blood PD sample is as follows:

Streck PD Blood Sample Processing Protocol

1. Collect 9-10mL whole blood in Cell-Free DNA BCT Streck Tube
2. Gently invert tube 8 times
3. De-identify tube by removing all patient identifiers
4. Label the tube with:
    a. Subject ID
    b. CTO registration ID
    c. Subject initials
    d. Date and time sample obtained
    e. Sample and Time point (ex: Streck PD C1D1)
5. Send sample and transmittal form at room temperature within 72 hours of collection to Dana-Farber Cancer Institute in Boston.

Urine Sample Processing Protocol

1. Collect 10mL-45mL urine in sterile collection cup and add 10-20% volume of Streck Cell-Free DNA Urine Preservative to sample
    a. Note time of addition of preserve on transmittal form
2. Gently invert container 5 times to make sure it is well mixed
3. Transfer urine with added preservative to 50 mL conical tube
4. De-identify tube by removing all patient identifiers
5. Label the tube with:

a. Subject ID
b. CTO registration ID
c. Subject initials
d. Date and time sample obtained
e. Sample and Time point (ex: Urine C7D1)

6. Send sample and transmittal form at room temperature within 72 hours of collection to Dana-Farber Cancer Institute in Boston.

CSF Sample Processing Protocol

1. Collect 1mL-10 mL CSF in Streck Cell-Free DNA BCT Streck Tube
2. Gently invert tube 10 times to ensure proper mixing of stabilization agent
3. De-identify tube by removing all patient identifiers
4. Label the tube with:
    a. Subject ID
    b. CTO registration ID
    c. Subject initials
    d. Date and time sample obtained
    e. Sample and Time point (ex: CSF C1D1)
5. Send sample and transmittal form at room temperature within 72 hours of collection to Dana-Farber Cancer Institute in Boston.

After receipt at Dana-Farber Cancer Institute in Boston, biomarker blood, urine, and CSF samples will be processed and sent to the BROAD Institute via courier for Cell-Free DNA analysis. This will include next generation sequencing to identify genomic events associated with the cancer cells.

Other Exploratory Biomarker Assessments Performed during the Study: During the study, in addition to the biomarkers specified above, exploratory biomarkers research may be conducted on any tumor and blood (including PK) samples. These studies would extend the search for other potential biomarkers relevant to the effects of the MEK162 drug and/or prediction of these effects and/or resistance to the treatment, and/or safety, and these additional investigations would be dependent upon clinical outcome, reagent and sample availability. While the goal of the biomarkers is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc). Therefore, depending on the results obtained during the study, sample collection/analysis may be omitted at the discretion of the PI.

Optional Additional Biomarker Assessments Using Remaining Tumor and/or Blood Samples: If the patient agrees, any remaining samples (tumor and blood) may be stored indefinitely and further analyzed to address scientific questions and/or development of biological tests related to MEK162 and/or cancer. The decision to perform such exploratory biomarker research studies would be based

on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability (see appendices III, IV, V, VI, VII, VIII and IX).

Pharmacodynamic and Biomarker Studies: Guidelines for Processing Biopsy Tumor Tissue Samples
Tissue Handling: The tissue should be kept frozen whenever possible by snap freezing via placement of tubes containing the tumor into a -70^{0}C freezer or placement onto dry ice within 1 hour (sooner is better) and shipped immediately to Dr. Keith Ligon for molecular analysis (see address above).

Immunohistochemistry will be performed at the lead site through Dr. Keith Ligon: pERK, pMEK, pS6 expression will be determined by immunohistochemistry (IHC). If sufficient tissue is available, additional IHC studies will be performed. Oncopanel sequencing and copy array assays will be performed to test for v600E and BRAF rearrangements, respectively. Oncopanel sequencing will be performed at the CLIA-certified BWH CAMD Molecular Diagnostics Laboratory (Dr. Neal Lindeman, Director) and copy array testing will be performed in the CLIA-certified BWH CAMD Clinical Cytogenetics Lab (Dr. Azra Ligon, Director).

Immunohistochemical Assay**:** Tissue will be fixed in 10% neutral buffered formalin for 6 to 24 hours (standard clinical fixation conditions). Samples will then be paraffin embedded, sectioned at a thickness of 5 microns, and adhered to Superfrost Plus slides (Fisher). The slides will be heated at 37° overnight in a dry oven. Antigen retrieval will be performed by incubation of the sections in 10ug/ml proteinase K in PBS for 10 minutes at room temperature. Antibodies to the specific target based on the vendor recommendations will be used. Appropriate controls as specified in the clinical laboratory will be included. Negative controls will be incubated with blocking serum alone.

Sample Reporting: Results from the Oncopanel and Array CGH tests are CLIA certified and will be reported to the institution. Confirmation of receipt of the email containing these reports from CHLA is required. Non-CLIA certified laboratory results (e.g. IHC, cell free DNA, PD studies) will be maintained with unique codes to ensure that none of this information is returned to the patient's medical record as per CHLA policy.

Molecular Profiles: Additional molecular profiling will be performed if sufficient material remains. Results of all molecular studies below as well as results from the matched normal blood will be maintained with unique codes to ensure that none of this information is returned to the patient's medical record as per CHLA policy.

If additional material becomes available, repeat molecular analyses will be performed and compared to the original baseline studies. A comparison will be made to the original tumor sample to study the effect the treatment had on the tumor.

If there is any tissue leftover after the optional analyses have been performed, the tissue will be stored and archived by Dr. Keith Ligon at DFCI within his research laboratory. This tissue may be used in the future if new molecular analyses tests become available. All samples will be stored in the

laboratory of Dr. Keith Ligon at the address above. Please see appendices III, IV, V, VI, VII, VIII, and IX for details regarding sample collection and storage.

Samples for cell free DNA analysis will be shipped to Dr. Ligon centrally and the testing will be performed in the laboratory of Dr. Mimi Bandopadhayay at the Broad Institute.

Samples for mass spectrometry imaging of drug in tumor tissue (0.3 cm^3/300 mg sample) will be shipped to Dr. Ligon centrally and then testing will be performed in the laboratory of Dr. Nathalie Agar at the Brigham and Women's Hospital.

8.3 Ophthalmologic Studies

For patients with tumors involving the optic pathway (including suprasellar/hypothalamic tumors) all of the assessments in this section are mandatory. For patients with tumors not involving the optic pathway, the retinal evaluation assessments are mandatory, but institutional standard of care procedures may be substituted for visual acuity.

Retinal Evaluation
As retinal events and intra-ocular hypertension are well-described toxicities of MEK inhibition, all study participants must go regular ophthalmologic evaluation for the duration of study treatment. Examination will include visual acuity testing and indirect fundoscopy with attention to retinal abnormalities, especially RPED-like events and RVO. Slit lamp examination, visual field testing, intraocular pressure (IOP) measurement and ocular coherence tomography should be performed if feasible. Age appropriate methods of evaluation are permitted. Ophthalmologic examination must be performed by a pediatric ophthalmologist for all patients <12 years old. For patients with clinical suspicion of retinal abnormalities (i.e. photopsia, metamorphopsia, impairment of visual acuity, etc.) or RVO, additional assessments of fluorescein angiography and/or optical coherence tomography (OCT) should be performed. Images of OCT and fluorescein angiography should be sent to the investigative site along with the results of the exam and maintained in the patient's source documentation file.

Visual Acuity (best corrected)
Teller acuity testing and/or ATS-HOTV must be attempted at each ophthalmology visit. For patients able to cooperate with HOTV, both Teller acuity testing and HOTV must be performed together (same visit) at least once. For patients who are literate and able to cooperate with Snellen visual acuity testing and whose tumors do not involve the optic pathway, Snellen may be performed in place of ATS-HOTV.

If the VA data at a particular visit is felt to be unreliable due to poor cooperation, testing should be repeated in 1-2 weeks. Only the visit believed to have yielded the most reliable data should be reported.

Teller acuity testing using TAC II cards will be performed in each eye separately at a distance of 55cm in all subjects. The tester will utilized the "Two down, one up" protocol to achieve the best visual acuity. Acuity will be reported in cycles/cm by the site and converted by the operations center to logMAR. Reasons for VA testing not being completed will be recorded.

Table 8-5: Visual acuity in feet and logMAR equivalents for acuity in cycles/cm

Card @ 55 cm (Cycles/cm)	VA equivalent	logMAR
38	20/16	-0.10
26	20/24	0.06
19	20/32	0.20
13	20/47	0.36
9.8	20/63	0.49
6.5	20/94	0.66
4.8	20/130	0.80
3.2	20/190	0.97
2.4	20/260	1.10
1.6	20/380	1.27
1.3	20/470	1.36
0.86	20/710	1.54
0.64	20/960	1.67
0.43	20/1400	1.84
0.32	20/1900	1.97

HOTV will be attempted on subjects who are old enough. HOTV will be performed using the PEDIG ATS-HOTV computerized protocol in each eye separately at a distance of 3 meters in all subjects.[26] For subjects with severe visual impairment at baseline (20/400 or less) HOTV may be performed at a distance of 1 meter, with appropriate refractive correction. Acuity will be reported in logMAR. Reasons for VA testing not being completed will be recorded.

For primary analysis, the VA endpoint will be the difference between best-corrected VA and age-based normal values (i.e. the age adjusted VA).

Visual Fields

Visual field testing will be performed by confrontation and reported as the number of quadrants (0, 1, 2, 3, or 4) with VF deficits. In addition, if feasible, Goldmann perimetry should be performed at baseline at the end of cycle 12 or at conclusion of therapy (whichever occurs first).

Optic Discs

Optic discs will be assessed for the presence or absence of pallor and edema.

8.4 Patient Reported Outcomes (Phase II)

For all subjects age ≥ 24 months at the time of visit with at least one English or Spanish-speaking parent, an age-specific Parent Report PedsQL™ Brain Tumor Module (attached as Appendix XVIII) will be administered to one parent at the time points below.

For all English or Spanish-speaking subjects age ≥ 5 years at the time of visit, an age-specific Self Report PedsQL™ Brain Tumor Module will be administered to the subject at the time points below.

The appropriate PedsQL™ Brain Tumor Module will be administered at the cycle 1 day 1 visit (or at a screening visit), on the day 1 visit of cycles 2, 4, and 7, and at end of cycle 12 or end of study therapy visit, whichever occurs first.

The module should be selected based on the age of the subject at the time of module administration. (For example, if a child reaches her eighth birthday during study participation, the "Parent Report for Young Children" and "Young Child Report" should be administered at the appropriate visits before her 8th birthday, and the "Parent Report for Children" and "Child Report" should be administered at the appropriate visits on or after her 8th birthday.)

- Age ≥2 and <5 at the time of administration: Parent Report for Toddlers
- Age ≥5 and <8: Parent Report for Young Children **and** Young Child Report.
- Age ≥8 and <13: Parent Report for Children **and** Child Report
- Age ≥13: Parent Report for Teens **and** Teen Report.

9. STUDY CALENDAR

Baseline evaluations are to be conducted *within the 2 weeks prior to start of protocol therapy*. Scans and baseline ophthalmologic exam must be done *≤4 weeks prior to enrollment*. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All study assessments and medications should be administered within +/-3 days of the protocol-specified date, unless otherwise noted.

Tumor samples should be submitted to the biological correlates laboratory within one week of enrollment

Additional assessments may be required to monitor for AEs (see section 6.4) or as clinically indicated.

Table 9-1: Phase I Required Observations
See section 6.4 for toxicity monitoring observations

		Screening[1]	Cycle 1					Subsequent Cycles	End of Tx	30 day f/u
Day of cycle[16]		**-28 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**Within 14 days of last dose**	
Demographics[2]/informed consent		X								
Inclusion / exclusion criteria		X								
Tumor sample		X								
Medical history[3] / current medical conditions		X	X					X	X	
Prior antineoplastic therapy		X								
Height, weight		X	X					X	X	
Vital signs[4]		X	X		X			X	X	
Physical examination[5]		X	X		X			X	X	
Ophthalmologic examination[6]		X						X[6]	X[6]	X[6]
Pregnancy test (females of child-bearing potential only)[7]		X	X					X	X	
Lansky/Karnofsky performance status (appendix X)		X	X					X	X	
ECG[8 and table 9-2]		X	X		X	X	X	X (table 9-2)	X	
ECHO[9]		X						X[9]	X	
Blood[15]	Hematology[10]	X	X		X	X	X	X	X	
	Biochemistry [11, 12, 13]	X	X		X	X	X	X	X	

		Screening[1]	Cycle 1					Subsequent Cycles	End of Tx	30 day f/u
Day of cycle[16]		**-28 to -1**	**1**	**2**	**8**	**15**	**22**	**1**	**Within 14 days of last dose**	
	Coagulation profile (PT/PTT/INR)	X	X		X	X	X	X	X	
	Thyroid Function Tests[14]	X						X[14]	X	
Urinalysis		X	X		X	X	X	X		
Radiologic tumor response/assessment [17]		X						X[17]	X[17]	
Pharmacokinetics			Refer to Table 8-1 for detailed timeline							
Pharmacodynamic Studies /Biomarkers			Refer to Table 8-2 for detailed timeline							

[1] The screening examination should start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his or her participation. The investigator must not start any study related procedure before ICF is signed and dated by patient and/or parents (and impartial witness, if applicable) and investigator.

[2] Demographic data includes age, sex, ethnicity and race as well as other background or relevant medical history. Additionally, cancer characteristics; diagnosis, history, extent of cancer, prior anticancer treatments including surgery, radiotherapy, adjuvant and/or first-line metastatic immunotherapy, date of progression prior to study entry will also be collected.

[3] Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions. Significant new findings that begin or worsen after informed consent must be recorded.

[4] Vital signs (heart rate, blood pressure (see appendix XI) and temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection.

[5] A full physical examination (PE) that evaluates all major organ systems will be performed at baseline. This should include a complete ophthalmologic and dermatologic exam. Subsequent PEs should be focused on sites of disease, clinical signs and symptoms, and include eye and skin exams.

[6] Ophthalmologic examination will be performed prior to initiation of therapy and at day 28 (+/- 1 week), and approximately every 8 weeks thereafter unless symptomatic or new abnormalities identified (see section 6.4). Patients completing all 12 cycles will have a 30 day follow-up examination while patients ending early will have an examination within 14 days of their last dose. Examination will include visual acuity testing and indirect fundoscopy with attention to retinal abnormalities, especially RPED-like events and RVO. Slit lamp examination, visual field testing, intraocular pressure (IOP) measurement and ocular coherence tomography should be performed if feasible. Age appropriate methods of evaluation are permitted. For patients with clinical suspicion of retinal abnormalities (i.e. photopsia, metamorphopsia, impairment of visual acuity, etc.) or RVO, additional assessments of fluorescein angiography and/or optical coherence tomography (OCT) and electroretinogram (ERG) are mandatory. Images of OCT and fluorescein angiography should be sent to the investigative site along with the results of the exam and maintained in the patient's source documentation file. Ophthalmologic examination must be performed by a pediatric ophthalmologist for all patients <12 years old.

[7] To ensure patient safety, each pregnancy in a patient on study drug must be reported to Array BioPharma and the IRB within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

[8] A standard 12-lead ECG will be performed after the patient has been resting for 5-10 min. On cycle 1 day 1 (pre-dose) the ECG will provide a baseline value for each patient. If an abnormal ECG is obtained at any time, patient's electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities. Each ECG tracing should be labeled with the patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities at screening should be recorded.

[9] ECHO will be performed to determine cardiac ejection fraction at 4 and 8 weeks after initiation of therapy and every 12 weeks thereafter.

[10] Complete blood count (CBC) with differential - white blood count (WBC), absolute neutrophil count, lymphocyte, hemoglobin, hematocrit, and platelet count.

[11] Sodium, potassium, chloride, bicarbonate, urea or BUN, creatinine, glucose, AST (SGOT), ALT (SGPT), total bilirubin (if abnormal, then direct and indirect bilirubin should be measured), LDH, albumin, calcium, magnesium, phosphate, alkaline phosphatase, and CK.

[12] CK and troponin will be performed at the same time points as the hematology collections as outlined above. Follow up for total creatine kinase (CK) ≥3 X ULN will include weekly assessment of isoenzymes and myoglobin in blood/or urine, and troponin as applicable.

[13] Bilirubin can be reported as direct and indirect, the sum of which will be counted as total. If only total bilirubin is reported to be within normal limits, reporting of direct and indirect fractions is not necessary.

[14] TSH level is recommended. If TSH abnormal, free T4 may be performed. For patients with known central hypothyroidism receiving thyroid supplementation, free T4 may be substituted for TSH level. Additional endocrinologic testing should be performed as clinically indicated

[15] Laboratory tests will be collected and analyzed as per institutional standards. Examinations may be performed more frequently at the investigator's discretion if medically indicated; results should be recorded. At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded.

[16] For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays if not explicitly specified otherwise. Laboratory assessments that were completed within 72 hours of Cycle 1, Day 1 (C1D1) do not need to be repeated.

[17] Imaging to assess response will be obtained on day 1 of the following cycles (+/- 1 week for cycle 2, +/- 2 weeks thereafter): cycle 2, cycle 4, cycle 7, and cycle 10, and within 28 days following completion of study treatment. Recommended follow-up for patients that complete therapy, including medical evaluation and MRI, will occur approximately every 3 months (can be more or less frequent) for the first year and then approximately yearly until progression or change of therapy.

Table 9-2: Phase I ECG Assessments

Scheduled time points (hours)		
Screening		Anytime during the screening period
Cycle	Day	Sampling time
1	1	pre-dose
1	1	2h post-dose (± 1hr)
1	1	4h post-dose (± 1hr)
1	8	pre-dose
1	15	pre-dose
1	15	2h post-dose (± 1hr)
1	22	pre-dose
1	22	2h post-dose (± 1hr)
1	22	4h post-dose (± 1hr)
2	1	pre-dose
2	15	Anytime during visit
C3-6	1	Anytime during visit
End of Tx		Within 14 days of last dose
Other		As clinically indicated

Table 9-3: Phase II Required Observations

See section 6.4 for toxicity monitoring observations

		Screening [1]	Cycle 1			Subsequent Cycles (Through end of cycle 12; see Table 9-4 for participants receiving continuation therapy)	End of Treatment (see Table 9-4 for participants receiving continuation therapy)	Disease Progression f/u
Day of cycle[14, 15]		**-28 to -1**	**1**	**2**	**15**	**1**	**Within 14 days of last dose, unless otherwise noted**	
Demographics[2]/informed consent		X						
Inclusion / exclusion criteria		X						
Tumor sample		X						
Medical history[3] / current medical conditions		X	X			X	X	X
Prior antineoplastic therapy		X						
Height, weight		X	X			X	X	
Vital signs[4]		X	X			X	X	
Physical examination[5]		X	X			X	X	
Ophthalmologic examination[6]		X				X[6]	X[6]	
Pregnancy test (females of child-bearing potential only)[7]		X	X			X	X	
Lansky/Karnofsky performance status (appendix X)		X	X			X	X	
ECHO and EKG[8,9]		X				X[9]	X	
Blood[12]	Hematology[10]	X	X		X	X	X	
	Biochemistry [11]	X	X		X	X	X	
Urinalysis		X	X		X	X		
Radiologic tumor response/assessment [13]		X				X[13]	X[13]	X
Pharmacokinetics			Refer to Table 8-1 for detailed timeline					
Pharmacodynamic Studies /Biomarkers			Refer to Table 8-2 for detailed timeline					
PedsQL Brain Tumor Module [16]		X	Refer to Section 8.4				X	

[1] The screening examination should start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his or her participation. The investigator must not start any study related procedure before ICF is signed and dated by patient and/or parents (and impartial witness, if applicable) and investigator.

[2] Demographic data includes age, sex, ethnicity and race as well as other background or relevant medical history. Additionally, cancer characteristics; diagnosis, history, extent of cancer, prior anticancer treatments including surgery, radiotherapy, adjuvant and/or first-line metastatic immunotherapy, date of progression prior to study entry will also be collected.

[3] Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions. Significant new findings that begin or worsen after informed consent must be recorded.

[4] Vital signs (heart rate, blood pressure (see appendix XI) and temperature) will be obtained in the same position, either sitting or supine, as appropriate prior to any blood collection.

[5] A full physical examination (PE) that evaluates all major organ systems will be performed at baseline. This should include a complete ophthalmologic, neurologic and dermatologic exam. Subsequent PEs should be focused on sites of disease, clinical signs and symptoms, and include neurologic, eye and skin exams.

[6] Ophthalmologic examination will be performed prior to initiation of therapy and at the end of cycle 1 (+/- 1 week), on day 1 of cycle 4 (+/- 2 weeks), and approximately every 12 weeks thereafter unless symptomatic or new abnormalities identified (see section 6.4). Patients completing all 12 cycles and discontinuing therapy will have a follow-up examination within 30 days of cycle 12 day 28, while patients ending early will have an examination within 14 days of their last dose. For patients continuing past 12 cycles see Table 9-4. See section 8.3 for details of the ophthalmologic evaluation.

[7] To ensure patient safety, each pregnancy in a patient on study drug must be reported to Array BioPharma and the IRB within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

[8] A standard 12-lead ECG will be performed at baseline and at the end of cycles 1, 3, 6 and 12, and/or within 30 days of discontinuing study treatment. If an abnormal ECG is obtained at any time, patient's electrolytes must be reviewed and repeat ECG measurements must be done after correction of electrolyte abnormalities. Each ECG tracing should be labeled with the patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities should be recorded.

[9] ECHO will be performed to determine cardiac ejection fraction at baseline and at the end (+/- 7 days) of cycles 1, 3, 6, 9 and 12, and/or within 30 days of discontinuing study treatment.

[10] Complete blood count (CBC) with differential - white blood count (WBC), absolute neutrophil count, lymphocyte, hemoglobin, hematocrit, and platelet count.

[11] Sodium, potassium, chloride, bicarbonate, urea or BUN, creatinine, glucose, AST (SGOT), ALT (SGPT), total bilirubin (if abnormal, then direct and indirect bilirubin should be measured), LDH, albumin, calcium, magnesium, phosphate, alkaline phosphatase, and CK. See section 6.4 for follow-up evaluation if CK $\geq$ 3X ULN.

[12] Laboratory tests will be collected and analyzed as per institutional standards. Examinations may be performed more frequently at the investigator's discretion if medically indicated; results should be recorded. At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded.

[13] Imaging to assess response will be obtained on day 1 of the following cycles (+/- 1 week for cycle 2, +/- 2 weeks thereafter): cycle 2, cycle 4, cycle 7, and cycle 10, and within 30 days following completion of study treatment. Cycle 2 imaging assessment is optional. Recommended follow-up for patients that complete therapy, including medical evaluation and MRI, will occur approximately every 3 months (can be more or less frequent) for the first year and then approximately yearly until progression or change of therapy.

[14] For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays if not explicitly specified otherwise. Laboratory assessments that were completed within 72 hours of Cycle 1, Day 1 (C1D1) do not need to be repeated.

[15] For patients enrolled on the target validation stratum, all screening evaluations should be repeated prior to beginning post-operative cycle 1. If eligibility criteria (excluding surgical time windows) are not met, postoperative cycle 1 day 1 should be delayed up to 30 days until all eligibility criteria are met.

[16] PedsQL brain tumor module will be administered at screening on day 1 of cycles 1, 2, 4, and 7each subsequent cycle, and at the end of cycle 12 or aton the off therapy visit (whichever occurs first). See section 8.4.

Table 9-4: Year 2 (Cycles 13-24) Required Observations

	Cycle 13	**Cycle 16**	**Cycle 19**	**Cycle 22**	**End of Treatment See Table 9-3 or Table 9-1**
Day 1 of cycle (+/- 2 weeks)	**1**	**1**	**1**	**1**	
Medical history / current medical conditions	X	X	X	X	
Height, weight	X	X	X	X	
Vital signs	X	X	X	X	
Physical examination	X	X	X	X	
Ophthalmologic examination (section 8.3)	X		X		
Pregnancy test (females of child-bearing potential only)	X	X	X	X	
Lansky/Karnofsky performance status (appendix X)	X	X	X	X	
ECHO	X	X	X	X	
CBC, differential, platelets	X	X	X	X	
BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, AST, ALT, bilirubin, CK	X	X	X	X	
Urinalysis	X	X	X	X	
Radiologic tumor response/assessment	X	X	X	X	

10. IMAGING PARAMETERS AND RESPONSE CRITERIA

10.1 General Considerations

The overall response assessment takes into account response in the target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

For this study, comparison of maximal 2-dimensional measurements, TxW (product of the longest diameter [width (W)] and its longest perpendicular diameter [transverse (T)] will be used for Response Criteria for Target Lesions.

Imaging: Standard MRI evaluation is required for disease evaluation as per institutional imaging parameters. Both 1.5T and 3.0 T magnets are acceptable.

Additional Imaging Studies: MR diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE), and T1 permeability perfusion MRI, and MR spectroscopy (MRS) are recommended as part of standard of care at each evaluation period. The data obtained from these studies will be correlated with patient response and outcome in an exploratory analysis.

10.2 Measurement of Effect

Methods for Evaluation of Measurable Disease: Whole Brain MRI With and Without Contrast. For target tumors outside the brain, clinically appropriate imaging modalities may be added or substituted.

The following sequences incorporate the standard CNS imaging protocol. Institutional brain tumor or solid tumor imaging protocols can be substituted as long as similar disease evaluation is possible.

10.3 Imaging Sequences

Imaging Sequences 1.5 T								
Sequence	**Slice Thickness**	**TR (ms)**	**TE (ms)**	**TI (ms)**	**Directions**	**B_0**	**FOV (cm)**	**Matrix**
Sagittal T1	5 mm skip 1	400	9				22	256 x 256
Axial FSE T2	2 mm skip 0	3800	102				20	256 x 256
Axial T2 FLAIR	4 mm skip 0	10000	160	2200			20	256 x 224
Axial diffusion	2.5 mm skip 0				12-30	1000	26	128 x 128 single shot
Sagittal T2	3 mm skip 1	3800	102				22	256 x 256
Axial MPGR	4 mm skip 0							

Axial T1	4 mm skip 0	500	min				20	320 x 224
Axial T1 with contrast	4 mm skip 0	500	min				20	320 x 224
Sagittal T1 FSPGR with contrast	1.5 mm skip 0		min, flip angle 15				24	256 x 256
T1 permeability perfusion sequence	5 mm skip 0 (See below)							
Single-voxel MR Spectroscopy PRESS	Volume: 15x15x15 mm^3	1500 ms	35ms					

Imaging Sequences 3.0 T				
Sequence	**Slice Thickness**	**TR (ms)**	**TE (ms)**	**Directions**
Sagittal T1 MPRAGE	1.0 mm skip 0	2530		
Sagittal T2	3.0 mm skip 1.0 mm			
Axial T2	2.5 mm no skip	11730	91	
Axial T2 FLAIR	4 mm, no skip	9000	137	
Axial diffusion	2 skip 0	9100	88	30
Sagittal MPRAGE	1.0 mm no skip			
Axial T1 post contrast	4.0 mm skip 0	650	9.7	
Axial SWI	1.25 mm no skip			
T1 permeability perfusion sequence	5 mm skip 0 (See Below)			
Single-voxel MR Spectroscopy PRESS	Volume: 15x15x15 mm^3	2000 ms	35ms	

T1 Permeability Imaging

T1 permeability should begin with a set of T1 maps with flip angles of 2, 5, 10, and 15 followed by the T1 permeability sequence. After the T1 map sequence with 15-degree flip angle, start the T1 permeability series and 20 seconds into it inject 0.1 mmol/kg of intravenous contrast. See below.

3D T1W Specifications for T_1 Maps and Dynamic Series	
Sequence type	Spoiled gradient echo
Imaging mode	3D
Slice orientation	Axial
Frequency direction	A/P
Phase direction	R/L
FOV - frequency	220 mm

FOV - phase	220 mm
Matrix - frequency	256
Matrix - phase	160-192
In-plane resolution	≤ 1 mm
Fat-suppression	No Fat Sat
TR	~4 msec
TE	Less than 2 msec or min full
TI (STIR sequence)	N/A
Flip Angle	DCE -15 degrees; T1 maps - 2, 5, 10 and 15
Slice thickness (acquired, not interpolated)	5mm, maximum 6mm
Number of slices	Minimum 10 prior to zero fill
Slice Gap	No gap
Parallel imaging factor	≤ 2
Number of averages	1 for DCE, 2 for T1 maps
k-space ordering	standard, non-centric
Temporal Resolution of "T1 DCE": (seconds per phase/measurement)	≤ 6 seconds
"T1 DCE" imaging duration	≥ 5 minutes

T1 Maps / DCE			
Series Name	**Sequence**	**Flip Angle**	**Notes**
T1 map15	3D fast GRE	15 degrees	Axial, 2 NEX
T1 map10	3D fast GRE	10 degrees	Axial, 2 NEX
T1 map05	3D fast GRE	5 degrees	Axial, 2 NEX
T1 map02	3D fast GRE	2 degrees	Axial, 2 NEX
T1 DCE	Dynamic Series, 3D fast GRE	15 degrees	Axial, 1 NEX, inject 20 sec into this

10.4 Response Assessment

The overall response assessment takes into account response in the target lesion(s), and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Table 10-1: Response Criteria for Target Lesions

Target Lesion(s)	New Lesions*	Overall Response
CR	No	CR
PR	No	PR
MR (phase II only)	No	MR
SD	No	SD
PD	Yes or No	PD
Any	Yes	PD

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Evaluation of Target Lesions

- **Complete Response (CR):** The disappearance of all abnormal signal
- **Partial Response (PR):** x≥50% decrease in the sum of the products of the two perpendicular diameters of the target lesion(s), taking as reference the initial baseline measurements.
- **Minor Response (MR) Phase II only:** ≥25% and <50% decrease in the sum of the products of the two perpendicular diameters of the target lesion(s), taking as reference the initial baseline measurements.
- **Stable Disease (SD):** Neither sufficient decrease in the products of the two perpendicular diameters of the target lesion(s) to qualify for PR or minor response, taking as reference the initial baseline measurements, nor sufficient increase in the target lesion(s) to qualify for PD, taking as reference the smallest disease measurement since the treatment started.
- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the two largest perpendicular diameters of the target lesion(s), taking as reference the smallest product observed since the start of treatment; or the appearance of one or more new lesions; or (for the phase II study only) new clinical symptoms that are clearly related to disease progression. For progressive disease by clinical criteria, confirmatory imaging studies should be obtained when feasible.
- **Unevaluable (UN):** Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

  Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is

available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free and Overall Survival: Progression-Free Survival (PFS) is defined as the duration of time from patient enrollment to time of objective disease progression or death from any cause.x

Overall Survival (OS): Overall survival is defined as the duration of time from patient enrollment to time of death from any cause.

10.6 Central Review

All responses will be reviewed at the end of the trial. Optional imaging studies will also be reviewed at the end of the trial. Images should be loaded onto CDs and forwarded to the data-imaging center at:

Children's Hospital Los Angeles
c/o Jasmine Pauly
Clinical Trials Office
4650 Sunset Boulevard, MS#54
Los Angeles, CA 90027

All images (DICOM) should be saved on a CD and mailed to Children's Hospital Los Angeles. Data must be anonymized and the appropriate study identifier must be added. Studies will be stored in an anonymized form on the secure hospital PACS system research site. For diffusion images, raw images and ADC maps should be sent. T1 permeability T1 maps and sequence should be sent. For MR spectroscopy, the raw data should be sent. Also, the position of the region of interest (ROI) used for the MRS acquisition should be documented. At the end of the study, images will be evaluated by central review including assessments of standard MR imaging parameters such as tumor signal intensity, absence or presence of blood products, size of tumor, and size of enhancement. Assessment of tumor cellularity will be done by diffusion imaging analyses of the tumor assessing ADC (both 2D and 3D), fractional anisotropy values, and involvement of key white matter tracts. Perfusion analyses will assess cerebral blood volume and permeability coefficient (ktrans) within the tumor. MRS data will be analyzed at CHLA using LCModel software. Association between imaging parameters and outcome will be assessed.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.
The severity rating of an AE refers to its intensity. The severity of each AE will be determined by the Investigator using the NCI CTCAE. For any term that is not specifically listed in the CTCAE scale, intensity should be assigned a Grade of 1 through 5 using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Fatal

Expectedness: Adverse events can be “Expected” or “Unexpected.” An assessment of causal relationship of study drug to each AE must be performed by the Investigator. Medical judgment should be used to determine the cause of the AE, considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication and de-challenge or re-challenge

Expected adverse event: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator’s Brochure, the package insert or is included in the informed consent document as a potential risk.

Unexpected adverse event: For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator’s Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

Attribution: Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

Definite – The AE is clearly related to the study treatment.

Probable – The AE is likely related to the study treatment.

Possible – The AE may be related to the study treatment.

Unlikely - The AE is doubtfully related to the study treatment.

Unrelated - The AE is clearly NOT related to the study treatment.

11.2 Serious Adverse Event (SAE)

An AE is considered "serious" if it results in any of the following outcomes:

- Results in Death: Death is an outcome of an SAE and not an SAE in itself. Death should only be reported as an SAE term when no additional information is known about a fatal event. When death is an outcome, the event(s) resulting in death should be reported (e.g., "pulmonary embolism" with a fatal outcome) and assigned severity Grade 5.
- Is immediately life-threatening (its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalization includes any hospital admission, even if for less than 24 hours. The following do not meet hospitalization serious criteria:
    - A visit to the emergency room, or outpatient observation that does not result in admission
    - Elective surgery, planned prior to signing consent
    - Routine health assessment requiring admission
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Based upon appropriate medical judgment, represents an important medical event that may jeopardize the patient or may require intervention to prevent one of the outcomes described above.

11.3 Procedures for AE and SAE Recording and Reporting

All SAEs occurring in patients from the first dose of Array study drug until 30 days after the last dose of study drug must be reported to Array BioPharma Inc. within 24 hours of the Investigator's knowledge by faxing a completed SAE form to Array BioPharma Inc. at the number provided on the SAE form or fax cover sheet. SAEs occurring greater than 30 days after the last dose of Array study drug should be reported to Array BioPharma Inc. only if considered related to the Array product.

If new information becomes available for a previously reported SAE, a follow-up SAE report should be sent within 24 hours. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported by the Sponsor and/or designee to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.
Reporting: Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time-points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Version 4.03 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.03 of the CTCAE is identified and located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE. Monitoring will occur before the clinical phase of the protocol begins and continue during protocol performance and completion.

Each participating investigator is required to abide by the reporting requirements set by CHLA. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the CHLA Study Chair on the local

institutional SAE form. This includes events in the table below. Investigators at CHLA will report SAEs directly to the CHLA IRB. Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the CHLA Study Chair within the timeframes detailed in the table below.

Table 11-1 Reportable AEs

	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days	5 calendar days	24 hours*
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

The CHLA Study Chair will submit SAE reports from outside institutions to the CHLA IRB according to CHLA IRB policies and procedures in reporting adverse events.

Report serious adverse events by telephone, email, or facsimile to:

Nathan J. Robison, MD
Tel (323) 361-8147
nrobison@chla.usc.edu
Fax (323) 361-7128

Within the following 48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the CHLA Study Chair on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB)

Investigators at CHLA will report all serious adverse events directly to the CHLA IRB.

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Nathan J. Robison, MD
Tel (323) 361-8147
nrobison@chla.usc.edu
Fax (323) 361-7128

The CHLA Principal Investigator will submit SAE reports from outside institutions to the CHLA IRB according to CHLA IRB policies and procedures in reporting adverse events.

Reporting to the Food and Drug Administration (FDA)
The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA. Events will be reported to the FDA by mail using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

Reporting to Study Investigators
All multicenter site investigators will be notified in a timely fashion of any SAE reported to the FDA. In most cases this will be no later than 24 hours after communication with the FDA.

Reporting to Hospital Risk Management
Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

Pregnancy or Drug Exposure during Pregnancy
Pregnancies (both those of female patients and female partners of male patients) must be reported to Array BioPharma Inc. or designee within 24 hours of the Investigator's knowledge. All pregnancies should be followed through to outcome and the outcome must be reported to Array BioPharma Inc. Pregnancies themselves are not considered AEs or SAEs. However, any AEs or SAEs occurring during pregnancy are to be reported following AE and SAE reporting guidelines.

Monitoring of Adverse Events and Period of Observation
All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-

up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the CHLA Study Chair and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

The CHLA Clinical Trials Office (CTO) will collect, manage, and monitor data for this study.

12.2 Data Submission

The schedule for completion and submission of case report forms is as follows:

Table 12-1: Data Submission Timelines

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 days of registration
Baseline Assessment Forms	Within 14 days of registration
Treatment Forms	Within 10 days of the last day of the cycle
Adverse Event Report Forms	Within 10 days of the last day of the cycle
DLT reporting	**Within 48 hours of the event**
Response Assessment Forms	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Forms	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Forms	Within 14 days of the protocol defined follow up visit date or call

All study data will be submitted via electronic data capture forms using the DataLabs Website. Please refer to the DataLabs user manual or contact the CHLA Operations Center if you need assistance.

12.3 Weekly Safety Review

The CHLA Study Operations Center conducts weekly (as needed) patient safety and review meetings with the protocol chair, research coordinators and other administrative team members to review all data submitted, non-serious adverse events and other correspondence pertaining to patients. Serious adverse events will be immediately evaluated by the study team and determination regarding notification of participating site will be made. All serious events will be sent to the CHLA IRB and DSMC if required. Any interim results that would affect patient safety would be immediately communicated to all participating sites. All correspondence with sites will be done via email.

12.4 Data Safety Monitoring Committee

An independent four member Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists who have no direct relationship with the study. Standing meetings will occur every 6 months. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. After DSMC review, the DSMC will issue a confidential report to the study PI and the CHLA operations center.

No more than 8 weeks after the DSMC meeting, a DSMC public review report will be created after approval of the confidential report and resolution of any issues by the PI. The public report will then be emailed to the participating sites for each study. These can be filed at the IRB at each site, in accordance with local IRB guidelines and requirements.

12.5 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the CHLA Study Chair (or Protocol Chair) or CHLA. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements.

Tom-Belle Davidson, MD, will the Medical Monitor for this study. She is a qualified physician and is not associated with this particular protocol. She will work closely with the Principal Investigator to monitor the participants' treatment while on this study.

For research determined to be greater than minimal risk, DODI 3216.02 requires **that the IRB approve, by name, an independent medical monitor with expertise consonant with the nature of risk(s) identified within the research protocol**. The IRB must approve a written summary of the research/medical monitors' duties, authorities, and responsibilities. The medical monitor's duties should be based on specific risks or concerns about the research. The medical monitor may perform oversight functions and report their observations and findings to the IRB or a designated official. The medical monitor may be identified from within or outside the PI's institution.

Medical monitor functions may include:

- observing recruitment and enrollment procedures and the consent process for individuals, groups or units,
- overseeing study interventions and interactions,
- reviewing monitoring plans and UPIRTSO reports;
- overseeing data matching, data collection, and analysis

There may be more than one medical monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.

At a minimum, the medical monitor:

- may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report;
- shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

In addition, on this study, the medical monitor is specifically required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed, and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The CHLA Study Chair (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- State laws
- CHLA research policies and procedures
- It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies. Study-related documents will be stored in a secured location accessible only to the investigators and formally designated study personnel.

13.6 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of Children's Hospital Los Angeles (CHLA).

The CHLA Study Chair/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs.

Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

Except in very unusual circumstances, each participating institution will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14. STATISTICAL CONSIDERATIONS

14.1 Primary Endpoints

The primary endpoint for the Phase I portion of the study is dose limiting toxicity during the first course of therapy, as defined in section 6.4.

The primary endpoint for the Phase II portion of the study is best overall response (BOR) during the first 12 cycles (nominally 48 weeks) of treatment. BOR will be assessed through the time of the post-12th cycle tumor assessment, or through the last tumor assessment time during this nominal period for patients in follow-up but who have withdrawn from protocol therapy, or through the last available tumor assessment for patients who are lost to follow-up during this time. The percent change in tumor sizes compared to baseline will be recorded at each evaluation time and will be used to define the categorical BOR as described below, per the definition of CR, PR, MR, SD, and PD in section 10.4.

- For tumors that regress compared to baseline during the assessment period without first satisfying the criteria for progressive disease (PD), BOR will be defined at the nadir of the tumor size compared to baseline provided that the percent reduction at the nadir satisfies the definition of CR, PR, or MR per section 10.4, with the BOR value of CR, PR, or MR determined by the percent reduction at this time. The associated time of BOR will also be recorded.
- For tumors that progress compared to baseline and satisfy the definition of PD without first satisfying the criterion at least for minor response (MR), BOR will be defined at the first time at which the percent increase in tumor size compared to baseline satisfies the criterion for PD. The BOR value will be PD. The associated time of BOR will also be recorded.
- For tumors that neither regress sufficient to satisfy the criterion for MR nor progress sufficiently to satisfy the criterion for PD during the assessment period, the BOR value will be SD. The time associated with BOR will be the last evaluation time during the 48 week evaluation period.

Patients will be considered evaluable for BOR if they have received at least one dose of treatment and have at least one post baseline tumor assessment.

14.2 Secondary Endpoints

Secondary endpoints for Phase I include the grade and duration of CTCAE toxicities observed during treatment.
The concentration of MEK162 and its metabolite (AR00426032) in blood drawn at specified time-points (Table 8-1).

Secondary endpoints for Phase II include:

- Duration and grade of CTCAE toxicities observed during treatment

- Time to event, defined as the time from start of treatment to the first occurrence of tumor recurrence, tumor progression, occurrence of a second malignancy, or death from any cause. Patients event-free at last follow-up will be censored in analysis.
- Time to tumor recurrence/progression, defined as the time from start of treatment to the first occurrence of tumor recurrence, tumor progression, or death from disease. Patients without tumor recurrence at last follow-up, or who experience a second malignancy, or who die for causes unequivocally unrelated to tumor recurrence, will be censored in analysis.
- The concentration of investigational compound in tumor tissue after treatment with MEK162.
- Immunohistochemical assessment of PD effects on Ras/Raf/MEK/ERK pathway inhibition within tumor tissue (Strata 4 only) as measured by ERK phosphorylation before and after treatment with MEK162 for 7-14 days. Blood pharmacodynamic assessment will also be performed and correlated with tumor results.

14.3 Study Design for Phase I

Dose levels and starting dose are described in section 6.2. Patients will be enrolled according to a 3+3 dose escalation design. In brief, three patients will initially be enrolled and treated at starting dose level 1. If no DLTs are observed, dose will be escalated to dose level 2. If 1 DLT is observed, three additional patient will be enrolled to dose level 1. If at most 1 DLT is observed in six patients during course 1 of treatment then the dose will be escalated to dose level 2. If 2 or more DLTs are observed at a dose level, then the dose will be de-escalated. The MTD will be the maximum dose at which 6 patients have been treated and no more than 1 DLT has been observed. Refer to Appendix XV for a detailed description of the escalation rules.

To be considered DLT-evaluable, a patient must either have experienced an adverse event meeting DLT criteria during the first cycle of treatment, or have received at least 85% of doses in the first cycle. Only DLT-evaluable patients will be considered for dose escalation determinations.

14.4 Study Design for Phase II and Target Validation

For Strata 1 through 3, the Phase II study is viewed as three distinct Phase II studies, one corresponding to each of the three strata described in section 1. Each will be a single cohort study using best overall response (BOR – section 14.1) as the primary endpoint. While the primary analysis will be in the intent-to-treat (ITT) cohort – i.e., including all patients who are BOR evaluable per section 14.1, target accrual will be in terms of BOR -evaluable patients with **sufficient treatment (BORwST)**, defined as receiving at least 12 weeks of treatment or experiencing disease progression or death prior to 12 weeks. For the Target Validation Stratum 4, tumor resection prohibits evaluation of BOR as described above, so that analysis tumor response in this stratum will be descriptive.

Each of Stratum 1 and Stratum 2, target minimum accrual is 20 eligible BORwST patients, with up to 30 eligible patients allowed to ensure that at least 20 BORwST are accrued. Accrual to strata 1 and 2

will be halted once it is reasonably certain that this 20-patient target will be achieved. In the unlikely case that minimum of 20 BORwST patients is not reached, the study committee will consider whether an amendment to increase accrual is warranted. The accrual rate to Stratum 1 and Stratum 2 is estimated at approximately 1 per month.

For Stratum 3, target minimum accrual is also 20 eligible BORwST patients, with up to 30 eligible patients allowed. Accrual to this stratum will be halted once it is reasonably certain that the target of 20 BORwST patients will be achieved, or once both stratum 1 and stratum 2 have met accrual goals, whichever occurs first.

For Target Validation Stratum 4, accrual will be halted once it is reasonably certain that 20 patients are enrolled with pre- and post-treatment tumor specimens, or once both Stratum 1 and Stratum 2 have met accrual goals, whichever occurs first.

There will be no statistical monitoring rules for halting the study early either for lack of efficacy or futility.

The primary analyses in Strata 1 and 2 will include all patients who are evaluable for BOR per section 14. The primary method of analysis will be an exact one-sided, one-sample test of the proportion of patients who achieve BOR of at least minor response (MR). With Type I error no greater than 10% at a response rate of 0.05, with a minimum of 20 patients there will be at least 85% power to detect a BOR CR/PR/MR rate of 25%. Hence, in each of Strata 1 and 2 there is sufficient power to discriminate between an unacceptable BOR rate of ≤0.05 and an achievable and clinical relevant BOR rate of ≥0.25. Secondary analyses in these strata will include analysis of BOR in the BORwST cohort, as well as estimation of 12-month event-free survival (EFS) and recurrent/progression free survival (PFS) *via* the product limit estimator, and summarization of rates of toxicities in both the ITT and BORwST cohorts.

Analysis in Strata 3 and 4 (target validation) will be descriptive, in the former comprising estimation of the BOR rate, EFS, PFS, and in the latter comprising analysis of MED162 tumor concentration, ERK phosphorylation as an indicator of Ras/Raf/MEK/ERK pathway inhibition, and other related endpoints. Rates of toxicities will also be summaries for both strata.

14.5 Accrual Rate and Study Duration

The Phase I portion of the study will require a minimum 4 patients and at maximum 36 patients. The Phase I portion will require 12 to 18 months to complete.

Phase II portion of the study will require 20-30 months to complete at an expected accrual rate of 1 per month in each of strata 1 and 2.

14.6 Toxicity Monitoring during Phase II

A minimum of 40 and possibly as many as 90 patients will be enrolled in strata 1, 2 and 3 combined during Phase II. Toxicity monitoring will continue during Phase II as described below, with patients in strata 1 through 3 combined in this analysis.

The primary endpoint for toxicity monitoring will be the occurrence of DLT during the first course of treatment. If the number of DLTs occurring in the first course of treatment equals or exceeds the number in the table below, the study will be suspended to accrual pending review of toxicities by the study committee, in consultation with the DSMC, to determine whether the study should continue as planned, be amended, or be terminated. This monitoring rule has at most 14% Type I error for true DLT rates of 15% or lower, which are considered acceptable, at least 80% power to detect DLT rates of 25% or more, and at least 95% power to detect DLT rates of 30% or more. The average numbers of patients that would be treated under these three scenarios are 75, 42, and 41 if the study were halted when the boundary was reached.

Table 14-1: Phase II DLT Monitoring Rule

# Patients Treated	# DLTs	# Patients Treated	# DLTs
1 – 5	-		
6 – 9	6	52 – 56	13
10 – 18	7	57 – 61	14
19 – 26	8	62 – 66	15
27 – 33	9	67 – 70	16
34 – 39	10	71 – 75	17
40 – 45	11	76 – 79	18
46 – 51	12	80	19

Toxicity monitoring for Stratum 4 will be independent of that for Strata 1 through 3. The primary endpoint will be DLT occurring any time pre-surgery through the end of the first course following surgery. The monitoring bounds describe in Table 14-1 will be used. If the number of DLTs equals or exceeds the number in the table, or if at least 5 patients have been treated on stratum 4 and the nominal rate of DLT exceeds that currently observed in strata 1 through 3 combined, the stratum will be suspended to accrual pending review of toxicities by the study committee, in consultation with the DSMC, to determine whether the stratum should continue as planned, be amended, or be terminated.

15. PUBLICATION PLAN

Timely publication will be the responsibility of the principal investigator. No data should be submitted for presentation at public meetings or in abstract form without approval of the principal investigator. Guidelines will follow the rules for publication for the University of Southern California and Children's Hospital Los Angeles.

The results should be made public within 24 months of the end of data collection, sooner if possible. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

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Appendix I: LIST OF MEDICATIONS WITH POSSIBLE CYP INTERACTIONS TO BE USED WITH CAUTION

CYP2C19 Inhibitors	CYP2C19 Inducers
cimetidine	efavirenz
esomeprazole	rifampin
felbamate	ritonavir
fluoxetine	St. John's Wort
fluvoxamine	
isoniazid	
ketoconazole	
lansoprazole	
omeprazole	
oral contraceptives	
pantoprazole	
ticlopidine	
voriconazole	
CYP1A2 Inhibitors	**CYP1A2 Inducers**
aminodarone *	carbamazepine
cimetidine	tobacco
efavirenz	rifampin
fluoroquinolones	char-grilled meats
fluvoxamine*	
ticlopidine	
CYP 2B6 Substrates	
artemisinin	
bupropion	
cyclophosphamide	
efavirenz	
ifosfamide	
ketamine	
meperidine	
methadone	
nevirapine	
propofol	
selegiline	

*Indicates strong/moderate inhibitor. Refer to the following website for a complete list: http://medicine.iupui.edu/clinpharm/ddis/clinical-table

Appendix II: MEK162 ADMINISTRATION

Dosing: The study drug will be administered based on body surface area and should be calculated approximately monthly.

Premedication: None required.

Route of Administration: MEK162 will be administered orally BID, as a suspension prepared by the on-site pharmacy (Appendix XVI), or as a tablet. Co-administration of both tablet and suspension is not permitted, but patients may switch from one form to the other at beginning of a cycle, or at the time of a dose-level change. Administration of suspension via nasogastric or gastrostomy tube is permitted. Prescribed doses should be taken twice daily, approximately 12 ± 2 hours apart.

If a patient vomits at any time after dosing, the dose of study drug should not be re-administered. Doses of study drug omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period.

Appendix III: MOLECULAR ANALYSIS

Due to the rapid development of techniques for protein, lipid and DNA/RNA analysis, newer approaches to those discussed below will be incorporated or substituted where appropriate. All samples should be shipped to Dr. Keith Ligon.

Keith Ligon, MD, PhD
C/O Sarah Becker
Dana-Farber Cancer Institute
450 Brookline Avenue JFB 215A
Boston, MA 02215
Dr. Ligon Telephone: (617) 632-2357
Sarah Becker: (617)632-6131
Fax: (617) 582-8760
Email: Keith_Ligon@dfci.harvard.edu
Email: pnotissuebanking@partners.org

Tissue Analysis: *Required Tissue Analysis:*

- **Oncopanel sequencing**
  - OncoPanel sequences ~500 genes known to be associated with cancer and includes the ability to detect selected translocations and copy number variation. This assay requires 10 formalin fixed paraffin embedded (FFPE) unstained slides with a minimum of 50% viable tumor nuclei and mean depth of coverage is 200X.
- **OncoScan copy array**
  - OncosScan copy arrays will be used to survey the DNA copy-number variations across the genome. This requires a minimum of 80ng of genomic DNA. Please send 10 unstained slides with at least 50% viable tumor, and more cellular areas are preferred.

Exploratory Tissue Analysis (if enough tissue available):

- Agilent Array CGH (substitute for Oncoscan if needed):
  Array CGH analysis will be performed using paraffin tissue. This array analysis will be directed by Dr. Keith Ligon from the Department of Neuropathology and will be performed at Brigham and Women's Hospital CAMD.
- OncoPanel:
  OncoPanel analysis will be conducted at the Brigham and Women's Hospital Center for Advanced Molecular Diagnostics using DNA derived from paraffin archival tissue. This unique technology allows rapid identification of known mutation within tumor suppressor genes, oncogenes and other major regulators of cellular proliferation.. Results from the OncoPanel may be returned to the patient's chart only if performed in a CLIA-certified lab; this information will be maintained with linkers to the database containing an abstraction of the patient's medical record and the database containing the results of the histopathologic analysis.

- Additional Sequencing:
  Sequencing, such as whole genome, whole exome, and RNA sequencing to form a more comprehensive view of the genomic changes in tumor tissue may be performed. If tissue is available for this testing such whole genome, whole exome, or RNA sequencing will be conducted at the Broad Institute, in the lab of Dr. Mimi Bandopadhayay.

- FISH Analysis:
  FISH analysis has become a routine method for the rapid evaluation of areas of chromosomal region gain or loss. This method uses standard paraffin sections and can be used to examine any chromosomal region that has been identified in the screens above.
- Methylation Array:
  Methylation array is a new technology that examines the regulation of gene expression at the chromosomal level rather than the DNA, RNA or protein level. Some pediatric tumors may result from the maintenance of gene expression that should have been silenced, or conversely as a result of the failure of an inhibitory gene product to be expressed at the correct time or location rather than by mutation. Methylation array survey the genome for regions that are differentially regulated compared to normal controls. This methodology for methylation analysis or just now becoming available and will be performed if tissue permits.
- RNA Analysis:
  The frozen tissue obtained will be processed using standard techniques for nucleic acid isolation. Total RNA will be processed for labeling and hybridization to the Affymetrix U133 Plus 2.0 array that contains probes for over 47,000 transcripts and variants including 38,500 well-characterized human genes. For limited amounts of starting material, less than 5 µg of RNA and less than 500 ng of DNA, an amplification step will precede labeling. As new chips become available, they may be substituted for those listed above.

Blood Analysis:

- **Genomic Blood**
  - Blood will be used as genomic normal control to compare to OncoPanel, whole exome, whole genome and gene expression arrays.
  - Peripheral blood serum will be used for exploratory analysis of proteins, lipids, and DNA/RNA

CSF Analysis

CSF Sample Preparation and Analysis:

- In order to assess the molecules in the CSF of patients with tumors, cell-free DNA analysis will be conducted at the Broad Institute.

Material from the Buffy coat will be used as controls for the molecular and genomic analyses including sequencing, whole exome, whole genome and gene expression arrays. Plasma will be used for exploratory analysis of proteins, lipids, and DNA/RNA.

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Appendix IV: SPECIMEN COLLECTION, PROCESSING AND STORAGE

Specimen collection and shipment

Patients enrolled on this study may provide specimens and/or clinical information. All specimens will be collected and processed according to site-specific banking procedures. All samples collected under this protocol/consent document will be tracked in the ODQ Neuro-Oncology database at Dana-Farber Cancer Institute.

It is mandatory to contact Jasmine Pauly and Sarah Becker prior to shipment to confirm proper materials are sent.

Tumor Tissue: Fresh Frozen Tumor Material

Collection: Tissue will be collected from any patient undergoing neurosurgical procedures as defined in this protocol with patient consent. One "green pea sized" specimen from previously banked snap frozen primary tumor material, regardless of time from surgery, should be rapidly transferred (without thawing) from long term frozen storage to a Styrofoam box filled with 7-10lbs of dry ice for shipment.

Shipment**:** Samples should be submitted in 1.5mL standard size Cryovials containing the tumor material and labeled according to table 8-2. Please ship in a Styrofoam box (minimum suggested internal dimensions of 30 cm x 30 cm x 30 cm) with 7-10lbs of dry ice. Please include all items on transmittal form including de-identified pathology report from current surgery and any prior surgeries, along with any additional molecular or genetic testing results previously generated. Ship to Dr. Keith Ligon's laboratory in Boston. .Follow instructions on transmittal form and confirm shipment with Sarah Becker and Jasmine Pauly.

Tumor Tissue: FFPE

Collection: The "best block" should be identified for advanced studies by the local pathologist. The block must contain viable tumor with greater than 50% tumor nuclei, less than 30% necrosis, and the tissue fragment size in total ~0.5cm in diameter. The block should contain sufficient tissue to provide 40 standard 5 micron FFPE slides for the planned advanced studies. If you are unable to send a block, please send 20-40 unstained slides and 1 H&E.

Shipment: Slides and blocks should be sent at room temperature in secure slide or block containers in a padded envelope. Please label according to table 8-2. Please include all items on transmittal form including de-identified pathology report from current surgery and any prior surgeries, along with any additional molecular or genetic testing results previously generated. Ship to Dr. Keith Ligon's laboratory in Boston. Follow instructions on transmittal form and confirm shipment with Sarah Becker and Jasmine Pauly.

Blood

Pharmacokinetic Blood

Collection: 2ml of blood collected in EDTA as indicated in Table 8-1. The tubes will be kept in an ice water bath after blood collection. Within 30 minutes, the tubes will be centrifuged between 3°C and 5°C for 10 minutes at approximately 1500g. Immediately after centrifugation, transfer at least 0.5ml of plasma into a 2ml polypropylene screw-cap tube. Place the tube in a freezer ≤-70°C until shipment.

Shipment: Samples should be submitted in 2ml polypropylene screw-cap tubes as per Section 8.0. Please ship in a Styrofoam box with 7-10lbs of dry ice to QPS Sample Coordination in Delaware, following the instructions on the transmittal form.

Biomarker Blood

Collection: 10ml of blood collected in Cell-Free DNA BCT Streck tube as indicated in Table 8-2 and processed per Section 8.0.

Shipment: Samples should be submitted in 10mL BCT Streck tubes labeled as per table 8-2. Store at room temperature up to 72 hours before shipping. Ship in a padded envelope or other secure packaging at room temperature within 72 hours of collection to Dr. Keith Ligon's laboratory in Boston. Follow instructions on transmittal form and confirm shipment with Sarah Becker and Jasmine Pauly.

Pharmacodynamic Blood

Collection: 6ml of blood collected in EDTA at time-points as indicated in Table 8-2. Whole blood must be aliquoted into as many 1.5mL standard cryovials (~1mL per tube) as needed. Blood should not be processed further and placed in a freezer -80°C until shipment.

Shipment: Samples should be submitted in 1.5mL standard cryovials labeled as per table 8-2. Samples should be shipped in a Styrofoam box with 7-10lbs of dry ice to Dr. Keith Ligon's laboratory in Boston. Follow instructions on transmittal form and confirm shipment with Sarah Becker and Jasmine Pauly.

CSF

Collection: CSF can be collected per institutional standards in a sterile, screw top tube and then transferred to a 10mL Cell-Free DNA BCT Streck tube. Store at room temperature up to 72 hours and shipment.

Shipment: in secure package at room temperature to Dr. Keith Ligon’s laboratory in Boston. Follow instructions on transmittal form and confirm shipment with Sarah Becker and Jasmine Pauly. Ensure tubes are de-identified and labeled with protocol number, patient ID, and draw date. Make note of time at which CSF was collected.

Urine

Collection: in sterile collection cup adding 10-20% volume of Streck Cell-Free DNA Urine Preservative to sample (i.e. 3mL preservative to 30mL urine), Secure cap tightly and gently invert container 5 times to make sure it is well mixed. Transfer to 50 mL conical tube. Stor at room temperature up to 72 hours.

Shipment: in secure package at room temperature to Dr. Keith Ligon's laboratory in Boston. Follow instructions on transmittal form and confirm shipment with Sarah Becker and Jasmine Pauly. Ensure tubes are de-identified and labeled with protocol number, patient ID, and draw date. Make note of time at which urine was collected and at which preservative was added.

Blood sample volume

The maximum blood volume drawn for all research studies should be no more than 2mL/kg in any one 24-hour period, and 4mL/kg in any one 30-day period, unless otherwise specified by institutional guidelines. In small children for whom the required sample volume would exceed the maximum allowance, the volume of individual samples should be reduced. Questions regarding sample size reduction can be discussed on a case by case basis with the study chair.

Specimen processing, storage, and coding

All specimens will be processed according to site-specific banking procedures; exceptions are made for samples that are required to go directly to the researcher and/or laboratory for immediate processing. The amount of each of the following samples will be tracked in the ODQ Neuro-Oncology database at the Dana-Farber Cancer Institute or other in-house tracking system. All biological samples will be coded with an internal numbering system to ensure patient confidentiality. The samples will be stored and distributed to researchers with this numbering code as the only identifier.

Specimen that circumvent the tissue bank and go directly to the researcher or laboratory

Samples that are required to go directly to the researcher and/or laboratory for immediate processing can be collected and not be entered in the bank: i.e. blood and tissue that requires immediate processing beyond the scope of the bank, such as for the creation of cell lines, if it is codified. All samples, including those that go for immediate processing outside the bank, are to be logged into and out of the ODQ Neuro-Oncology database.

Specimen tracking of all samples collected and distributed under this protocol

All samples collected and distributed for the use of future research studies are to be tracked, and logged into and out of ODQ DFCI database**.** The database will be able to generate reports of what is available in storage, and provide a history of samples obtained and distributed.

If the formal tissue bank wishes to track samples using an internal tracking system with similar features, this will be noted with the description of the bank in Appendix XII. If this option is chosen by a facility, it should be noted that samples obtained using this protocol that are not logged into the bank's internal tracking system, for instance samples which circumvent the tissue bank are to be tracked

in this database. The internal tracking system must track not only what is in store, but provide a history of samples obtained and distributed. The ODQ Neuro-Oncology database also has the useful capability of allowing samples to be reserved, succeeding permission from the respective oversight committee.

Samples after a patient withdraws from the study

Should a participant or his/her legally authorized representative or his/her next of kin withdraw consent from the study, any unused tissue specimens will be removed from the tissue bank and will be discarded. Tissue, its derivatives, and results from samples previously obtained and distributed to third parties (outside of the respective main tissue bank) will not be recalled or destroyed.

Coding of samples given to investigators

All biological samples will be coded with a numbering system to ensure patient confidentiality.
The samples will be stored and distributed to researchers with this numbering code as the only identifier on the sample.

QPS (Pharmacokinetic Blood):

QPS Sample Coordination
3 Innovation Way
Suite 240
Newark, DE 19711

Dr Ligon's Laboratory (all other samples):

Keith Ligon C/O Sarah Becker
Dana-Farber Cancer Institute
450 Brookline Ave JFB215A
Boston, MA 02215

Appendix V: SPECIMEN AND DATA USE

Research uses of Tissue and Clinical Data

Any leftover tissue samples will be banked for future analyses that are not yet available.
Clinical data and tissue samples, independently and together, will be used for non-therapeutic research that advances the diagnosis, evaluation, etiology, prevention, and outcome improvement of nervous system diseases. Research on tissue samples may include detailed genetic and molecular analysis and cell line development. In general, these findings will be linked to clinical care and outcome to maximize research findings. Studies may include tumor biology studies, biomarker identification studies, drug target studies, genomics and proteomics studies, genetic susceptibility studies, drug development efforts, epidemiological studies, and outcomes studies.

Retrospective analysis on clinical data performed outside of prospective formal clinical trial data will be linked with outcomes to create research findings and provide preliminary data to support further investigations.

For a comprehensive list of research use of tissue and clinical data, see Appendix VI.

Commercial uses of Tissue and Clinical Data

Tissue samples collected and/or stored in the bank may be made available to commercial or corporate scientific collaborators only as part of a scientific collaboration. Derivative products from the participant tissues including cell lines, diagnostics tests, or other items may arise from study of these tissues. Participants will not have any ownership or financial benefit from their tissue samples and derivatives.

Uses which may affect determination of treatment (clinical care) and/or eligibility onto clinical trials

In rare circumstances, findings from tissue testing may be clinically relevant and affect treatment decisions. All testing results communicated back to the participant's treating clinician and/or placed into the participant's medical record must be CLIA compliant. If the testing is first done in a lab that does not meet these criteria, yet the results are felt to be clinically significant, the testing will be repeated in a CLIA environment prior to informing the participant's clinician and/or placement in the participant's medical record. The participant's treating clinician is responsible for treatment decisions including whether and how to inform the participant of any results.

Appendix VI: LIST OF RESEARCH USES OF TISSUE AND CLINICAL DATA

Drug development efforts may include, but are not limited to:

- evaluation of tumor cell sensitivity to experimental drugs
- evaluation of compounds for the ability to overcome tumor drug resistance

Biomarker studies may include, but are not limited to:

- identification of biomarkers that predict tumor sensitivity to drugs
- identification of early detection biomarkers
- identification of biomarkers that aid in tumor classification
- identification of methods to detect minimal residual disease

Tumor biology studies may include, but are not limited to:

- classification of tumors via a molecular taxonomy
- investigation of tumorigenesis mechanisms
- investigation of tumor invasion mechanisms
- investigation of apoptosis mechanisms
- investigation of signal transduction pathways
- investigation of cellular metabolic pathways
- investigation of tumor microenvironment
- investigation of tumor immunology
- phenotypic analysis
- analysis of tumor transformation from sequentially obtained samples
- study of drug sensitivity and resistance mechanisms

Genomics, epigenomics, and proteomics studies may include, but are not limited to:

- DNA and RNA sequencing
- analysis of gene expression profiles and protein products in normal and cancer samples
- analysis of genomic or protein polymorphisms in normal and cancer samples
- identification of cancer causing genetic aberrations
- identification of cancer causing proteins
- functional analysis of abnormal genes and proteins
- genome wide association studies
- analysis of germline mutations
- identification of somatic deletions, point mutations and amplifications
- Analysis of tumor transformation from sequentially obtained samples

Immune function studies may include, but are not limited to the following:

- phenotypic analysis of blood cells
- evaluation of functional responses to mitogens and specific antigens
- analysis of T cell repertoire
- assessment of thymic function and generation of new T cells
- phenotypic and functional assessment of regulatory T cells
- analysis of target antigens recognized by immune responses

Tumor microenvironment studies may include, but are not limited to the:

- analysis of cell populations in the tumor microenvironment including stem cells, and endothelial cells and normal hematopoietic cells

Epidemiological, genetic susceptibility and outcomes studies may include, but are not limited to:

- identification of genetic, behavioral or environmental factors that may modify the onset of cancer
- correlation of clinical prognostic factors with patient treatments and outcomes
- identification of genes that predict sensitivity to particular drugs
- identification of behavioral (e.g., exercise, diet) or environmental factors that influence treatment success

Laboratory experiments may be large or small in scale and may include but are not limited to the following techniques:

- generation of immortalized cell lines
- immunohistochemistry,
- in situ hybridization,
- DNA and RNA microarrays,
- DNA and RNA sequencing including oncomapping
- flow cytometry,
- high throughput mass-spectrometric based assay
- gene methylation analysis,
- whole genome copy number variation analysis,
- whole genome sequencing for mutation identification,

Outcomes under study may include but are not limited to:

- Survival
- Time to progression
- Rate of progression
- Time and probability to recurrence
- Quality of life
- Subjective side effects
- Laboratory findings
- Duration of hospitalization

Methodologies under study may include but are not limited to:

- Assessment of progression
- Radiology assessments
- Surgical methods
- Diagnosis via pathology
- Diagnosis via imaging,

Appendix VII: Pathology Testing Information

Clinically Relevant Testing performed in a CLIA–certified laboratory (all available to treating clinician through official medical record)

1. MGMT methylation testing
2. 1p/19q FISH testing
3. IDH1(R132H) IHC
4. EGFR amplification FISH/CISH
5. GBM Dx Expression profiling assay
6. Snapshot Mutation Assay
7. BRAFv600e
8. BRAF duplication FISH
9. PTEN IHC
10. pAKT IHC
11. pS6 IHC
12. pPRAS40 IHC
13. EGFRvIII IHC
14. EGFRvIII PCR

Research Testing performed in non-CLIA environment or not validated (not available to treating clinician or patient at current time)

1. Oncomap Somatic Mutation Genotyping Assay
2. Whole genome sequencing
3. Whole exome sequencing
4. Whole genome array CGH/SNP copy number analysis
5. Whole genome expression profiling

Appendix VIII: TISSUE AND CLINICAL DATA USE OVERSIGHT COMMITTEES

Oversight Committee Name	Chairs on October 15, 2010	Committee Make Up	Minimal Charge
BWH/DFCI Neuro-oncology Steering Committee	Keith L. Ligon, M.D., Ph.D.	Multi-disciplinary teams of at least one pathologist and one other representative. Efforts are made to have representation from neuro-oncology, radiation-oncology, radiology, neurosurgery	Review and approval of Usage Agreements and Named investigator Research Annual review of a site specific report to include, but not limited to: · Estimated rate of participant accrual of all new and current neuro-oncology · Percentage of patients who declined participation in the study · Participant breakdown of tumor/disease, by recruitment · Investigator projects · Use of QACT Neuro-Oncology Database · Tissue obtained by tumor type · Tissue distributed by tumor type · Description of clinical results transferred back to participants · Publications, abstracts associated resulting from research involved in this protocol Feedback of relevant findings of annual report to colleague investigators and DF/HCC Oversight Committee
MGH Neuro-Oncology Steering Committee	Anat O. Stemmer-Rachamimov, MD		
Pediatric (CHB) Neuro-Oncology Steering Committee	Susan Chi, MD		
DF/HCC Neuro-Oncology Steering Committee	Department Program Co-Leaders: Robert L. Martuza, MD, Charles Stiles, PhD, Mark Kieran, MD, PhD	Department Program Co-Leaders*, Clinical Trials Chairs*, Site Lead Investigators,	Review of annual reports and site oversight committee findings Bi-annual new research findings ensuring that clinically relevant information form appropriate (ie. CLIA) testing is being provided to participant's clinicians, and facilitating access of new and appropriate testing to patients (non-participants) with CNS tumors across DF/HCC.

* see DF/HCC Clinical Research Unit (CRU) on DF/HCC website or link to:
http://www.dfhcc.harvard.edu/fileadmin/DFHCC_Admin/Clinical_Trials/CRO/Contacts/Program_Leader_List_for_Endorsement_Forms.pdf

Appendix IX: Dana-Farber/Boston Children's Hospital TISSUE BANK

Name of Tissue Repository	Location of Tissue Repository (physical address)	Capabilities– sample processing and storage—last updated 10/25/10	Tracking System
CHB Neuro-oncology Tissue Repository	Children's Hospital Boston Pathology Department; DFCI Dry Dock Facility; Children's Hospital Boston 300 Longwood Avenue Department of Pathology Bader -1	Frozen storage of tissue and blood	Excel Database

Appendix X: PERFORMANCE STATUS CRITERIA

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
Score	**Description**	**Score**	**Description**
• 100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Appendix XI: NORMAL BLOOD PRESSURE BY HEIGHT AND AGE

The normal blood pressure by height and age tables are included in this Appendix. In order to use these tables, note that the height percentile is determined by the standard growth charts. The child's measured systolic and diastolic BP is compared with the numbers provided in the table (boys or girls) for age and height percentile.

- The child is normotensive if BP is below the 90th percentile.
- If the child's BP (systolic or diastolic) is at or above the 95th percentile, the child may be hypertensive and repeated measurements are indicated.
- BP measurements between the 90th and 95th percentiles are high normal and warrant further observation and consideration of other risk factors.

Standards for systolic and diastolic BP for infants younger than 1 year are available in the second task force report. Recently, additional data has been published. In children younger than 1 year, systolic BP has been used to define hypertension.

Source:
DHHS, PHS, NIH, National Heart, Lung, and Blood Institute. *Update on the Task Force Report (1987) on High Blood Pressure in Children and Adolescents*: A Working Group Report from the National High Blood Pressure Education Program. NIH Publication 96-3790; 1996; 7-9.
The entire NIH document can be viewed at:
http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

90th and 95th Percentile BP for Girls 1-17 Years

Age (y)	Blood Pressure Percentile	Systolic Blood Pressure by Percentile of Height (mm Hg)							Diastolic Blood Pressure by Percentile of Height (mm Hg)						
		5%	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*	*5%*	*10%*	*25%*	*50%*	*75%*	*90%*	*95%*
1	90th	94	95	97	98	100	102	102	50	51	52	53	54	54	55
	95th	98	99	101	102	104	106	106	55	55	56	57	58	59	59
2	90th	98	99	100	102	104	105	106	55	55	56	57	58	59	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	111	112	113	63	63	64	65	66	67	67
4	90th	102	103	105	107	109	110	111	62	62	63	64	65	66	66
	95th	106	107	109	111	113	114	115	66	67	67	68	69	70	71
5	90th	104	105	106	108	110	112	112	65	65	66	67	68	69	69
	95th	108	109	110	112	114	115	116	69	70	70	71	72	73	74
6	90th	105	106	108	110	111	113	114	67	68	69	70	70	71	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	90th	106	107	109	111	113	114	115	69	70	71	72	72	73	74
	95th	110	111	113	115	116	118	119	74	74	75	76	77	78	78
8	90th	107	108	110	112	114	115	116	71	71	72	73	74	75	75
	95th	111	112	114	116	118	119	120	75	76	76	77	78	79	80
9	90th	109	110	112	113	115	117	117	72	73	73	74	75	76	77
	95th	113	114	116	117	119	121	121	76	77	78	79	80	80	81
10	90th	110	112	113	115	117	118	119	73	74	74	75	76	77	78
	95th	114	115	117	119	121	122	123	77	78	79	80	80	81	82
11	90th	112	113	115	117	119	120	121	74	74	75	76	77	78	78
	95th	116	117	119	121	123	124	125	78	79	79	80	81	82	83
12	90th	115	116	117	119	121	123	123	75	75	76	77	78	78	79
	95th	119	120	121	123	125	126	127	79	79	80	81	82	83	83
13	90th	117	118	120	122	124	125	126	75	76	76	77	78	79	80
	95th	121	122	124	126	128	129	130	79	80	81	82	83	83	84
14	90th	120	121	123	125	126	128	128	76	76	77	78	79	80	80
	95th	124	125	127	128	130	132	132	80	81	81	82	83	84	85
15	90th	123	124	125	127	129	131	131	77	77	78	79	80	81	81
	95th	127	128	129	131	133	134	135	81	82	83	83	84	85	86
16	90th	125	126	128	130	132	133	134	79	79	80	81	82	82	83
	95th	129	130	132	134	136	137	138	83	83	84	85	86	87	87
17	90th	128	129	131	133	134	136	136	81	81	82	83	84	85	85
	95th	132	133	135	136	138	140	140	85	85	86	87	88	89	89

90th and 95th Percentile BP For BOYS 1-17 Years

Age (y)	Blood Pressure Percentile	Systolic Blood Pressure by Percentile of Height (mm Hg)							Diastolic Blood Pressure by Percentile of Height (mm Hg)						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	90th	94	95	97	98	100	102	102	50	51	52	53	54	54	55
	95th	98	99	101	102	104	106	106	55	55	56	57	58	59	59
2	90th	98	99	100	102	104	105	106	55	55	56	57	58	59	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	111	112	113	63	63	64	65	66	67	67
4	90th	102	103	105	107	109	110	111	62	62	63	64	65	66	66
	95th	106	107	109	111	113	114	115	66	67	67	68	69	70	71
5	90th	104	105	106	108	110	112	112	65	65	66	67	68	69	69
	95th	108	109	110	112	114	115	116	69	70	70	71	72	73	74
6	90th	105	106	108	110	111	113	114	67	68	69	70	70	71	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	90th	106	107	109	111	113	114	115	69	70	71	72	72	73	74
	95th	110	111	113	115	116	118	119	74	74	75	76	77	78	78
8	90th	107	108	110	112	114	115	116	71	71	72	73	74	75	75
	95th	111	112	114	116	118	119	120	75	76	76	77	78	79	80
9	90th	109	110	112	113	115	117	117	72	73	73	74	75	76	77
	95th	113	114	116	117	119	121	121	76	77	78	79	80	80	81
10	90th	110	112	113	115	117	118	119	73	74	74	75	76	77	78
	95th	114	115	117	119	121	122	123	77	78	79	80	80	81	82
11	90th	112	113	115	117	119	120	121	74	74	75	76	77	78	78
	95th	116	117	119	121	123	124	125	78	79	79	80	81	82	83
12	90th	115	116	117	119	121	123	123	75	75	76	77	78	78	79
	95th	119	120	121	123	125	126	127	79	79	80	81	82	83	83
13	90th	117	118	120	122	124	125	126	75	76	76	77	78	79	80
	95th	121	122	124	126	128	129	130	79	80	81	82	83	83	84
14	90th	120	121	123	125	126	128	128	76	76	77	78	79	80	80
	95th	124	125	127	128	130	132	132	80	81	81	82	83	84	85
15	90th	123	124	125	127	129	131	131	77	77	78	79	80	81	81
	95th	127	128	129	131	133	134	135	81	82	83	83	84	85	86
16	90th	125	126	128	130	132	133	134	79	79	80	81	82	82	83
	95th	129	130	132	134	136	137	138	83	83	84	85	86	87	87
17	90th	128	129	131	133	134	136	136	81	81	82	83	84	85	85
	95th	132	133	135	136	138	140	140	85	85	86	87	88	89	89

Appendix XII: DOSAGE OF MEK162

Dosing table (15 mg tablets)

BSA (m^2)	Level -1 (12mg/m^2)	Level 1 (16mg/m^2)	Level 2 (20mg/m^2)	Level 3 (24mg/m^2)	Level 4 (28mg/m^2)	Level 5 (32mg/m^2)
≤0.42	*	*	*	*	*	*
0.43-48	*	*	*	*	*	15 mg (1 tablet)
0.49-0.55	*	*	*	*	15 mg (1 tablet)	15 mg (1 tablet)
0.55-0.63	*	*	*	15 mg (1 tablet)	15 mg (1 tablet)	*
0.64-0.67	*	*	*	15 mg (1 tablet)	*	*
0.68-0.72	*	*	15 mg (1 tablet)	15 mg (1 tablet)	*	*
0.73-0.84	*	*	15 mg (1 tablet)	*	*	*
0.85-0.97	*	15 mg (1 tablet)	*	*	*	30 mg (2 tablets)
0.98-1.06	*	15 mg (1 tablet)	*	*	30 mg (2 tablets)	30 mg (2 tablets)
1.07-1.12	*	*	*	*	30 mg (2 tablets)	30 mg (2 tablets)
1.13-1.24	15 mg (1 tablet)	*	*	30 mg (2 tablets)	30 mg (2 tablets)	*
1.25-1.35	15 mg (1 tablet)	*	*	30 mg (2 tablets)	*	45 mg (3 tablets)
1.36-1.44	15 mg (1 tablet)	*	30 mg (2 tablets)	30 mg (2 tablets)	*	45 mg (3 tablets)
1.45-1.66	*	*	30 mg (2 tablets)	*	45 mg (3 tablets)	45 mg (3 tablets)
1.67-1.87	*	*	*	45 mg (3 tablets)	45 mg (3 tablets)	60 mg (4 tablets)
≥1.88	*	*	*	45 mg (3 tablets)	60 mg (4 tablets)	60 mg (4 tablets)

*Tablet form not permitted at this BSA for this dose level. See suspension dosing table below.
Dose should be given twice daily (every 12 hours).

Dosing table (suspension)

BSA (m^2)	Level -1 (12mg/m^2)	Level 1 (16mg/m^2)	Level 2 (20mg/m^2)	Level 3 (24mg/m^2)	Level 4 (28mg/m^2)	Level 5 (32mg/m^2)
≤0.14	1	2	2	2	3	3
0.15-0.24	2	3	4	5	6	6
0.25-0.34	4	5	6	7	8	10
0.35-0.44	5	6	8	10	11	13
0.45-0.54	6	8	10	12	14	16
0.55-0.64	7	10	12	14	17	19
0.65-0.74	8	11	14	17	20	22
0.75-0-.85	10	13	16	19	22	26
0.85-0.94	11	14	18	22	25	29
0.95-1.04	12	16	20	24	28	32
1.05-1.14	13	18	22	26	31	35
1.15-1.24	14	19	24	29	34	38
1.25-1.34	16	21	26	31	36	42
1.35-1.44	17	22	28	34	39	45
1.45-1.54	18	24	30	36	42	48
1..55-1.64	19	26	32	38	45	51
1.65-1.74	20	27	34	41	48	54
1.75-1.84	22	29	36	43	50	58
≥1.85	23	30	38	45	53	61

Quantities listed are individual doses in mg amounts.
Dose should be given twice daily (every 12 hours).

Appendix XIII: GUIDELINES FOR THE MANAGEMENT OF MEK162 INDUCED SKIN TOXICITY

Clinical judgment and experience of the treating physician should guide the management plan of each patient. In general, the following interventions are in addition to the MEK162 induced rash dosing guidelines, Recommended Dose Modifications Associated with Treatment Related Adverse Events, in section 6.4.

Prophylactic treatment for skin toxicity is recommended. Prophylaxis of skin toxicity to be initiated 24 hours prior to the first treatment with MEK162 or later as needed. Apply topical agents to the mostly common affected areas such as face, scalp, neck, upper chest, upper back.

- Non oily sunscreen (PABA free, SPF ≥ 15, UVA/UVB protection)
- Topical steroid (e.g., mometasone cream, applied sparingly daily)
- Topical erythromycin
- Consider low-dose oral doxycycline for the first 2-3 weeks of study drug administration.

Topical agents should be applied on a daily basis starting on Day 1 of study treatment or 24 hours prior to first treatment, and more often as needed.

Effective medications also include antihistamines, other topical corticosteroids, other topical antibiotics, and low-dose systemic corticosteroids.

The treatment algorithm based on CTCAE grade is as follows:

Mild Rash (CTCAE Grade 1)

- Consider prophylactic rash treatment as described above if not already started
- Topical mometasone cream or other topical corticosteroid and/or topical antibiotic (erythromycin (2%)) are recommended.
- The patient should be reassessed after 2 weeks or sooner if rash worsens or as per investigator opinion.

Moderate Rash (CTCAE Grade 2)

- Although there has been no evidence of phototoxicity or photosensitivity in patients being treated with MEK162, doxycycline (or minocycline as second-line) should be used with careful UV protection (i.e., avoid direct exposure to sunlight, use sunglasses, use sunscreen, etc.).
- Use of topical erythromycin or clindamycin (1%) plus mometasone or pimecrolimus (1% cream) plus oral antibiotics such as oral doxycycline or minocycline.

Severe Rash (CTCAE Grade 3-4)

CTCAE Grade 3

- In addition to the interventions recommended for moderate rash, consider oral prednisolone at a dose of 0.5 mg/kg. Upon improvement, taper the dose in a stepwise manner.
- Alternatively, in addition to the interventions recommended for moderate rash, consider oral isotretinoin (low doses, i.e. 0.3 to 0.5 mg/kg) (Lacouture et al 2011).

CTCAE Grade 4

- Immediately discontinue the patient from study drug and treat the patient with oral and topical medications (see recommendation CTCAE Grade 3).

Symptomatic treatment:

It is strongly recommended that patients who develop rash/skin toxicities receive symptomatic treatment:

- For pruritic lesions, use of cool compresses and oral antihistamine agents
- For fissuring, use of Monsel's solution, silver nitrate, or zinc oxide cream is. If not sufficient, use mild steroid ointments or combination of steroids and antibiotics such as Fucicort.
- For desquamation, use emollients with mild pH 5/ (best containing urea 10%)
- For paronychia, antiseptic bath and local potent corticosteroids, use oral antibiotics and, if no improvement is seen, refer to a dermatologist or surgeon
- For infected lesions, obtain bacterial and fungal cultures and treat with topical or systemic antibiotics based on sensitivity of culture

References

Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, et al (2011) Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer; 19: 1079–95

Appendix XIV: GUIDELINES FOR THE MANAGEMENT OF MEK162 INDUCED DIARRHEA

Proactively investigate for occurrence of diarrhea

Educate patient

1. Remind patients at each visit to contact the site immediately upon the first sign of loose stool or symptoms of abdominal pain. Additionally, at each study visit, each patient should be specifically asked regarding occurrence of diarrhea or diarrhea-related symptoms. If the patient had symptoms, the patient should be asked regarding the actions taken for these symptoms and re-instruct if indicated.
2. In addition to dietary modification, the patients should be instructed on early warning signs of diarrhea and potentially life-threatening illnesses (e.g. severe cramping → severe diarrhea, fever with diarrhea → infection and dizziness on standing might be a sign for shock).
3. Patients should be instructed on what to report to the investigator if possible (i.e. number of stools, stool composition, stool volume)

Anti-diarrhea therapy

In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education, as well as proper management of diarrhea is mandatory.

Management of diarrhea should be instituted at the first sign of abdominal cramping, loose stools, or overt diarrhea. All concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications eCRF. It is recommended that patients be provided loperamide tablets and are instructed on the use of loperamide on the first day of MEK162 treatment. In addition to the MEK162 induced diarrhea dosing guidelines, Recommended Dose Modifications Associated with Treatment Related Adverse Events, in section 6.4 the protocol, these instructions should be provided at each visit and the site should ensure that the patient understands the instructions.

Explain the frequency of diarrhea and its relationship to NCI CTCAE grading

Determine if diarrhea is complicated versus uncomplicated (section 6.4)

Rule out other or concomitant causes.

These may include:

- Infection by Candida spp, Salmonella spp., Clostridium difficile, Campylobacter spp. Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients,
- Medication-induced diarrhea
- Malabsorption/lactose intolerance
- Fecal impaction, partial bowel obstruction

For uncomplicated Grade 1 to Grade 2 diarrhea

- Stop all lactose-containing products and alcohol and eat frequent small meals that include bananas, rice, applesauce or toast)
- Stop laxatives, bulk fiber (i.e. Metamucil®) and stool softeners (e.g. docusate sodium; Colace®)

- Stop high-osmolar food supplements such as Ensure® Plus and Jevity® Plus (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade® or broth)
- Consider administration of standard dose loperamide.

Note: Oral antibiotics may be started as prophylaxis for infections under the discretion of the physician.

For complicated Grade 1 to Grade 2 diarrhea or Grade 3 to 4 diarrhea

- The patient must call the investigator immediately
- If loperamide has not been initiated, initiate standard dose loperamide immediately.
- Administer IV fluids and electrolytes as needed. In case of severe dehydration, replace loperamide by octreotide.
- Monitor/Continue IV fluids and antibiotics as needed. Intervention should be continued until the patient is diarrhea free for at least 24 hours.
- Hospitalization may need to be considered.

Appendix XV: 3+3 Dose Escalation Decision Grid

# of Eligible Patients at Dose Level	# of DLTs Observed to Date	# of Patients Pending DLT evaluation	3 + 3 Decision
1	0	0	Continue enrollment
1	1	0	Continue enrollment
1	0	1	Continue enrollment
2	0	0	Continue enrollment
2	1	0	Continue enrollment
2	2	0	De-escalate
2	0	1	Continue enrollment
2	1	1	Continue enrollment
2	0	2	Continue enrollment
3	0	0	Escalate
3	1	0	Continue enrollment
3	2	0	De-escalate
3	3	0	De-escalate
3	0	1	Suspend enrollment
3	1	1	Suspend enrollment
3	2	1	De-escalate
3	0	2	Suspend enrollment
3	1	2	Suspend enrollment
3	0	3	Suspend enrollment
4	0	0	Continue enrollment
4	1	0	Continue enrollment
4	2	0	De-escalate
4	3	0	NA
4	4	0	NA
4	0	1	Continue enrollment
4	1	1	Continue enrollment
4	2	1	NA
4	3	1	NA
4	0	2	NA
4	1	2	NA
4	2	2	NA
4	0	3	NA
4	1	3	NA
4	0	4	NA
5	0	0	Continue enrollment
5	1	0	Continue enrollment
5	2	0	De-escalate

# of Eligible Patients at Dose Level	# of DLTs Observed to Date	# of Patients Pending DLT evaluation	3 + 3 Decision
5	3	0	De-escalate
5	4	0	NA
5	5	0	NA
5	0	1	Continue enrollment
5	1	1	Continue enrollment
5	2	1	De-escalate
5	3	1	NA
5	4	1	NA
5	0	2	Continue enrollment
5	1	2	Continue enrollment
5	2	2	NA
5	3	2	NA
5	0	3	NA
5	1	3	NA
5	2	3	NA
5	0	4	NA
5	1	4	NA
5	0	5	NA
6	0	0	Escalate
6	1	0	Escalate
6	2	0	De-escalate
6	3	0	De-escalate
6	4	0	De-escalate
6	5	0	NA
6	6	0	NA
6	0	1	Escalate
6	1	1	Suspend enrollment
6	2	1	De-escalate
6	3	1	De-escalate
6	4	1	NA
6	5	1	NA
6	0	2	Suspend enrollment
6	1	2	Suspend enrollment
6	2	2	De-escalate
6	3	2	NA
6	4	2	NA
6	0	3	Suspend enrollment
6	1	3	Suspend enrollment
6	2	3	NA

# of Eligible Patients at Dose Level	# of DLTs Observed to Date	# of Patients Pending DLT evaluation	3 + 3 Decision
6	3	3	NA
6	0	4	NA
6	1	4	NA
6	2	4	NA
6	0	5	NA
6	1	5	NA
6	0	6	NA

Appendix XVI: Instructions for preparation of MEK162 Oral Suspension

Objective

This document describes in detail the preparation procedure of MEK162 (binimetinib) oral suspensions from MEK162 15 mg film-coated tablet (FCT) and Ora Sweet®/ water 3:1 (v/v) vehicle. This document also provides the instruction for administration of the reconstituted oral suspensions to the subjects.

Safety instructions

General remarks

Utmost care must be exercised while handling (preparation and dosing) MEK162 oral suspensions. Follow the "Disposition of hazardous waste procedure" applicable to the clinic's site for the disposal of contaminated material (e.g. gloves, paper towels, syringes etc.). Avoid direct contact with clothes and skin.

Consideration of events

Spillage of a MEK162 suspension on hard washable surface, e.g., work bench, table or floor:

- Cleaning should be done while wearing protective equipment (minimum requirement: disposable gloves).
- Wipe the area with clean paper towel until the area is dry.
- Use fresh, clean paper towel for each wiping action.
- Wipe the area twice with Ethanol 70% (wear chemically resistant gloves).
- Wipe the area with clean water and dry with a clean paper towel.
- Dispose the wet towels in the appropriate waste bags.

Breakage of a glass bottle containing the MEK162 suspension:

- Do not attempt to pick up broken glass as it can pierce through gloves and might cut the skin.
- Use a brush to pick up the broken glass pieces.
- Wipe the area with a wet paper towel to remove any trace of broken glass.
- Wipe the area with clean paper towel until the area is dry.
- Wipe the area twice with Ethanol 70% (wear chemically resistant gloves).
- Wipe the area with clean water and dry with a clean paper towel.
- Dispose the waste in the appropriate waste bags.

In case of contact with clothes or skin, remove contaminated clothing, and rinse contaminated skin immediately with plenty of water and soap.

Materials

- MEK162 15 mg film coated tablet (provided by Array BioPharma)
- 125 mL glass bottle or 4oz plastic bottle
- Child-resistant screw cap
- Uncarbonated potable water (from any commercial source).
- 30 mL syringe (i.e. 30 mL accuracy ± 0.5 mL).
- Dosing cup adapted to target administration volume (i.e. 15 to 50 mL).
- Exacta-Med syringe type dispenser sets
- Ethanol 70% (disinfectant and cleaning agent; used in event of spillage).
- Plastic bags (large enough to hold one 125 mL brown glass bottle).
- Ora Sweet®vehicle
- Disposable gloves.

Preparation of MEK162 oral suspension at 1mg/mL

Note: Preparation of oral solution is to be carried out by the on-site Pharmacy using clean glassware, measuring syringe, etc. Suspension, Exacta-Med syringe type dispenser sets, and dosing cups are provided to the patients after preparation. The suspension must be stored at room temperature (below 25°C) and should not be refrigerated. It should be used within 30 days after preparation.

• Step 1: Measure 15 mL uncarbonated potable water using the 30 mL syringe and transfer it into the 125 mL brown bottle (or 4 oz plastic bottle).
• Step 2: Add four (4) MEK162 15 mg film coated tablets into the 125mL brown bottle (or 4oz plastic bottle)
• Step 3: Close the bottle using the screw cap and let the bottle sit for 10 minutes.
• Step 4: Shake the bottle for 1-3 minutes until the tablets are completely dispersed. Remove the cap from the brown bottle.
• Step 5: Measure 45 mL Ora Sweet using a 30 mL syringe and transfer it into the 125 mL brown bottle (or 4oz plastic bottle).
• Step 6: Shake the bottle for 1-3 minutes. Confirm the suspension is homogenous.

Administration of MEK162 oral suspension at 1mg/mL
Note: Each administration should be performed using a new Exacta-Med syringe type dispenser. If dosing cups are used for administration, a new dosing cup needs to be used for each dispensing. The suspension must be stored at room temperature (below 25°C) and should not be refrigerated. It should be used within 30 days after preparation.
• Remove the screw cap from the brown bottle which contains the oral suspension.
• Plug the 10 mL syringe adapter onto the bottleneck and close the brown bottle with the screw cap.
• Gently handshake the bottle of oral suspension for 60 seconds just prior to dosing to make sure the content is homogeneous.
• Remove the screw cap from the brown bottle and connect the syringe tip to the adapter with the bottle in upright position.
• Hold the adapter and bottle in upside-down position, and carefully draw the required volume of oral suspension using the 10 mL syringe. After this is done, hold the bottle in upright position and remove the filled syringe from the adapter.
• Transfer the content directly from the syringe into the mouth of the patient. Use a new syringe for each administration if more than 10mL of suspension is needed (discard the syringe after every use).

If more than 10mL of suspension is needed, the content from the syringes can alternatively be transferred into a dosing cup, and administered to the patient from the cup. In this case, care has to be taken to ensure all the suspension contained in the cup is administered. Use a new dosing cup for each administration.
• Close the brown bottle with the cap immediately after use.
• The Exacta-Med syringe type dispenser set and the dosing cup should be discarded after each administration.
• The dosing bottle containing the remaining of the prepared suspension can be stored at room temperature, below 25°C, and should not be refrigerated. It should be discarded after 30 days.
• The dosing bottle with any unused suspension should be returned to the on-site pharmacy.

Storage instructions
The reconstituted suspension can be stored at room temperature no greater than 25°C and should not be refrigerated. It must be used within 30 days after preparation.

Appendix XVII: Patient Diary

MEK162 Subject ID:	**CTO Registration Number:**	**Dose Volume:** BID (twice a day)

INSTRUCTIONS

- **Suspension Administration**: Use a new or rinsed clean syringe and/or dosing cup (provided by your site Pharmacy) for each dose
  - Remove the screw cap from the bottle which contains the oral suspension
  - Plug the syringe adapter onto the bottleneck and close the bottle with the screw cap
  - Gently handshake the bottle of oral suspension for 60 seconds just prior to dosing to make sure the content is evenly mixed
  - Remove the screw cap from the bottle and connect the syringe tip to the adapter with the bottle in upright position.
  - Hold the adapter and bottle in upside down position and carefully draw the required volume of oral suspension using the syringe. After this is done, hold the bottle in upright position and remove the filled syringe from the adapter.
  - Transfer the content directly from the syringe into the mouth of the patient. Use a new or rinsed clean syringe for each administration if more suspension is needed (discard or rinse clean syringe after every use).
    - If more suspension is needed, the content from the syringes can alternatively be transferred into a dosing cup, and administered to the patient from the cup. In this case, care has to be taken to ensure all the suspension contained in the cup is administered. Use a new dosing cup for each administration.
  - Close the bottle with the cap immediately after use.
  - The syringe dispenser set and the dosing cup should be discarded or rinsed clean after each administration.
  - Doses should be taken 12 hours apart (+/- 2 hours) with a glass of water
  - Do not retake dose if vomiting occurs or make up missed doses
- **Storage**: Room temperature (below 25°C or 77°F), do NOT refrigerate. Suspension must be used within 30 days of Pharmacy preparation.
- **Return**: Bottle with any unused suspension, these completed drug diary forms
- **Diary**: Please complete this document in pen, include comments regarding missed doses or side effects experienced and sign at the end

Cycle _____

Week 1

Date:	/ /	/ /	/ /	/ /	/ /	/ /	/ /
AM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							
PM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							

Week 2

Date:	/ /	/ /	/ /	/ /	/ /	/ /	/ /
AM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							
PM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							

Week 3

Date:	/ /	/ /	/ /	/ /	/ /	/ /	/ /
AM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							
PM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							

Week 4

Date:	/ /	/ /	/ /	/ /	/ /	/ /	/ /
AM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							
PM	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose	__:__ Missed Dose
Comments (Missed Dose or Side Effects)							

Parent/Participant Signature: _____ Date: _____

Reviewed by Treating Physician: _____ Date: _____

Appendix XVIII: PedsQL Brain Tumor Modules

ID# _____

Date:_____

PedsQL™

Brain Tumor Module

Version 1.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

Children with brain tumors sometimes have special problems. On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has your child had with …*

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4
3. Getting headaches	0	1	2	3	4

MOVEMENT AND BALANCE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her balance	0	1	2	3	4
2. Difficulty using his/her legs	0	1	2	3	4
3. Difficulty using his/her hands	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) causing him/her pain	0	1	2	3	4
2. Getting anxious about having blood drawn	0	1	2	3	4
3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

NAUSEA *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Becoming nauseated during medical treatments	0	1	2	3	4
2. Food not tasting very good to him/her	0	1	2	3	4
3. Becoming nauseated while thinking about medical treatments	0	1	2	3	4
4. Feeling too nauseous to eat	0	1	2	3	4
5. Some foods and smells making him/her nauseous	0	1	2	3	4

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Worrying about side effects from medical treatments	0	1	2	3	4
2. Worrying about whether or not his/her medical treatments are working	0	1	2	3	4
3. Worrying that the cancer will reoccur or relapse	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Brain Tumor Module

Version 1.0

YOUNG CHILD REPORT (ages **5-7**)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

Think about how you have been doing for the past 7 days. Please listen carefully to each

sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

COGNITIVE PROBLEMS ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Is it hard for you to know what to do when something bothers you	0	2	4
2. Is it hard for you to work with numbers or do math	0	2	4
3. Is it hard for you to pay attention to things	0	2	4
4. Is it hard for you to remember what is read to you	0	2	4
5. It is hard for you to learn new things	0	2	4
6. Do you get mixed up easily	0	2	4

PAIN AND HURT ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Do you ache or hurt in your bones and/or muscles	0	2	4
2. Do you hurt a lot	0	2	4
3. Do you have headaches	0	2	4

MOVEMENT AND BALANCE ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. It is hard for you to keep your balance	0	2	4
2. It is hard for you to use your legs	0	2	4
3. It is hard for you to use your hands	0	2	4

PROCEDURAL ANXIETY ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Do needle sticks (i.e. shots, blood tests, IV's) hurt you	0	2	4
2. Do you get scared when you have to have blood tests	0	2	4
3. Do you get scared about having needle sticks (i.e. shots, blood tests, IV's)	0	2	4

Think about how you have been doing for the past 7 days. Please listen carefully to each sentence and tell me how much of a problem this is for you.

NAUSEA ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Does your medicine make you sick to your stomach	0	2	4
2. Does food taste bad to you	0	2	4
3. Do you get sick to your stomach when you think about your medicine	0	2	4
4. Do you feel too sick to your stomach to eat	0	2	4
5. Do some foods and smells make you sick to your stomach	0	2	4

WORRY ***(problems with…)***	**Not at all**	**Some-times**	**A lot**
1. Do you worry about how medicines make you feel	0	2	4
2. Do you worry about whether or not your medicine is working	0	2	4
3. Do you worry that your cancer illness will come back	0	2	4

How much of a problem is this for you?

Not at all

Sometimes

A lot

ID# _____

Date:_____

PedsQL™

Brain Tumor Module

Version 1.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

Children with brain tumors sometimes have special problems. On the following pages is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has your child had with …*

COGNITIVE PROBLEMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty figuring out what to do when something bothers him/her	0	1	2	3	4
2. Difficulty working with numbers or doing math	0	1	2	3	4
3. Difficulty paying attention to things	0	1	2	3	4
4. Difficulty remembering what is read to him/her	0	1	2	3	4
5. Difficulty learning new things	0	1	2	3	4
6. Getting mixed up easily	0	1	2	3	4

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4
3. Getting headaches	0	1	2	3	4

MOVEMENT AND BALANCE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her balance	0	1	2	3	4
2. Difficulty using his/her legs	0	1	2	3	4
3. Difficulty using his/her hands	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) causing him/her pain	0	1	2	3	4
2. Getting anxious about having blood drawn	0	1	2	3	4
3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

*In the past **7 days,** how much of a **problem** has your child had with …*

NAUSEA ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Becoming nauseated during medical treatments	0	1	2	3	4
2. Food not tasting very good to him/her	0	1	2	3	4
3. Becoming nauseated while thinking about medical treatments	0	1	2	3	4
4. Feeling too nauseous to eat	0	1	2	3	4
5. Some foods and smells making him/her nauseous	0	1	2	3	4

WORRY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Worrying about side effects from medical treatments	0	1	2	3	4
2. Worrying about whether or not his/her medical treatments are working	0	1	2	3	4
3. Worrying that the cancer will reoccur or relapse	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Brain Tumor Module

Version 1.0

CHILD REPORT (ages **8-12**)

DIRECTIONS

Children with brain tumors sometimes have special problems. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has this been for you …*

COGNITIVE PROBLEMS ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to figure out what to do when something bothers me	0	1	2	3	4
2. I have trouble solving math problems	0	1	2	3	4
3. I have trouble writing school papers or reports	0	1	2	3	4
4. It is hard for me to pay attention to things	0	1	2	3	4
5. It is hard for me to remember what I read	0	1	2	3	4
6. It is hard for me to learn new things	0	1	2	3	4
7. I get mixed up easily	0	1	2	3	4

PAIN AND HURT ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I ache or hurt in my joints and/or muscles	0	1	2	3	4
2. I hurt a lot	0	1	2	3	4
3. I get headaches	0	1	2	3	4

MOVEMENT AND BALANCE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to keep my balance	0	1	2	3	4
2. It is hard for me to use my legs	0	1	2	3	4
3. It is hard for me to use my hands	0	1	2	3	4

PROCEDURAL ANXIETY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Needle sticks (i.e. injections, blood tests, IV's) hurt me	0	1	2	3	4
2. I get scared when I have to have blood tests	0	1	2	3	4
3. I get scared about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

*In the past **7 days,** how much of a **problem** has this been for you …*

NAUSEA ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I become sick to my stomach when I have medical treatments	0	1	2	3	4
2. Food does not taste very good to me	0	1	2	3	4
3. I become sick to my stomach when I think about medical treatments	0	1	2	3	4
4. I feel too sick to my stomach to eat	0	1	2	3	4
5. Some foods and smells make me sick to my stomach	0	1	2	3	4

WORRY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I worry about side effects from medical treatments	0	1	2	3	4
2. I worry about whether or not my medical treatments are working	0	1	2	3	4
3. I worry that my cancer will come back or relapse	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Brain Tumor Module

Version 1.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

Children with brain tumors sometimes have special problems. On the following pages is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has your child had with …*

COGNITIVE PROBLEMS ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Difficulty figuring out what to do when something bothers him/her	0	1	2	3	4
2. Trouble solving math problems	0	1	2	3	4
3. Trouble writing school papers or reports	0	1	2	3	4
4. Difficulty paying attention to things	0	1	2	3	4
5. Difficulty remembering what he/she reads	0	1	2	3	4
6. Difficulty learning new things	0	1	2	3	4
7. Getting mixed up easily	0	1	2	3	4

PAIN AND HURT ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4
3. Getting headaches	0	1	2	3	4

MOVEMENT AND BALANCE ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Difficulty keeping his/her balance	0	1	2	3	4
2. Difficulty using his/her legs	0	1	2	3	4
3. Difficulty using his/her hands	0	1	2	3	4

PROCEDURAL ANXIETY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Needle sticks (i.e. injections, blood tests, IV's) causing him/her pain	0	1	2	3	4
2. Getting anxious about having blood drawn	0	1	2	3	4
3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

*In the past **7 days,** how much of a **problem** has your child had with …*

NAUSEA ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Becoming nauseated during medical treatments	0	1	2	3	4
2. Food not tasting very good to him/her	0	1	2	3	4
3. Becoming nauseated while thinking about medical treatments	0	1	2	3	4
4. Feeling too nauseous to eat	0	1	2	3	4
5. Some foods and smells making him/her nauseous	0	1	2	3	4

WORRY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Worrying about side effects from medical treatments	0	1	2	3	4
2. Worrying about whether or not his/her medical treatments are working	0	1	2	3	4
3. Worrying that the cancer will reoccur or relapse	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Brain Tumor Module

Version 1.0

TEEN REPORT (ages **13-18**)

DIRECTIONS

Teens with brain tumors sometimes have special problems. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has this been for you …*

COGNITIVE PROBLEMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to figure out what to do when something bothers me	0	1	2	3	4
2. I have trouble solving math problems	0	1	2	3	4
3. I have trouble writing school papers or reports	0	1	2	3	4
4. It is hard for me to pay attention to things	0	1	2	3	4
5. It is hard for me to remember what I read	0	1	2	3	4
6. It is hard for me to learn new things	0	1	2	3	4
7. I get mixed up easily	0	1	2	3	4

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I ache or hurt in my joints and/or muscles	0	1	2	3	4
2. I hurt a lot	0	1	2	3	4
3. I get headaches	0	1	2	3	4

MOVEMENT AND BALANCE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my balance	0	1	2	3	4
2. It is hard for me to use my legs	0	1	2	3	4
3. It is hard for me to use my hands	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) hurt	0	1	2	3	4
2. I get scared when I have to have blood tests	0	1	2	3	4
3. I get scared about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

*In the past **7 days,** how much of a **problem** has this been for you …*

NAUSEA ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I become sick to my stomach when I have medical treatments	0	1	2	3	4
2. Food does not taste very good to me	0	1	2	3	4
3. I become sick to my stomach when I think about medical treatments	0	1	2	3	4
4. I feel too sick to my stomach to eat	0	1	2	3	4
5. Some foods and smells make me sick to my stomach	0	1	2	3	4

WORRY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I worry about side effects from medical treatments	0	1	2	3	4
2. I worry about whether or not my medical treatments are working	0	1	2	3	4
3. I worry that my cancer will come back or relapse	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Brain Tumor Module

Version 1.0

PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

Teens with brain tumors sometimes have special problems. On the following pages is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **7 days,** how much of a **problem** has your teen had with …*

COGNITIVE PROBLEMS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty figuring out what to do when something bothers him/her	0	1	2	3	4
2. Trouble solving math problems	0	1	2	3	4
3. Trouble writing school papers or reports	0	1	2	3	4
4. Difficulty paying attention to things	0	1	2	3	4
5. Difficulty remembering what he/she reads	0	1	2	3	4
6. Difficulty learning new things	0	1	2	3	4
7. Getting mixed up easily	0	1	2	3	4

PAIN AND HURT *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Aches in joints and/or muscles	0	1	2	3	4
2. Having a lot of pain	0	1	2	3	4
3. Getting headaches	0	1	2	3	4

MOVEMENT AND BALANCE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her balance	0	1	2	3	4
2. Difficulty using his/her legs	0	1	2	3	4
3. Difficulty using his/her hands	0	1	2	3	4

PROCEDURAL ANXIETY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Needle sticks (i.e. injections, blood tests, IV's) causing him/her pain	0	1	2	3	4
2. Getting anxious about having blood drawn	0	1	2	3	4
3. Getting anxious about having needle sticks (i.e. injections, blood tests, IV's)	0	1	2	3	4

*In the past **7 days,** how much of a **problem** has your teen had with …*

NAUSEA ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Becoming nauseated during medical treatments	0	1	2	3	4
2. Food not tasting very good to him/her	0	1	2	3	4
3. Becoming nauseated while thinking about medical treatments	0	1	2	3	4
4. Feeling too nauseous to eat	0	1	2	3	4
5. Some foods and smells making him/her nauseous	0	1	2	3	4

WORRY ***(problems with…)***	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. Worrying about side effects from medical treatments	0	1	2	3	4
2. Worrying about whether or not his/her medical treatments are working	0	1	2	3	4
3. Worrying that the cancer will reoccur or relapse	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Módulo de Tumores Cerebrales

Versión 1.0

REPORTE DE LOS PADRES (edades **2- 4)**

INSTRUCCIONES

Algunas veces, los niños(as) con tumores cerebrales tienen problemas especiales. A continuación hay una lista de situaciones que pueden ser un problema para **su hijo(a).** Por favor díganos **qué tanto problema** ha sido cada una de éstas para **su hijo(a)** durante **los últimos siete días.** Por favor circule su respuesta

0 si **nunca** es un problema
1 si **casi nunca** es un problema
2 si **algunas veces** es un problema
3 si **a menudo** es un problema
4 si **casi siempre** es un problema

No hay respuestas correctas o incorrectas.
Si no entiendes una pregunta, por favor pide ayuda.

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

DOLOR Y MOLESTIAS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dolores en las articulaciones y/o músculos	0	1	2	3	4
2. Teniendo mucho dolor	0	1	2	3	4
3. Teniendo dolores de cabeza	0	1	2	3	4

MOVIMIENTO Y EQUILIBRIO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dificultad manteniendo su equilibrio	0	1	2	3	4
2. Dificultad usando las piernas	0	1	2	3	4
3. Dificultad usando las manos	0	1	2	3	4

ANSIEDAD POR PROCEDIMIENTO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Los piquetes de agujas (ej. inyecciones, pruebas de sangre, sueros) le causan dolor	0	1	2	3	4
2. Sintiendo ansiedad porque le van a sacar sangre	0	1	2	3	4
3. Sintiendo ansiedad porque le van a picar con agujas (ej. inyecciones, pruebas de sangre, sueros)	0	1	2	3	4

NÁUSEA ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Sintiendo náuseas durante los tratamientos médicos	0	1	2	3	4
2. La comida no le sabe muy bien	0	1	2	3	4
3. Sintiendo náuseas cuando piensa en los tratamientos médicos	0	1	2	3	4
4. Sintiendose con mucha náusea para comer	0	1	2	3	4
5. Algunos alimentos y olores le provocan náusea	0	1	2	3	4

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

PREOCUPACIONES ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Preocupándose por los efectos secundarios de los tratamientos médicos	0	1	2	3	4
2. Preocupándose acerca de si sus tratamientos médicos están funcionando o no	0	1	2	3	4
3. Preocupándose de que el cáncer regrese o empeore	0	1	2	3	4

ID# _____

Date:_____

PedsQL™

Módulo de Tumores Cerebrales

Versión 1.0

REPORTE de **NIÑOS** (edades **5 – 7)**

Instrucciones para el/ la entrevistador(a):

Te voy a hacer algunas preguntas acerca de cosas que podrían ser un problema para algunos(as) niños(as). Quisiera saber qué tanto problema serían estas cosas para tí.

Muéstrele al/ la niño(a) el dibujo con las caritas y señale las respuestas a medida que las lee.

Si ésto nunca es un problema para tí, señala la cara sonriente

Si ésto algunas veces es un problema para tí, señala la cara de en medio

Si ésto es muchas veces problema para tí, señala la cara enojada

Te voy a leer cada pregunta. Señala los dibujos para enseñarme qué tanto problema es ésto para tí. Vamos a practicar con el primero.

	Nunca	Algunas Veces	Muchas Veces
Es difícil para tí tronar tus dedos	☺	😐	☹

Pídale al niño que le muestre cómo truena sus dedos para determinar si la pregunta fue contestada correctamente o no. Repita la pregunta si el/la niño(a) parece responder de una manera diferente a como actúa.

Piensa en cómo te ha ido en los últimos siete días. Por favor escucha con cuidado
cada oración y dime qué tanto problema ha sido ésto para tí.

Después de leer cada oración, refiérase a los dibujos. Si el niño duda o parece no entender cómo contestar, lea las opciones de respuesta mientras señala las caras.

PROBLEMAS COGNITIVOS ***(problemas con…)***	**Nunca**	**Algunas Veces**	**Muchas Veces**
1. Es difícil para tí saber qué hacer cuando hay algo que te molesta	0	2	4
2. Se te hace difícil usar números o hacer matemáticas	0	2	4
3. Te es difícil poner atención	0	2	4
4. Te es difícil recordar lo que se te lee	0	2	4
5. Te es difícil aprender cosas nuevas	0	2	4
6. Te confundes fácilmente	0	2	4

DOLOR Y MOLESTIAS ***(problemas con…)***	**Nunca**	**Algunas Veces**	**Muchas Veces**
1. Tienes dolores en tus huesos y/o músculos	0	2	4
2. Tienes mucho dolor	0	2	4
3. Te dan dolores de cabeza	0	2	4

MOVIMIENTO Y EQUILIBRIO ***(problemas con…)***	**Nunca**	**Algunas Veces**	**Muchas Veces**
1. Es difícil para tí mantener el equilibrio	0	2	4
2. Es difícil para tí usar las piernas	0	2	4
3. Es difícil para tí usar las manos	0	2	4

ANSIEDAD POR PROCEDIMIENTOS ***(problemas con…)***	**Nunca**	**Algunas Veces**	**Muchas Veces**
1. Te duelen los piquetes de agujas (ej. piquetes, pruebas de sangre, sueros)	0	2	4
2. Te da miedo cuando te tienen que sacar sangre	0	2	4
3. Te da miedo cuando te tienen que picar con agujas (ej. piquetes, pruebas de sangre, sueros)	0	2	4

Piensa en cómo te ha ido en los últimos siete días . Por favor escucha con cuidado
cada oración y dime qué tanto problema ha sido ésto para tí.

NÁUSEA ***(problemas con…)***	**Nunca**	**Algunas Veces**	**Muchas Veces**
1. Te hacen sentirte mal del estómago tus medicinas	0	2	4
2. Te sabe mal la comida	0	2	4
3. Te enfermas del estómago cuando piensas en tus medicinas	0	2	4
4. Te sientes tan mal del estómago que no puedes comer	0	2	4
5. Algunos alimentos y olores te hacen sentir mal del estómago	0	2	4

PREOCUPACIONES ***(problemas con…)***	**Nunca**	**Algunas Veces**	**Muchas Veces**
1. Te preocupas de como tus medicinas te hacen sentir	0	2	4
2. Te preocupa saber si tus medicinas están funcionando o no	0	2	4
3. Te preocupa que la enfermenda del cáncer regrese	0	2	4

¿Cuánto problema es ésto para tí?

Nunca

A Veces

Muchas Veces

ID# _____

Date:_____

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Módulo de Tumores Cerebrales

Versión 1.0

REPORTE DE LOS PADRES (edades **5- 7)**

INSTRUCCIONES

Algunas veces, los niños(as) con tumores cerebrales tienen problemas especiales. A continuación hay una lista de situaciones que pueden ser un problema para **su hijo(a).** Por favor díganos **qué tanto problema** ha sido cada una de éstas para **su hijo(a)** durante **los últimos siete días.** Por favor circule su respuesta

0 si **nunca** es un problema
1 si **casi nunca** es un problema
2 si **algunas veces** es un problema
3 si **a menudo** es un problema
4 si **casi siempre** es un problema

No hay respuestas correctas o incorrectas.
Si no entiendes una pregunta, por favor pide ayuda.

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

PROBLEMAS COGNITIVOS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dificultades sabiendo qué hacer cuando algo le molesta	0	1	2	3	4
2. Dificultades resolviendo problemas de matemáticas	0	1	2	3	4
3. Dificultades poniendo atención	0	1	2	3	4
4. Dificultades recordando lo que se le lee	0	1	2	3	4
5. Dificultades con aprender cosas nuevas	0	1	2	3	4
6. Confundiéndose fácilmente	0	1	2	3	4

DOLOR Y MOLESTIAS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dolores en las articulaciones y/o músculos	0	1	2	3	4
2. Teniendo mucho dolor	0	1	2	3	4
3. Teniendo dolores de cabeza	0	1	2	3	4

MOVIMIENTO Y EQUILIBRIO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dificultad manteniendo su equilibrio	0	1	2	3	4
2. Dificultad usando las piernas	0	1	2	3	4
3. Dificultad usando las manos	0	1	2	3	4

ANSIEDAD POR PROCEDIMIENTO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Los piquetes de agujas (ej. inyecciones, pruebas de sangre, sueros) le causan dolor	0	1	2	3	4
2. Sintiendo ansiedad porque le van a sacar sangre	0	1	2	3	4
3. Sintiendo ansiedad porque le van a picar con agujas (ej. inyecciones, pruebas de sangre, sueros)	0	1	2	3	4

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

NÁUSEA ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Sintiendo náuseas durante los tratamientos médicos	0	1	2	3	4
2. La comida no le sabe muy bien	0	1	2	3	4
3. Sintiendo náuseas cuando piensa en los tratamientos médicos	0	1	2	3	4
4. Sintiendose con mucha náusea para comer	0	1	2	3	4
5. Algunos alimentos y olores le provocan náusea	0	1	2	3	4

PREOCUPACIONES ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Preocupándose por los efectos secundarios de los tratamientos médicos	0	1	2	3	4
2. Preocupándose acerca de si sus tratamientos médicos están funcionando o no	0	1	2	3	4
3. Preocupándose de que el cáncer regrese o empeore	0	1	2	3	4

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Módulo de Tumores Cerebrales

Versión 3.0

REPORTE de **NIÑOS** (edades **8 – 12)**

INSTRUCCIONES

Niños con tumores cerebrales tienen a veces problemas especiales.
Por favor circula èstos y díganos **cuán problemático** ha sido para ti cada uno de éstos durante **los últimos siete días**:

0 si **nunca** es un problema
1 si **casi nunca** es un problema
2 si **algunas veces** es un problema
3 si **a menudo** es un problema
4 si **casi siempre** es un problema

No hay respuestas correctas o incorrectas.
Si no entiendes una pregunta, por favor pide ayuda.

*En los **últimos 7 días**, cuán **problemático** ha sido para tí …*

PROBLEMAS COGNITIVOS *(problemas con…)*	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Me es difícil saber qué hacer cuando algo me molesta	0	1	2	3	4
2. Tengo dificultad resolviendo problemas de matemáticas	0	1	2	3	4
3. Tengo dificultad haciendo tareas y reportes de la escuela	0	1	2	3	4
4. Me es difícil poner atención	0	1	2	3	4
5. Me es difícil recordar lo que leo	0	1	2	3	4
6. Es difícil para mí aprender cosas nuevas	0	1	2	3	4
7. Me confundo fácilmente	0	1	2	3	4

DOLOR Y MOLESTIAS *(problemas con…)*	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Tengo dolores en las articulaciones y/o músculos	0	1	2	3	4
2. Tengo mucho dolor	0	1	2	3	4
3. Tengo dolores de cabeza	0	1	2	3	4

MOVIMIENTO Y EQUILIBRIO *(problemas con…)*	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Es difícil para mí mantener el equilibrio	0	1	2	3	4
2. Es difícil para mí el usar las piernas	0	1	2	3	4
3. Es difícil para mí usar las manos	0	1	2	3	4

ANSIEDAD POR PROCEDIMIENTO *(problemas con…)*	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Los piquetes de agujas (ej. inyecciones, pruebas de sangre, sueros) me duelen	0	1	2	3	4
2. Me da miedo cuando me tienen que sacar sangre	0	1	2	3	4
3. Me da miedo cuando me tienen que picar con agujas (ej. inyecciones, pruebas de sangre, sueros)	0	1	2	3	4

*En los **últimos 7 días**, cuán **problemático** ha sido para tí …*

NÁUSEA ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Me enfermo del estómago cuando tengo tratamientos médicos	0	1	2	3	4
2. La comida no me sabe muy bien	0	1	2	3	4
3. Me enfermo del estómago cuando pienso en los tratamientos médicos	0	1	2	3	4
4. Me siento tan mal del estómago que no puedo comer	0	1	2	3	4
5. Algunos alimentos y olores hacen que me sienta mal del estómago	0	1	2	3	4

PREOCUPACIONES ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Me preocupan los efectos de los tratamientos médicos	0	1	2	3	4
2. Me preocupa saber si los tratamientos médicos están funcionando o no	0	1	2	3	4
3. Me preocupa que el cáncer regrese o empeore	0	1	2	3	4

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Date:_____

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REPORTE DE LOS PADRES (edades **8- 12)**

INSTRUCCIONES

Algunas veces, los niños(as) con tumores cerebrales tienen problemas especiales. A continuación hay una lista de situaciones que pueden ser un problema para **su hijo(a).** Por favor díganos **qué tanto problema** ha sido cada una de éstas para **su hijo(a)** durante **los últimos siete días.** Por favor circule su respuesta

0 si **nunca** es un problema
1 si **casi nunca** es un problema
2 si **algunas veces** es un problema
3 si **a menudo** es un problema
4 si **casi siempre** es un problema

No hay respuestas correctas o incorrectas.
Si no entiendes una pregunta, por favor pide ayuda.

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

PROBLEMAS COGNITIVOS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dificultades sabiendo qué hacer cuando algo le molesta	0	1	2	3	4
2. Dificultades resolviendo problemas de matemáticas	0	1	2	3	4
3. Problemas haciendo tareas y reportes de la escuela	0	1	2	3	4
4. Dificultades poniendo atención	0	1	2	3	4
5. Dificultades recordando lo que lee	0	1	2	3	4
6. Dificultades con aprender cosas nuevas	0	1	2	3	4
7. Confundiéndose fácilmente	0	1	2	3	4

DOLOR Y MOLESTIAS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dolores en las articulaciones y/o músculos	0	1	2	3	4
2. Teniendo mucho dolor	0	1	2	3	4
3. Teniendo dolores de cabeza	0	1	2	3	4

MOVIMIENTO Y EQUILIBRIO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dificultad manteniendo su equilibrio	0	1	2	3	4
2. Dificultad usando las piernas	0	1	2	3	4
3. Dificultad usando las manos	0	1	2	3	4

ANSIEDAD POR PROCEDIMIENTO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Los piquetes de agujas (ej. inyecciones, pruebas de sangre, sueros) le causan dolor	0	1	2	3	4
2. Sintiendo ansiedad porque le van a sacar sangre	0	1	2	3	4
3. Sintiendo ansiedad porque le van a picar con agujas (ej. inyecciones, pruebas de sangre, sueros)	0	1	2	3	4

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

NÁUSEA ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Sintiendo náuseas durante los tratamientos médicos	0	1	2	3	4
2. La comida no le sabe muy bien	0	1	2	3	4
3. Sintiendo náuseas cuando piensa en los tratamientos médicos	0	1	2	3	4
4. Sintiendose con mucha náusea para comer	0	1	2	3	4
5. Algunos alimentos y olores le provocan náusea	0	1	2	3	4

PREOCUPACIONES ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Preocupándose por los efectos secundarios de los tratamientos médicos	0	1	2	3	4
2. Preocupándose acerca de si sus tratamientos médicos están funcionando o no	0	1	2	3	4
3. Preocupándose de que el cáncer regrese o empeore	0	1	2	3	4

ID# _____

Date:_____

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Módulo de Tumores Cerebrales

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REPORTE de **ADOLESCENTES** (edades **13 – 18)**

INSTRUCCIONES

Adolescentes con tumores cerebrales tienen a veces problemas especiales. Por favor circula èstos y díganos **cuán problemático** ha sido para ti cada uno de éstos durante **los últimos siete días**:

0 si **nunca** es un problema
1 si **casi nunca** es un problema
2 si **algunas veces** es un problema
3 si **a menudo** es un problema
4 si **casi siempre** es un problema

No hay respuestas correctas o incorrectas.
Si no entiendes una pregunta, por favor pide ayuda.

*En los **últimos 7 días**, cuán **problemático** ha sido para tí …*

PROBLEMAS COGNITIVOS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Me es difícil saber qué hacer cuando algo me molesta	0	1	2	3	4
2. Tengo dificultad resolviendo problemas de matemáticas	0	1	2	3	4
3. Tengo dificultad haciendo tareas y reportes de la escuela	0	1	2	3	4
4. Me es difícil poner atención	0	1	2	3	4
5. Me es difícil recordar lo que leo	0	1	2	3	4
6. Es difícil para mí aprender cosas nuevas	0	1	2	3	4
7. Me confundo fácilmente	0	1	2	3	4

DOLOR Y MOLESTIAS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Tengo dolores en las articulaciones y/o músculos	0	1	2	3	4
2. Tengo mucho dolor	0	1	2	3	4
3. Tengo dolores de cabeza	0	1	2	3	4

MOVIMIENTO Y EQUILIBRIO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Es difícil para mí mantener el equilibrio	0	1	2	3	4
2. Es difícil para mí el usar las piernas	0	1	2	3	4
3. Es difícil para mí usar las manos	0	1	2	3	4

ANSIEDAD POR PROCEDIMIENTO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Los piquetes de agujas (ej. inyecciones, pruebas de sangre, sueros) me duelen	0	1	2	3	4
2. Me da miedo cuando me tienen que sacar sangre	0	1	2	3	4
3. Me da miedo cuando me tienen que picar con agujas (ej. inyecciones, pruebas de sangre, sueros)	0	1	2	3	4

*En los **últimos 7 días**, cuán **problemático** ha sido para tí …*

NÁUSEA *(problemas con…)*	Nunca	Casi Nunca	Algunas Veces	A Menudo	Casi Siempre
1. Me enfermo del estómago cuando tengo tratamientos médicos	0	1	2	3	4
2. La comida no me sabe muy bien	0	1	2	3	4
3. Me enfermo del estómago cuando pienso en los tratamientos médicos	0	1	2	3	4
4. Me siento tan mal del estómago que no puedo comer	0	1	2	3	4
5. Algunos alimentos y olores hacen que me sienta mal del estómago	0	1	2	3	4

PREOCUPACIONES *(problemas con…)*	Nunca	Casi Nunca	Algunas Veces	A Menudo	Casi Siempre
1. Me preocupan los efectos de los tratamientos médicos	0	1	2	3	4
2. Me preocupa saber si los tratamientos médicos están funcionando o no	0	1	2	3	4
3. Me preocupa que el cáncer regrese o empeore	0	1	2	3	4

ID# _____

Date:_____

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Módulo de Tumores Cerebrales

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REPORTE DE LOS PADRES (edades **13- 18)**

INSTRUCCIONES

Algunas veces, los adolescentes con tumores cerebrales tienen problemas especiales. A continuación hay una lista de situaciones que pueden ser un problema para **su hijo(a).** Por favor díganos **qué tanto problema** ha sido cada una de éstas para **su hijo(a)** durante **los últimos siete días.** Por favor circule su respuesta

0 si **nunca** es un problema
1 si **casi nunca** es un problema
2 si **algunas veces** es un problema
3 si **a menudo** es un problema
4 si **casi siempre** es un problema

No hay respuestas correctas o incorrectas.
Si no entiendes una pregunta, por favor pide ayuda.

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

PROBLEMAS COGNITIVOS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dificultades sabiendo qué hacer cuando algo le molesta	0	1	2	3	4
2. Dificultades resolviendo problemas de matemáticas	0	1	2	3	4
3. Problemas haciendo tareas y reportes de la escuela	0	1	2	3	4
4. Dificultades poniendo atención	0	1	2	3	4
5. Dificultades recordando lo que lee	0	1	2	3	4
6. Dificultades con aprender cosas nuevas	0	1	2	3	4
7. Confundiéndose fácilmente	0	1	2	3	4

DOLOR Y MOLESTIAS ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dolores en las articulaciones y/o músculos	0	1	2	3	4
2. Teniendo mucho dolor	0	1	2	3	4
3. Teniendo dolores de cabeza	0	1	2	3	4

MOVIMIENTO Y EQUILIBRIO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Dificultad manteniendo su equilibrio	0	1	2	3	4
2. Dificultad usando las piernas	0	1	2	3	4
3. Dificultad usando las manos	0	1	2	3	4

ANSIEDAD POR PROCEDIMIENTO ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Los piquetes de agujas (ej. inyecciones, pruebas de sangre, sueros) le causan dolor	0	1	2	3	4
2. Sintiendo ansiedad porque le van a sacar sangre	0	1	2	3	4
3. Sintiendo ansiedad porque le van a picar con agujas (ej. inyecciones, pruebas de sangre, sueros)	0	1	2	3	4

*En los **últimos 7 días,** qué tanto **problema** tuvo su hijo(a) con…*

NÁUSEA ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Sintiendo náuseas durante los tratamientos médicos	0	1	2	3	4
2. La comida no le sabe muy bien	0	1	2	3	4
3. Sintiendo náuseas cuando piensa en los tratamientos médicos	0	1	2	3	4
4. Sintiendose con mucha náusea para comer	0	1	2	3	4
5. Algunos alimentos y olores le provocan náusea	0	1	2	3	4

PREOCUPACIONES ***(problemas con…)***	**Nunca**	**Casi Nunca**	**Algunas Veces**	**A Menudo**	**Casi Siempre**
1. Preocupándose por los efectos secundarios de los tratamientos médicos	0	1	2	3	4
2. Preocupándose acerca de si sus tratamientos médicos están funcionando o no	0	1	2	3	4
3. Preocupándose de que el cáncer regrese o empeore	0	1	2	3	4