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July 22, 2022

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #7 to protocol **ADVL1521**, *A Phase 2 Study of the MEK inhibitor Trametinib (NSC# 763093) in Children with Relapsed or Refractory Juvenile Myelomonocytic Leukemia.*

Amendment #7 is in response to Mr. Howells' May 23, 2022 Request for Amendment regarding updates to the trametinib tablet formulation pharmaceutical information. The protocol was updated to reflect this change.

Please let me know if you have any questions or need additional information.

Sincerely,

Christine Petrossian, Associate Director (for)

Elliot Stieglitz, M.D., **ADVL1521** Study Chair
Brenda J. Weigel, MD, COG Developmental Therapeutics Chair

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SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol.
Additions are in boldfaced font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	-	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Table of Contents	3-4	Updated for re-pagination.
4.	6.1	49	Updated drug monograph date
5.	6.1	54-55	Revised formulation and stability to include additional details regarding investigationally-labeled bottles and commercially-labeled bottles.
6.	6.1	55	Added clarification for water for irrigation during reconstitution of powder.

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Activated: 10/06/17 Version Date: 07/22/22
Closed: Amendment #: 7

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ADVL1521

A Phase 2 Study of the MEK inhibitor Trametinib (NSC# 763093) in Children with Relapsed or Refractory Juvenile Myelomonocytic Leukemia

A Groupwide Phase 2 Study limited to the United States

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CHILDREN'S ONCOLOGY GROUP

CONTACT INFORMATION		
For Regulatory Requirements	**For patient enrollments:**	**For Data Submission**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://open.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (ie, patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (ie, unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT	NSC#	IND#
Trametinib	NSC#763093	

IND Sponsor:
DCTD, NCI

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SEE SECTION 7.2 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

Juvenile myelomonocytic leukemia (JMML) is an aggressive myeloproliferative disorder of childhood. The biochemical hallmark of JMML is aberrant signaling through the Ras pathway caused by initiating mutations in *NF1, NRAS, KRAS, RRAS, RRAS2, PTPN11* and *CBL*. The only known cure for JMML is hematopoietic stem cell transplantation (HSCT), yet 5-year event free survival after transplant is only ~50%, with relapse being the most common cause of morbidity and mortality.

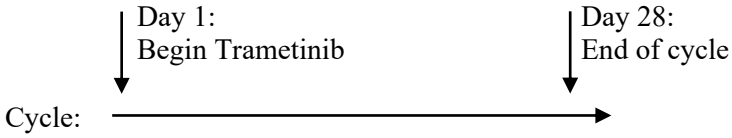
Trametinib is an orally bioavailable, reversible, highly selective allosteric inhibitor of MEK1/2 which is downstream of Ras/MAPK signaling. Trametinib is FDA-approved for the treatment of adults with advanced melanoma with a BRAF V600E or V600K mutation. It is currently being investigated in over 50 trials as a single agent or in combination with other targeted/cytotoxic therapies in patients with a variety of solid tumors and hematologic malignancies. This trial will evaluate the activity of trametinib in children and adolescents with relapsed or refractory JMML. The planned starting dose is 0.032 mg/kg/day for children aged 1 month to < six years of age and 0.025 mg/kg/day for children six years of age and older. These are the recommended phase 2 doses (RP2D) that were established in a pediatric trial for children with solid tumors. No further dose escalation is planned.

Based on the genetics and predicted biochemical sequelae of increased signaling through the Ras/MAPK pathway, MEK inhibition is a logical treatment approach for patients with JMML. We will collect sequential samples from all patients enrolled to assess the clinical and molecular response at study entry and at disease progression if applicable. This trial will provide an opportunity to interrogate the genetic, biochemical, and functional perturbations of response and resistance to trametinib in patients with JMML.

The primary objective of this study is to determine the response rate to trametinib after twelve cycles of therapy in children with relapsed/refractory JMML. Secondary objectives are (1) to further define and describe the toxicities of trametinib administered as monotherapy (2) to further characterize the pharmacokinetics (steady state trough concentration) of trametinib in children with JMML (3) to prospectively evaluate mutant allele burden as a marker of disease activity in JMML (4) to measure the rate of complete responses in children with JMML and (5) to measure the duration of response among responders.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schema:



*Trametinib is administered orally.

A cycle of therapy is 28 days. Therapy may consist of up to 12 cycles, for a total duration of therapy approximating 12 months, absent disease progression or unacceptable toxicity.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To determine the objective response rate to trametinib in children with recurrent or refractory Juvenile Myelomonocytic Leukemia (JMML).

1.2 Secondary Aims

1.2.1 To further define and describe the toxicities of single agent trametinib in children with recurrent or refractory JMML.

1.2.2 To further characterize the pharmacokinetics of trametinib in children with recurrent or refractory JMML.

1.2.3 To prospectively evaluate mutant allele burden as a marker of disease activity in JMML.

1.2.4 To measure the rate of complete responses in children with recurrent or refractory JMML.

1.2.5 To measure the duration of response among responders.

1.3 Exploratory Aims

1.3.1 To describe the distribution of JMML diagnostic criteria in children with recurrent or refractory JMML.

2.0 BACKGROUND

2.1 Rationale for Development

Whereas many pediatric cancers are curable, the outcome remains dismal for patients with JMML. Following high dose chemotherapy and allogeneic hematopoietic stem cell transplant (HSCT), relapse occurs in about half of patients, with death resulting from progressive infiltration of myeloid cells into major organs or transformation to an incurable secondary acute leukemia.[2] Moreover, the quality of life for patients with JMML is compromised by massive splenomegaly, failure to thrive, chronic anemia and thrombocytopenia. Innovative new approaches to treat and cure this devastating disorder are needed.

2.1.1 Defining the Genetic Basis of JMML

The association between JMML and certain inherited syndromes advanced understanding of both disorders. The incidence of JMML is increased 200-500 fold in neurofibromatosis type 1 (NF1).[3] *NF1* encodes neurofibromin, a GTPase activating protein (GAP) for Ras, which negatively regulates Ras output.[4] Noonan syndrome (NS) is characterized by multiple developmental defects, and some patients develop a transient JMML-like myeloproliferative neoplasm (MPN).[5] The discovery of germline missense mutations in the *PTPN11* in ~50% of NS[6] patients proved critical for understanding the associated transient MPN and led to the discovery that somatic *PTPN11* mutations are the most common cause of JMML.[7] [8] The discovery of homozygous *CBL* mutations in JMML led to further investigations demonstrating that such lesions are usually heterozygous germline events with somatic loss of heterozygosity in the hematopoietic compartment, similar to what occurs in *NF1* mutated JMML. [9] In total, 95% of patients with JMML harbor mutations in genes that regulate the Ras pathway: *PTPN11* 40%, *NRAS/KRAS/RRAS/RRAS2* 35%, *NF1* loss 10% [10] and homozygous *CBL* 10%. [7,11-15] The majority of these mutations are mutually exclusive in individual patients, which suggests that these aberrant proteins act as drivers, encoding components of a conserved biochemical network that regulates the proliferation, differentiation, and survival of cancer initiating stem cells (HSC) and their progeny. However, recent analyses have shown that certain JMML patients will harbor compound mutations in Ras related genes and others and that they have a higher risk of relapse compared to patients with a single Ras pathway mutation. Emerging targeted therapies for JMML are based on findings that Ras pathway mutations drive disease.[16] In the absence of viable strategies to directly inhibit Ras-GTP, targeting the RAF-MEK-ERK pathway is a rational treatment approach for JMML.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Mx1-Cre, Nf1$^{flox/flox}$ mice and *Mx1-Cre, Kras*^{G12D} mice develop an MPN with many similarities to JMML.[17] [18] Treatment with the MEK inhibitor PD0325901 in these *Nf1* and *Kras* mutant mice induced a durable decrease in leukocyte counts, enhanced erythropoietic function, reduced spleen size and prolonged

survival. MEK inhibition restored a normal pattern of erythroid differentiation, reduced extramedullary hematopoiesis, and normalized aberrantly increased early progenitors, including the stem-like KLS (c-Kit$^+$ lin$^-$Sca-1$^+$) cells, which are likely required for leukemia initiation and maintenance.[19,20] Genetic analysis revealed persistence of mutant hematopoietic cells, indicating that MEK inhibition modulates the proliferation and differentiation of mutant cells *in vivo* rather than eliminating them. Similar responses were seen in *Nf1* and *Kras* mutant mice treated with the MEK inhibitor trametinib (T. Chang, unpublished data). In primary human cells, MEK inhibitors abrogate the classic JMML features of hypersensitivity of myeloid progenitors to granulocyte-macrophage colony stimulating factor (GM-CSF), which functionally supports a behavioral shift in cytokine sensitive myelopoiesis.

2.2.2 Animal Toxicology

In juvenile rat toxicity studies, there were dose-dependent effects on growth (body weight and long bone length), bone (physeal thickening), serum phosphorus (increased), eye (corneal mineralization/dystrophy), skin, liver, heart (increased heart weight) and the female reproductive system (delay in a physical landmark of sexual maturity and mammary gland development, lower corpora lutea and ovarian weights). All of the female reproductive effects were reversible. With the exception of the heart and eye findings, similar effects have been observed in adult animals given trametinib.

In bone, physeal thickening was reversible following a recovery period. Bone changes may be associated with inhibition of MEK-dependent fibroblast growth factor (FGF) signaling, as similar effects have been observed in rats given a small molecule inhibitor of FGF receptor (FGFR) tyrosine kinase[21] as well as in FGFR-3-deficient mice[22]. Unlike in adults, where bone growth has completed and the physeal plates have closed, children (2 to 11 years of age) and adolescents (12 to <18 years of age) may represent sensitive populations to chronic MEK inhibitor treatment, manifested as decreased growth velocity.

Gonadal maturation and development is a potentially sensitive process in children who have yet to reach sexual maturity. In female rats given trametinib at subclinical exposures, ovarian function perturbations were observed, including increases in cystic follicles and decreases in cystic corpora lutea. Pharmacologic inhibition of MEK activity in ovarian granulosa cell cultures blocked ovulatory gene expression, follistatin signaling and granulosa cell survival,[23-25] indicating a potential role of MEK in folliculogenesis. In juvenile rats, similar ovarian findings occurred, as well as delays in onset of physical hallmarks of sexual maturity and mammary gland development. Therefore, onset of female reproductive maturation is a theoretical concern in pediatric populations receiving trametinib.

2.2.3 Preclinical Pharmacology

Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in the bone marrow of rats.[26]

2.3 Adult Studies

2.3.1 Adult Phase I Studies

A phase 1/2 trial of single agent trametinib in adults with *RAS* mutated, multiply relapsed or refractory myeloid malignancies (n=57) demonstrated a 21% response rate compared with a 3% response rate in patients with *RAS* wild-type or unknown leukemia (n=30). Hepatic toxicities (9%), gastrointestinal disorders (7%) and rash (5%) were the most frequent Grade 3/4 AEs. AEs possibly related to inhibition of MEK signaling were blurred vision (total, 13%; Grade 3, 1%) and decreased cardiac ejection fraction (total, 9%; Grade 3, 6%).[27]

The Maximum Tolerated Dose (MTD) of trametinib in adults is 3 mg once daily, and the RP2D of trametinib is 2 mg once daily. Five monotherapy studies administered trametinib 2 mg daily to 499 adult subjects. The most common adverse events were rash, diarrhea, fatigue, peripheral edema, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin. In these studies, up to 32% of subjects reported serious AEs (SAEs), and up to 13% permanently discontinued study treatment due to AEs. Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (observed with other MEK inhibitors) or potentially life-threatening.

Cardiac-related adverse events are known to occur in adults treated with trametinib. In a phase 2 trial, patients (n=97) underwent serial assessment of LVEF, three patients (3%) developed asymptomatic and reversible Grade 3 LVEF reduction.[28] In a phase 3 trial comparing trametinib versus dacarbazine plus paclitaxel, 14 of the 211 patients who received at least one dose of trametinib developed cardiac-related adverse events (7%), 11 developed decreased LVEF, and three had LV dysfunction.[29] Cardiomyopathy resolved in 10 of the 14, but four patients had serious cardiac-related events that were considered to be drug-related and led to permanent discontinuation of the study drug. Across clinical trials of trametinib at the recommended adult dose (2 mg daily), approximately 11% of patients have developed evidence of decrease in LVEF below the institutional lower limits of normal with an absolute decrease in LVEF ≥10% below baseline; 5% have developed decrease in LVEF below the institutional lower limits of normal with an absolute decrease in LVEF of ≥20% below baseline.[30]

Ocular effects and visual impairments, including central serous retinopathy (CSR), retinal pigment epithelium detachment, and retinal vein occlusion (RVO), are reported with trametinib as well as other MEK inhibitors in clinical development. At the 2 mg daily dose, 14% to 18% of the subjects in three clinical trials experienced visual disorders. The majority of these were Grades 1 or 2 in severity (71% to 93%); 7% to 29% of subjects experienced Grade 3 and none experienced Grade 4 visual disorders. With the exception of Grade 3 RVO and Grade 2 CSR, all cases were reversible with or without drug interruption. CSR is a visual impairment due to fluid accumulation under the retina, which causes blurry vision. As of September 18th 2014, 17 (1.2%) cases of CSR have been reported amongst subjects treated with trametinib, either as monotherapy or in combination with other anti-cancer agents. Two cases (0.3%) of RVO have been

observed with trametinib, of which one case was considered drug-related. (5.6.7.2. Investigator Brochure).

2.3.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

In adults, the mean trametinib area under the concentration-time curve over the dosing interval (AUC0-τ) and Cmax increased in a dose proportional manner. The trametinib terminal half-life was 5.3 days with steady state achieved by Day 15. In adults receiving the recommended phase 2 trametinib for 15 days (n=13) the geometric mean (coefficient of variation [CV] %) AUC (0-24h) was 370 (22%) ng h/mL, Cmax 22.2 (28%) ng/mL, Tmax 1.75 (range 1-3), and Cτ 12.1 (19%, 95% CI 10.9, 13.4 ng/mL). An oral liquid formulation (0.05 mg/mL) had similar bioavailability to the trametinib tablet (0.125, 0.5, 2 mg) formulation. Single dose administration of trametinib as a 2 mg oral solution compared to the oral tablet resulted in a 10% increase in AUC (0-last).

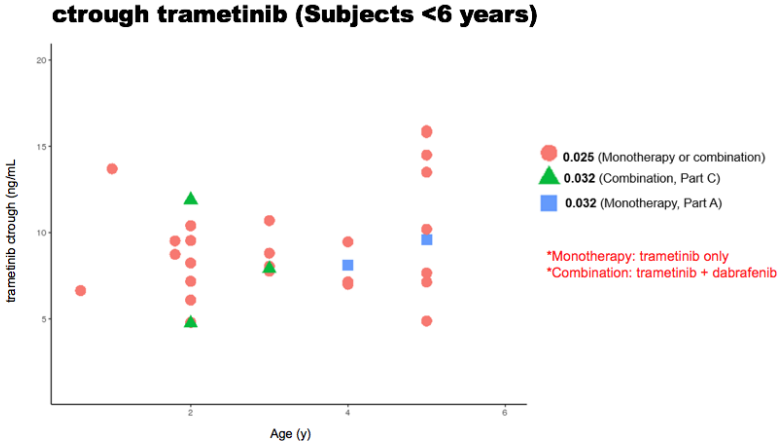
2.3.3 Efficacy (Phase 2 and 3 studies)

Data from phase 1, 2 and 3 studies indicate substantial clinical activity of trametinib in unresectable, BRAF mutation positive melanoma[31-33]. The pivotal phase 3 study, MEK114267 (METRIC), showed significant improvement in 6 month overall survival (OS, 81% vs 67%, P=0.01) and progression-free survival (PFS, 4.8 months versus 1.5 months, P<0.001) in favor of trametinib over standard dacarbazine or paclitaxel chemotherapy in the treatment of patients with advanced or metastatic BRAF V600E/K mutation positive melanoma.[34,35]

2.4 Pediatric Studies

2.4.1 Pediatric Phase 1 Studies

A 3-part phase 1/2, open-label, multicenter study of trametinib in pediatric subjects 1 month or older with recurrent or refractory tumors (NCT02124772) is underway. Results from part A, the dose escalation portion of the study which included 40 subjects has been presented in abstract form.[36] Dose limiting toxicity (rash and mucositis) occurred in 5/15 patients (33.3%) receiving 0.04 mg/kg/dose, whereas a dose of 0.025 mg/kg resulted in dose limiting toxicity in 3/19 (16%) patients. However, more than 50% of patients under the age of 6 receiving a dose of 0.025mg/kg were noted to have steady state trough levels (see 'ctrough trametinib' table below) below the target level established in adults with melanoma treated at the approved trametinib dose that is associated with efficacy (ctrough of ~11 ng/mL).



A dose of 0.032 mg/kg/dose was therefore evaluated in 12 patients under the age of 6 and there were no dose limiting toxicities. Ten of those 12 patients are still on treatment (range of 3-18 months) and two patients experienced progression of disease and have come off therapy. Steady state trough levels are not yet available for all 12 patients treated at 0.032 mg/kg/day (3 patients are included above) but there has been a linear trend in terms of pharmacokinetic troughs and previous dose levels. The recommended phase 2 dose, based on this exposure and tolerability data, is therefore 0.032 mg/kg per day in children one month to < six years of age and 0.025mg/kg/dose for children six years and older.

No significant safety concerns specific to pediatric patients were noted in a preliminary analysis beyond what is already known from prior adult studies including in patients between 1 month and 6 years of age. In particular, the only

serious adverse event in the 12 patients under 6 years of age treated at 0.032 mg/kg/day was mitral valve regurgitation in one patient who had received trametinib for 6 months which resolved after holding treatment and the patient has since resumed trametinib at 0.025 mg/kg/day without further toxicity. In total there have been 5 patients who are 2 years of age or younger (including two infants, 5 and 6 months of age) who have been treated at 0.032 mg/kg/day or 0.04 mg/kg/day. There has been one serious adverse event (seizures) which was deemed unrelated to trametinib in a patient with a brain tumor and pre-existing seizure disorder. There have been no dose limiting toxicities in these 5 patients, 2 years of age or younger or adverse events not previously seen in older patients (personal communication, Novartis).

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies
This data is not yet available from the ongoing pediatric phase 1 study in children with solid tumors.

2.5 Overview of Proposed Pediatric Phase 2 Trial

This trial will enroll children with relapsed/refractory JMML, and evaluate objective response using JMML-specific response criteria[37] (see Appendix III). Participants will also be evaluated for toxicity using CTCAE v5. Stopping rules for toxicity and response are included in the statistical section. Patients will receive oral trametinib daily in continuous 28-day cycles at the recommended phase 2 dose (RP2D) established in an ongoing industry-sponsored trial (NCT02124772) of trametinib in pediatric patients with relapsed/refractory solid tumors. The RP2D is 0.032 mg/kg per day for children one month to < six years of age and is 0.025 mg/kg per day for children six years of age and older. A single dose reduction (see section 5.0 and dosing nomogram in Appendix II) will be permitted in individual patients who experience DLT and have evidence of clinical benefit and is assessed per the investigator (i.e., improvement in leukemia-related symptoms, reduction in transfusion frequency, reduction or clearance of peripheral blasts). Minimal residual disease (MRD) testing using mutant allele frequency will be performed at baseline and after the first cycles of therapy and every odd other cycle thereafter (3, 5, 7, etc.). Pharmacokinetics will be obtained on Days 1 and 15 at hours 0 and 4. Optional correlative pharmacodynamic studies (see Section 7.0) will be conducted to determine the effect of single-agent trametinib on Ras signaling. In the absence of toxicity, patients who do not experience clinical or genetic progressive disease (cPD or gPD) as defined in Table 2 of Appendix III, can be treated for up to 12 cycles (approximately 1 year). Ten to twenty-four participants will be enrolled on this trial.

2.6 Rationale for Amendment #1- Dosing and Reduced Age Range

With Amendment #1, the protocol has been updated to include a lower age range eligibility from 2 years to 1 month. The lower age limit is based on safety data from a phase 1 pediatric study (NCT02124772) using trametinib in children with solid tumors. Additionally, patients under six years of age will be dosed at 0.032 mg/kg per day. The higher dose for children under six years is based on pharmacokinetic data from the same study (NCT02124772) indicating that children under six years of age require higher doses to achieve therapeutic levels. Therefore, the RP2D is 0.032 mg/kg per day for children one month to < six years of age and is 0.025 mg/kg per day for children six years of age and older.

2.7 Rationale for Amendment #3

Historically, the period for determination of best response in phase 2 studies of acute leukemia has been 2-4 cycles. When the protocol for ADVL1521, the first trial in COG for relapsed JMML, was originally written, the 4 cycle period was used by default. However, recognizing that JMML is an overlapping myelodysplastic / myeloproliferative disorder of childhood and not an acute leukemia, we now believe that 12 cycles (the maximum number of cycles permitted on this study) is the most appropriate time frame to assess for responses in this chronic condition. The only other study assessing for responses in relapsed JMML is a retrospective analysis of azacitidine. All three of the patients that achieved a complete response to azacitidine required at least 6 cycles of therapy reflecting the chronic nature of the disease and the treatment.[1] Any patients enrolled at the time this amendment is approved would be affected by this change in the statistical design.

3.0 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

NOTE: In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB

Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be submitted to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. However, these sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study so that the study approval can be applied to those institutions. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system. Patients must be enrolled within 5 calendar days of making a reservation.

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

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

   Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions: https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.1.4 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.5 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 7 business days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible and will not be able to receive further protocol therapy.**

See Section 3.2 for timing requirements for eligibility studies and for timing requirements for baseline studies to be obtained prior to start of therapy. **Note: Repeat laboratory and imaging studies may be required if enrollment and start of therapy do not occur on the same day.**

Institutions are advised to plan ahead to ensure adequate and timely delivery of the investigational agent (see Section 6.1 for details).

3.1.6 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.2 Eligibility: Inclusion Criteria

Important note: The inclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Bone marrow aspirate (and biopsy, if applicable), must be obtained within 2 weeks prior to start of protocol therapy. If a bone marrow aspirate cannot be obtained, the patient is not eligible for enrollment.

3.2.1 Age: Patients must be ≥ 1 month and < 22 years of age at the time of study entry.

3.2.2 Diagnosis: Patients must have had histologic verification of juvenile myelomonocytic leukemia (JMML) at original diagnosis and currently have relapsed or refractory disease. The diagnosis is made based on the following criteria.

3.2.2.1 JMML Category 1 (all of the following):*
- Splenomegaly
- > 1000 ($1x10^9$/μL) circulating monocytes
- < 20% Blasts in the bone marrow or peripheral blood
- Absence of the t(9;22) or BCR/ABL fusion gene

*The diagnostic criteria must include all features in category 1 and EITHER (i) one of the features in Category 2 OR (ii) two features from Category 3 to make the diagnosis.

3.2.2.2 JMML Category 2 (at least one of the following if at least two Category 3 criteria are not present):
- Somatic mutation in *RAS* or *PTPN11*
- Clinical diagnosis of NF1 or *NF1* gene mutation
- Homozygous mutation in *CBL*
- Monosomy 7

3.2.2.3 JMML Category 3 (at least two of the following if no Category 2 criteria are met):
- Circulating myeloid precursors
- White blood cell count, >10 000 ($10x10^9$/ μL)
- Increased Hemoglobin F for age
- Clonal cytogenetic abnormality
- GM-CSF hypersensitivity

3.2.3 Disease Status for Juvenile Myelomonocytic Leukemia (JMML) Patients:

3.2.3.1 Patients with refractory or relapsed JMML must have had at least one cycle of intensive frontline therapy or at least 2 cycles of a DNA demethylating agent with persistence of disease, defined by clinical symptoms or the presence of a clonal abnormality. Frontline therapy is defined as one cycle of intravenous chemotherapy that includes of any of the following agents: fludarabine, cytarabine, or any anthracycline but specifically excludes oral 6-mercaptopurine. Frontline therapy will also include any conditioning regimen as part of a stem cell transplant. Patients who transform to AML at any point with more than 20% blasts are not eligible for this trial.

3.2.3.2 Performance Level

Patients must have a Lansky or Karnofsky performance status score of ≥ 50, corresponding to ECOG categories 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
(See https://members.childrensoncologygroup.org/prot/reference_materials.asp)

3.2.4 Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to study enrollment.

a. Myelosuppressive chemotherapy:
Patients must have completely recovered from all acute toxic effects of chemotherapy, immunotherapy or radiotherapy prior to study enrollment. At least 14 days must have elapsed since the completion of cytotoxic therapy, with the exception of hydroxyurea.

Note: Cytoreduction with hydroxyurea can be initiated and continued for up to 24 hours prior to the start of protocol therapy.

b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g., pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

c. Biologic (anti-neoplastic agent): At least 7 days must have elapsed since completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period prior to enrollment must be extended beyond the time during which adverse events are known to occur.

d. Monoclonal antibodies:

   i. At least 30 days after the completion of any type of immunotherapy, e.g. tumor vaccines.

   ii. At least 3 half-lives must have elapsed since prior therapy that included a monoclonal antibody. (See posting of half-lives for commonly used monoclonal antibodies on the DVL homepage (https://members.childrensoncologygroup.org/Disc/devtherapeutics/default.asp).

e. Radiotherapy:

   i. ≥ 2 weeks must have elapsed since local palliative XRT (small port)

   ii. ≥ 6 months must have elapsed if prior craniospinal XRT was received, if ≥ 50% of the pelvis was irradiated, or if TBI was received

   iii. ≥ 4 weeks must have elapsed if other substantial bone marrow irradiation was given.

f. Stem Cell Transplant or Rescue without TBI: No evidence of active graft vs. host disease and ≥ 3 months must have elapsed since transplant. ≥ 4 weeks must have elapsed since any donor lymphocyte infusion.

3.2.5 Organ Function Requirements

3.2.5.1 Adequate Bone Marrow Function Defined As:

- Patients must not be known to be refractory to red blood cell or platelet transfusions.

3.2.5.2 Adequate Renal Function Defined As:

- Creatinine clearance **or** radioisotope GFR ≥ 70 mL/min/1.73 ^{m2} **or** a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC. [38]

3.2.5.3 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 3 x ULN (135 U/L (for the purpose of this study, the ULN for SGPT is 45 U/L)
- Serum albumin ≥ 2 g/dL.

3.2.5.4 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram OR Ejection fraction of ≥ 50% by MUGA
- Corrected QT (QTcB) interval <450 msecs

3.2.6 Patients must be able to swallow tablets or liquid; use of a nasogastric or G tube is also allowed.

3.3 Eligibility: Exclusion Criteria

Important note: The exclusion criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record. These source documents must be available for verification at the time of audit.

3.3.1 Pregnancy or Breast-Feeding

Patients who are pregnant or breast-feeding are not eligible for this study as there is yet no available information regarding human fetal or teratogenic toxicities. Negative pregnancy tests must be obtained in girls who are post-menarchal. Patients of reproductive potential may not participate unless they have agreed to

use an effective contraceptive method for the duration of study therapy. Women of childbearing potential should be advised to use effective contraception for 4 months after the last dose of trametinib. Trametinib may also potentially be secreted in milk and therefore breastfeeding women are excluded. Female patients should not breastfeed during treatment with trametinib, and for 4 months following the last dose. Male patients must use a condom during intercourse and agree not to father a child during therapy and for 4 months following discontinuation of trametinib to avoid unnecessary exposure of trametinib to the fetus.

3.3.2 Concomitant Medications (Please see Section 4.1 for the concomitant therapy restrictions for patients during the study).3.3.2.1 Corticosteroids: Patients requiring corticosteroids who have not been on a stable or decreasing dose of corticosteroid for the 7 days prior to enrollment are not eligible. If used to modify immune adverse events related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

Note: hydrocortisone used as a pre-medication to prevent transfusion related reactions is not considered a concomitant corticosteroid.

3.3.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

3.3.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except patients receiving hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy].

3.3.2.4 Anti-GVHD or agents to prevent organ rejection post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant are not eligible for this trial.

3.3.2.5 Cardiac Medications: Any medications for treatment of left ventricular systolic dysfunction.

3.3.3 Infection:Patients who have an uncontrolled infection are not eligible.

3.3.4 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

3.3.5 Veno-occlusive Disease: Patients with a history of hepatic sinusoid obstructive syndrome (veno-occlusive disease) within the prior 3 months are not eligible.

3.3.6 Patients with a history of or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) are not eligible.

3.3.6.1 Ocular Conditions: Patients with a history of RVO or CSR, or predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension.

3.3.7 Systemic Diseases: Patients with uncontrolled systemic disease(s) such as hypertension or diabetes mellitus are not eligible. Blood pressure must be ≤ the 95th percentile for age, height, and gender (Appendix IX) measured as described

in Section 5.4.9.1.

3.3.8 Allergic Reactions: Patients with a history of allergic reaction attributed to compounds of similar chemical or biologic composition to the MEK inhibitor, trametinib are not eligible.

3.3.9 Noonan Syndrome: Patients with a clinical diagnosis of Noonan syndrome are not eligible. **Note:** patients with Casitas B-lineage lymphoma (CBL) syndrome, also known as Noonan-like syndrome, are eligible to enroll.

3.4 Regulatory

3.4.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.4.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

A single-arm open label study, with trametinib administered at 0.032 mg/kg/dose (< 6 years of age) and 0.025 mg/kg/dose (≥ 6 years of age) with a maximum of 2 mg orally once daily on a continuous 28-day cycle, for up to 12 total cycles. Dosing will be performed based on weight in kilograms (kg) obtained within 7 days of starting each cycle. For patients (< 6 years of age) who receive 0.032 mg/kg/dose, in the absence of dose limiting toxicity, their dose will remain 0.032 mg/kg/dose for up to 12 cycles even if they become 6 years of age during protocol therapy.

4.1.1 Dose Reduction

A single dose reduction (25% dose reduction for patients receiving oral solution and see Appendix II for tablet formulation dose reductions) will be allowed for toxicities as outlined in Section 5.0 for patients who recover to starting criteria as outlined in Section 3.2 within 7 days following planned administration.

4.1.2 Dose Escalation

There will be no drug dose escalation.

4.1.3 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient does not meet criteria for progressive disease (PD) (See Section 10.2 and Appendix III), and required pre-cycle assessments (see Therapy Delivery Maps Sections 4.2, 4.3 and 4.4) have

again met laboratory parameters defined in the eligibility section, Section 3.2.5. Note: albumin is not required for starting subsequent cycles.

4.1.4 Concomitant Therapy

4.1.1.1 No other cancer chemotherapy, radiotherapy, or immunomodulating agents will be used.

4.1.1.2 Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Nausea and vomiting has been observed commonly in adult patients treated with trametinib. It is recommended to provide all patients a 5-HT_3-receptor antagonist (e.g., ondansetron or granisetron) at the start of treatment to be used as needed or prophylactically. In the event of breakthrough nausea/vomiting, additional antiemetics may be added as needed.

4.1.5 Study Specific Supportive Care:

Prophylactic Treatment for prevention of dermatologic toxicity is:

1. Broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily.
2. Thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
3. Mild strength topical steroid (e.g., hydrocortisone 1% cream) and topical antibiotics (e.g., clindamycin) applied at least twice daily starting on Day 1 of study treatment, to body areas such as face, chest and upper back with escalation to higher strength and/or oral steroid as detailed in Section 5.4.
4. Triamcinolone acetonide 0.1% dental paste for oral sores that arise while receiving study medication.
5. Non-alcohol containing mouth rinse (e.g. Biotene, Peridex, or biosimilars) for patients experiencing mouth sores related to swallowing study drug.

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.1.6 Study Specific Ophthalmologic Exams

An age-appropriate ophthalmologic examination that avoids any sedation should be performed by an ophthalmologist at baseline, at the end of Cycle 1, and every 12 weeks thereafter, while on study. This includes a Snellen examination (if age appropriate as determined by the investigator). The examination must include a funduscopic evaluation to rule out retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED), can be dilated or non-dilated at discretion of ophthalmologist and can be accomplished using imaging with a non-mydriatic fundus camera.

4.2 Cycle 1

4.2.1 Therapy Delivery Map – Cycle 1 This therapy Delivery Map (TDM) relates to Cycle 1. Each cycle lasts 28 days.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 3.2.5. Treatment details are provided in Section 4.2.3.
This treatment delivery map is **two (2)** pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Trametinib Do not use commercial supply	PO	Age-based dosing: < 6 years= 0.032 mg/kg/dose ≥ 6 years = 0.025 mg/kg/dose Max dose= 2 mg	Daily	See Appendix II for tablet formulation dosing nomogram.

Enter Cycle #: _____Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**Trametinib** ____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg	a-f, (g-p)*, q, r%
		2	_____mg	
		3	_____mg	
		4	_____mg	d
		5	_____mg	
		6	_____mg	
		7	_____mg	
		8	_____mg	a, d, e
		9	_____mg	
		10	_____mg	
		11	_____mg	d
		12	_____mg	
		13	_____mg	
		14	_____mg	
		15	_____mg	a, d, e, q
		16	_____mg	
		17	_____mg	
		18	_____mg	d
		19	_____mg	
		20	_____mg	
		21	_____mg	
		22	_____mg	a, d, e
		23	_____mg	
		24	_____mg	
		25	_____mg	d
		26	_____mg	
		27	_____mg	
		28	_____mg	(a, d, e, g-m, r)#
		29	#Following the completion of Cycle 1 therapy, perform the disease evaluations a, d, e, g-m, and r within 3 days, and prior to the start of the next cycle. Please continue onto the next cycle no later than 14 days from the end of the previous cycle. The next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.5), whichever occurs later.	

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Cycle 1

4.2.2 Required Observations in Cycle 1

All baseline observations must be collected prior to starting protocol therapy unless otherwise indicated below. All other observations can be collected within ± 1 day of their prescribed due date.

***For Day 1 observations, g- p samples may be collected up to 14 days prior the start of therapy.**
%JMML panel for mutant allele burden may be collected up to 14 days prior to the start of therapy if sent as a correlative biology study on this trial or up to 30 days prior to the start of therapy if the same test was ordered as fee-for-service and processed at UCSF.

a. Physical exam (including VS with triplicate BPs), and adverse events
b. Concomitant medications
c. Performance status
d. CBC, differential, platelets (see Section 7.2 for details regarding Central Review).
e. Electrolytes including Ca^{2+}, Mg^{2+}, and PO_4, BUN and creatinine, creatine kinase bilirubin (total and direct), AST, and ALT
f. Dermatologic exam. Performed by the treating physician (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam throughout the study. Photographs of suspect lesions at baseline are recommended. Photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits
g. An age-appropriate ophthalmologic examination with a funduscopic evaluation that avoids any sedation to be performed by an ophthalmologist at baseline. This includes a Snellen examination (if age appropriate as determined by the investigator). See Section 4.1.6
h. Peripheral blood smear (See Section 7.2 for details regarding Central Review)
i. BMA/clot section or biopsy and aspirate smear (see Section 7.2 for details regarding Central Review)
j. BMA cytogenetics and FISH (It is recommended that cytogenetics/FISH be performed by a COG-approved laboratory)
k. For patients that consent, collect bone marrow for Genomic, Epigenomic, and Functional assays (see Section 7.3.3)
l. Echocardiogram or MUGA
m. ECG
n. CSF for cell count, cytospin (lumbar puncture only required if clinical suspicion of CNS involvement)
o. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test
p. Imaging (CT or MRI) of chloroma (if present)
q. For patients that consent, collect peripheral blood for Pharmacokinetic and Pharmacodynamic studies (see Section 7.4.1)
r. Peripheral blood sample for the JMML panel using mutant allele burden (see Section 7.3.1)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Cycle 1

Comments
(Include any held doses, or dose modifications)

Cycle 1

4.2.3 Treatment Details: Cycle 1

Trametinib: PO daily
Days: 1-28
Age-based Dosing:
< 6 years of age = 0.032 mg/kg/dose (Maximum dose = 2 mg/day)

NOTE: All patients less than 26.6 kg must receive oral solution. Patients ≥ 26.6 kg may receive oral solution **OR** tablets; however, tablets are preferred if possible.

≥ 6 years = 0.025 mg/kg/dose (Maximum dose = 2 mg/day)

NOTE: All patients less than 35 kg must receive oral solution. Patients ≥ 35 kg may receive oral solution **OR** tablets; however, tablets are preferred if possible.

Trametinib should be taken by mouth on an empty stomach, at least 1 hour before or 2 hours after a meal. Nasogastric or G-tube administration of trametinib oral solution is permitted. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs after taking oral solution formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. If vomiting occurs within 30 minutes of taking the tablet formulation, the dose of trametinib can be repeated once.

See Appendix II for tablet formulation dosing nomogram. Doses of tablet formulation should be rounded to the nearest 0.5 mg.

Trametinib is available is **0.05 mg/mL** reconstituted oral solution. Doses of trametinib oral solution should be rounded to the nearest 0.1 mL (0.005 mg) for doses ≤ 0.11 mg (in oral syringes ≤ 3 mL), to the nearest 0.2 mL (0.01 mg) for doses > 0.11 mg (in oral syringes 5-10 mL volume), and to the nearest 1 mL (0.05 mg) for doses > 0.375 mg. Since trametinib is a hazardous agent, it is recommended that oral dosing syringes should be filled up to 75% of the maximum volume.

Trametinib is distributed by CTEP, DCTD, NCI. **Do not use commercial supply.**

See Section 5.0 for Dose Modifications based on Toxicities.

Complete the end of cycle disease evaluations within three days of the last dose of trametinib on Day 28.

Following completion of Cycle 1, the next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.5), whichever occurs later. Please continue onto the next cycle no later than 14 days from the end of the previous cycle. Results of the JMML mutant allele burden test collected at the end of the cycle are not required to proceed to the next cycle.

4.3 Cycle 2

4.3.1 Therapy Delivery Map – Cycle 2 This therapy Delivery Map (TDM) relates to Cycle 2. Each cycle lasts 28 days.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 3.2.5. Extensive treatment details are in Section 4.3.3.
This treatment delivery map is **two (2)** pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Trametinib Do not use commercial supply	PO	Age-based dosing: < 6 years= 0.032 mg/kg/dose ≥ 6 years = 0.025 mg/kg/dose Max dose= 2 mg	Daily	See Appendix II for tablet formulation dosing nomogram.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**Trametinib** _____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg	a-f
		2	_____mg	
		3	_____mg	
		4	_____mg	
		5	_____mg	
		6	_____mg	
		7	_____mg	
		8	_____mg	d
		9	_____mg	
		10	_____mg	
		11	_____mg	
		12	_____mg	
		13	_____mg	
		14	_____mg	
		15	_____mg	a, d, e
		16	_____mg	
		17	_____mg	
		18	_____mg	
		19	_____mg	
		20	_____mg	
		21	_____mg	
		22	_____mg	d
		23	_____mg	
		24	_____mg	
		25	_____mg	
		26	_____mg	
		27	_____mg	
		28	_____mg	(d, e, g-l)[#]
		29	[#]Following the completion of Cycle 2 therapy, complete observations d, e, g-l within 3 days, and prior to the start of the next cycle. The next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.5), whichever occurs later. Please continue onto the next cycle no later than 14 days from the end of the previous cycle.	

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

Cycle 2

4.3.2 Required Observations in Cycle 2

a. Physical exam (including VS) and adverse events
b. Concomitant medications
c. Performance status
d. CBC, differential, platelets (see Section 7.2 for details regarding Central Review)
e. Electrolytes including Ca^{2+}, Mg^{2+}, and PO_4, BUN and creatinine, creatine kinase, Total and direct bilirubin, AST, and ALT
f. Dermatologic exam. Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam throughout the study. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits
g. Peripheral blood smear (see Section 7.2 for details regarding Central Review)
h. BMA/clot section or biopsy and aspirate smear (see Section 7.2 for details regarding Central Review)
i. BMA cytogenetics and FISH (It is recommended that cytogenetics/FISH be performed by a COG-approved laboratory)
j. For patients that consent, collect bone marrow for Genomic, Epigenomic, and Functional assays (see Section 7.3.3)
k. Echocardiogram or MUGA
l. ECG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Cycle 2

4.3.3 Treatment Details: Cycle 2

Trametinib: PO daily
Days: 1-28
Age-based Dosing:
< 6 years of age = 0.032 mg/kg/dose (Maximum dose = 2 mg/day)

NOTE: All patients less than 26.6 kg must receive oral solution. Patients ≥ 26.6 kg may receive oral solution **OR** tablets; however, tablets are preferred if possible.

≥ 6 years of age = 0.025 mg/kg/dose (Maximum dose = 2 mg/day)

NOTE: All patients less than 35 kg must receive oral solution. Patients ≥ 35 kg may receive oral solution **OR** tablets; however, tablets are preferred if possible.

Trametinib should be taken by mouth on an empty stomach, at least 1 hour before or 2 hours after a meal. Nasogastric or G-tube administration of trametinib oral solution is permitted. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs after taking oral solution formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. If vomiting occurs within 30 minutes of taking the tablet formulation, the dose of trametinib can be repeated once.

See Appendix II for tablet formulation dosing nomogram. Doses of tablet formulation should be rounded to the nearest 0.5 mg.

Trametinib is available is **0.05 mg/mL** reconstituted oral solution. Doses of trametinib oral solution should be rounded to the nearest 0.1 mL (0.005 mg) for doses ≤ 0.11 mg (in oral syringes ≤ 3 mL), to the nearest 0.2 mL (0.01 mg) for doses > 0.11 mg (in oral syringes 5-10 mL volume), and to the nearest 1 mL (0.05 mg) for doses > 0.375 mg. Since trametinib is a hazardous agent, it is recommended that oral dosing syringes should be filled up to 75% of the maximum volume.

Trametinib is distributed by CTEP, DCTD, NCI. **Do not use commercial supply.**

See Section 5.0 for Dose Modifications based on Toxicities.

Complete the end of cycle disease evaluations within three days of the last dose of trametinib on Day 28.

Following completion of Cycle 2, the next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.5), whichever occurs later. Please continue onto the next cycle no later than 14 days from the end of the previous cycle.

Cycle 2

All Subsequent Cycles

4.4 Cycle 3 and All Subsequent Cycles

4.4.1 Therapy Delivery Map – All Subsequent Cycles This therapy Delivery Map (TDM) relates to all subsequent cycles. Each cycle lasts 28 days. Use a copy of this page once for each cycle (please note cycle number below).	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 3.2.5. Treatment details are in Section 4.4.3.
This therapy delivery map is **two (2)** pages in length.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Trametinib Do not use commercial supply	PO	Age-based dosing: < 6 years= 0.032 mg/kg/dose ≥ 6 years = 0.025 mg/kg/dose Max dose= 2 mg	Daily	See Appendix II for tablet formulation dosing nomogram.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**Trametinib** ____mg	Studies
			Enter calculated dose above and actual dose administered below	
		1	_____mg	a-g
		2	_____mg	
		3	_____mg	
		4	_____mg	
		5	_____mg	
		6	_____mg	
		7	_____mg	
		8	_____mg	
		9	_____mg	
		10	_____mg	
		11	_____mg	
		12	_____mg	
		13	_____mg	
		14	_____mg	
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		16	_____mg	
		17	_____mg	
		18	_____mg	
		19	_____mg	
		20	_____mg	
		21	_____mg	
		22	_____mg	
		23	_____mg	
		24	_____mg	
		25	_____mg	
		26	_____mg	
		27	_____mg	
		28	_____mg	h, i#, j, k
		29	#See note on page 2 of TDM regarding observation i. Following completion of the cycle, the next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.5), whichever occurs later. Please continue onto the next cycle no later than 14 days from the end of the previous cycle.	

See Section 5.0 for Dose Modifications for Toxicities and the COG Member website for Supportive Care Guidelines.

4.4.2 Required Observations in All Subsequent Cycles

Collect observations beginning in Cycle 3.

a. Physical exam (including VS) and adverse events
b. Concomitant medications
c. Performance status
d. CBC, differential, platelets
e. Electrolytes including Ca^{2+}, Mg^{2+}, and PO_4, BUN and creatinine, creatinine kinase, Total and direct bilirubin, AST, and ALT
f. Dermatologic exam. Performed by the investigator (or dermatologist, at the discretion of the investigator). If possible, the same physician should perform each exam throughout the study. Photographs of suspect lesions at baseline are recommended with photographs and/or biopsies of any new or changing lesions recommended at subsequent on-study visits
g. Collect a peripheral blood sample for the JMML panel using mutant allele burden. (see Section 7.3.1)
h. Complete an age-appropriate ophthalmologic examination with a funduscopic evaluation that avoids any sedation to be performed by an ophthalmologist at the end of Cycle 4 and every 12 weeks after while on study. Snellen examination (if age appropriate as determined by the investigator). See Section 4.1.6.
i. Bone marrow; to be collected on every odd numbered cycle only (i.e. cycle 3, 5, 7 etc.). **Note**: Only obtain if the bone marrow blast percentage and karyotype are the only remaining variables required to determine response classification as documented in Appendix III Tables 1 and 2
j. ECG to be collected every 3 cycles after Cycle 2 (i.e. cycle 5, cycle 8, cycle 11)
k. ECHO/MUGA: every 3 cycles after Cycle 2 (i.e. cycle 5, cycle 8, cycle 11)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

All Subsequent Cycles

4.4.3 Treatment Details: All Subsequent Cycles

Trametinib: PO daily
Days: 1-28
Age-based Dosing:
< 6 years of age = 0.032 mg/kg/dose (Maximum dose = 2 mg/day)

NOTE: All patients less than 26.6 kg must receive oral solution. Patients ≥ 26.6 kg may receive oral solution **OR** tablets; however, tablets are preferred if possible.

≥ 6 years of age = 0.025 mg/kg/dose (Maximum dose = 2 mg/day)

NOTE: All patients less than 35 kg must receive oral solution. Patients ≥ 35 kg may receive oral solution **OR** tablets; however, tablets are preferred if possible.

Trametinib should be taken by mouth on an empty stomach, at least 1 hour before or 2 hours after a meal. Nasogastric or G-tube administration of trametinib oral solution is permitted. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs after taking oral solution formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. If vomiting occurs within 30 minutes of taking the tablet formulation, the dose of trametinib can be repeated once.

See Appendix II for tablet formulation dosing nomogram. Doses of tablet formulation should be rounded to the nearest 0.5 mg.

Trametinib is available is **0.05 mg/mL** reconstituted oral solution. Doses of trametinib oral solution should be rounded to the nearest 0.1 mL (0.005 mg) for doses ≤ 0.11 mg (in oral syringes ≤ 3 mL), to the nearest 0.2 mL (0.01 mg) for doses > 0.11 mg (in oral syringes 5-10 mL volume), and to the nearest 1 mL (0.05 mg) for doses > 0.375 mg. Since trametinib is a hazardous agent, it is recommended that oral dosing syringes should be filled up to 75% of the maximum volume.

Trametinib is distributed by CTEP, DCTD, NCI. **Do not use commercial supply.**

See Section 5.0 for Dose Modifications based on Toxicities.

Complete the end of cycle disease evaluations within three days of the last dose of trametinib on Day 28.

Following completion of the cycle, the next cycle starts on Day 29 or when starting criteria are met (see Section 3.2.5), whichever occurs later. Please continue onto the next cycle no later than 14 days from the end of the previous cycle. Results of the JMML mutant allele burden test collected at the end of odd numbered cycle are not required to proceed to the next cycle.

5.0 DEFINITIONS AND DOSE MODIFICATION FOR TOXICITY

All dose modifications should be based on the worst preceding toxicity.

5.1 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to trametinib.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.1.1 Non-Hematological Dose-Limiting Toxicity

- See Section 5.4 for management guidelines for toxicities of special interest, note that dose modification or discontinuation of trametinib for toxicity is considered a dose limiting toxicity.
- Any Grade 4 non-hematological toxicity with specific exclusion of:
  - Grade 4 fever/pyrexia that resolves to Grade < 2 within 72 hours with supportive care (anti-pyretics)
- Dose-limiting hypertension will be considered as the following:
  - Grade 4 hypertension,
  - A blood pressure > 25 mm Hg above the 95th percentile for age, height, and gender, confirmed by repeated measurement

  Note: if elevated, take 3 serial blood pressure readings from the same extremity with the patient in the same position, separated by at least 5 minutes. Avoid using the lower extremity if possible. Use the mean average of the 3 measurements.
- Any Grade 3 non-hematological toxicity with the specific exception of:
  - Grade 3 nausea and vomiting of less < 3 days duration
  - Grade 3 fever or infection < 7 days duration.
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia and/or hypomagnesemia responsive to oral supplementation within 7 days
- Grade 2 allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity
- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption
- Grade 2 left ventricular ejection fraction disease
- Grade 2 cardiac valvular toxicity (mitral/aortic/tricuspid)
- Grade 2 pneumonitis
- Treatment interruption longer than 14 days due to delayed recovery from toxicity will be dose limiting

5.1.2 Hematological dose limiting toxicity

a) Hematologic DLT will be defined as failure to recover a peripheral ANC > 500/µL and platelets > 20,000/µL by 42 days after the first treatment day, not due to malignant infiltration.

Note: Grade 4 febrile neutropenia will not be considered a dose-limiting toxicity.

5.2 Dose Modifications for Hematological Toxicity

There are no modifications for patients with persistent JMML who have never experienced recovery of normal hematologic parameters. If a patient does have recovery of normal hematologic parameters and then experiences Grade 4 neutropenia or Grade 4 thrombocytopenia, the treatment will be held. Counts should be checked twice weekly during this time. If the toxicity resolves to peripheral absolute neutrophil count (ANC) ≥ 1000/μL and platelet count ≥ 75,000/μL within 14 days of drug discontinuation, the patient may resume treatment with 25% dose reduction in patients receiving oral solution or the specified dose reduction in patients receiving tablets (See Appendix II). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

If toxicity does not resolve to peripheral absolute neutrophil count (ANC) ≥ 1000/μL and platelet count ≥ 75,000/μL within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

If dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the patient must be removed from protocol therapy.

5.3 Dose Modifications for Non-Hematological Toxicity

If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.1.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment with 25% dose reduction in patients receiving oral solution or the specified dose reduction in patients receiving tablets (See Appendix II). Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

If toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

If any dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose level, the patient must be removed from protocol therapy.

5.4 Guidelines and Dose Modifications for Trametinib Events of Special Interest

Dose modification and adverse event (AE) guidelines are outlined in the sections below for AEs that are deemed possibly related to trametinib:

- AEs not otherwise specified
- Rash
- Visual changes
- Diarrhea
- Liver chemistry elevation

- Ejection fraction changes
- Hypertension
- Prolonged QTc
- Pneumonitis

5.4.1 Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections:

Trametinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Trametinib (This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).	
CTCAE v5 Grade	**Dose Modification**
Grade 1 and tolerable Grade 2	• Continue trametinib at current dose level • Monitor closely • Provide supportive care according to institutional standards
Intolerable Grade 2 and Grade 3	• Interrupt treatment until resolution to Grade 1 or baseline • Upon resolution to baseline or Grade 1, restart with 25% dose reduction in patients receiving oral solution or the specified dose reduction in patients receiving tablets (See Appendix II) • If the intolerable Grade 2 or Grade 3 toxicity recurs, permanently discontinue trametinib
Grade 4	• Interrupt treatment • Monitor closely • Provide supportive care according to institutional standards • If event resolves to Grade 1 or baseline discuss potential continuation of trametinib with study chair; if continuation of treatment agreed, then restart trametinib with 25% dose reduction in patients receiving oral solution or at specified dose reduction in patients receiving tablets (See Appendix II) • If event does not resolve, permanently discontinue trametinib

5.4.2 Trametinib Dose Modifications for Rash:

Dermatologic complications are frequent adverse events in subjects receiving trametinib and a proactive approach should be taken. All subjects should avoid unnecessary sunlight and use sunscreen whenever there is possible exposure. See Section 4.1.5 for prophylactic treatment for prevention of dermatologic toxicity

Reactive Management:

It is strongly recommended that subjects who develop rash/skin toxicities receive evaluations by a dermatologist for management of the specific side effect.

For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.

For fissuring, the use of Monsel's solution, silver nitrate or zinc oxide cream is advised.

For desquamation, thick emollients and mild soap are recommended.

For paronychia, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended, and if no improvement is seen, a dermatology or surgery consultation is recommended.

For infected lesions, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

Management and Trametinib Dose Modification for Rash		
Event CTCAE Grade	**Management Guideline**	**Action and Dose Modification**
Grade 1	Initiate prophylactic and symptomatic treatment measures.[a] Use moderate strength topical steroid.[b] Reassess after 2 weeks.	Continue trametinib.
Grade 2	Initiate prophylactic and symptomatic treatment measures.[a] Use moderate strength topical steroid.[b] Reassess after 2 weeks.	Continue trametinib If rash does not recover to ≤ Grade 1 within 2 weeks, interrupt trametinib until recovery to ≤ Grade 1, restart trametinib at reduced dose (25% dose reduction in patients receiving oral solution or at specified dose reduction in patients receiving tablets (See Appendix II))
Grade ≥3	Use moderate strength topical steroids[b] (PLUS) methylprednisolone dose pack. Consult dermatologist.	Interrupt trametinib until rash recovers to Grade ≤1. Restart with trametinib at reduced dose (25% dose reduction in patients receiving oral solution or at specified dose reduction in patients receiving tablets (See Appendix II) If no recovery to Grade ≤ 2 within 2 weeks, permanently discontinue trametinib.

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream
c. Notify the study chair.

5.4.3 Trametinib Dose Modifications for Visual Changes (Eye Disorders)

Trametinib is known to be associated with visual adverse events. An age-appropriate ophthalmologic examination should be performed by an ophthalmologist (without sedation) at screening, may be performed without dilation at discretion of ophthalmologist and can be accomplished using imaging with a non-mydriatic fundus camera. During the study, ophthalmologic exams will be repeated by an ophthalmologist at the end of cycle 1 and every 12 weeks thereafter. If the child or parent report visual problems they will be referred promptly for an ophthalmology assessment.

If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention will be given to retinal findings (*e.g.*, retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (*i.e.*, branch or central retinal vein occlusions [RVO]). For subjects with clinical suspicion of RPED or RVO, fundus photography, and optical coherence tomography will be performed.

The ophthalmology exam can include best corrected visual acuity, visual field examination, tonometry, slit lamp biomicroscopic examination, and indirect ophthalmoscopy as indicated. Optical coherence tomography will be performed if retinal abnormalities are suspected. Other types of ancillary testing including visual field examination, fundus photography, and fluorescein angiography may also be indicated as determined by clinical exam.

Guidelines regarding event management and dose reduction for visual changes considered to be related to study treatment are provided in the table below.

Management and Trametinib Dose Modification for Visual Changes and/or Ophthalmic Examination Findings		
Event CTCAE Grade	**Management Guideline**	**Dose Modification**
Asymptomatic; clinical or diagnostic observations only *	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue/or restart trametinib at same dose. • If RPED suspected/diagnosed: See RPED dose modification table below (following this table); **report as SAE**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**.
Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL	• Consult ophthalmologist immediately.	• Hold trametinib • If RPED or RVO excluded, restart trametinib at same dose. • If RPED diagnosed: See RPED dose modification table below; **report as SAE**. • If RVO: **Permanently discontinue trametinib and report as SAE**.
Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye	• Consult ophthalmologist immediately. • Report as SAE.	• Hold Trametinib • If RPED/RVO excluded, may restart trametinib at same or reduced dose after discussion with the study chair. • **If RVO or RPED, permanently discontinue trametinib**.

Management and Trametinib Dose Modification for Visual Changes and/or Ophthalmic Examination Findings		
Event CTCAE Grade	**Management Guideline**	**Dose Modification**
Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event *If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.		

Trametinib Dose Modification for RPED	
Event CTCAE Grade	**Action and Dose Modification**
RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.
RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with a reduced dose (25% dose reduction in patients receiving oral solution or at specified dose reduction in patients receiving tablets (See Appendix II) • If no recovery within 4 weeks permanently discontinue trametinib

5.4.4. Trametinib Dose Modification for Diarrhea

Etiology and attribution. Consider evaluation for an alternative etiology of diarrhea as clinically indicated. These include medications (e.g., stool softeners, laxatives, antacids, etc.), infection by C. difficile, partial bowel obstruction, malabsorption/lactose intolerance, fecal impaction, or diets high in fiber or lactose.

For Grade ≤ 2 diarrhea:
Dietary modifications may include: stop all lactose-containing products and eat small meals. A bananas, rice, apples, toast (BRAT) diet can be helpful.

Encourage oral hydration according to institutional weight oral hydration guidelines as clinically appropriate.

For all subjects consider administration of loperamide (Table 5.4.4.1) with dosing per institutional guidelines or as suggested below. Continuation of loperamide is suggested until the subject is diarrhea-free for at least 12 hr.

If diarrhea resolves to Grade ≤ 1 within 72 hr of anti-diarrheal measures or supportive care measures, continue study treatment without interruption or dose reduction.

If Grade 2 diarrhea persists after 72 hr total treatment with loperamide or supportive measures in children < 2 years, hold study treatment and consider start of second-line agents (octreotide) as clinically indicated. If diarrhea resolves to Grade ≤ 1 or baseline within 7 days resume study treatment with dose reduction. If Grade > 2 diarrhea does not resolve in ≤ 7 days without study treatment, discontinue protocol therapy.

Table 5.4.4.1 Loperamide Dosing

Age	Weight (kg)	Initial Dose (start after first loose bowel movement)	Subsequent Doses	Maximum daily dose
> 1 mo to ≤ 12 years	<13	0.5 mg	0.5 mg every 3 hr while awake, every 4 hr during sleep	4 mg/day
	13 to < 20	1 mg	1 mg every 4 hr	6 mg/day
	20 to < 30	2 mg	1 mg every 3 hr while awake, every 4 hr during sleep	8 mg/day
	30 to < 43	2 mg	1 mg every 2 hr while awake, every 4 hr during sleep	12 mg/day
≥ 13 years	≥ 43	4 mg	2 mg every 2 hr while awake, every 4 hr during sleep	16 mg/day

For Grade 3 or 4 diarrhea:
Hold study treatment until symptoms resolve to ≤ Grade 1 or baseline then may resume study treatment with a dose reduction (25% dose reduction in patients receiving oral solution or specified dose reduction in patients receiving tablets (See **Appendix II**).

If loperamide has not been initiated, initiate loperamide immediately using institutional or protocol guidelines for dosing.

For dehydration, use intravenous fluids as appropriate; if severe dehydration, consider administration of octreotide.

5.4.5. Trametinib Dose Modification for Liver Chemistry Changes:

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Upper limit of normal (ULN) for ALT in this study will be 45 U/L and ULN for AST is 50 U/L. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See Appendix X for toxicity grading table. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. ALT ≥3 times upper limit of normal (ULN) and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and international normalization ratio [INR] >1.5)

i. NOTE: Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

2. ALT ≥5 times ULN.

3. ALT ≥3 times ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

4. ALT ≥3 times ULN persists for ≥4 weeks.

5. ALT ≥3 times ULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment(s) as long as they can be monitored weekly for 4 weeks. See following section for details on weekly follow-up procedures for these subjects.

5.4.5.1. Liver Chemistry Follow-up Procedures

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria 1 through 5 defined in Section 5.4.5:

- Immediately discontinue study treatment.
- Notify the study chair within 24 hr of learning of the abnormality to confirm the subject's study treatment(s) cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- If the event also meets the criteria of a SAE (see Section 11.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not re-challenge with study treatment(s).

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN:

- Monitor subjects weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects meeting stopping criterion 1 (ALT ≥3 times ULN and bilirubin ≥2 times ULN [or ALT ≥3 times ULN and INR >1.5]):

- This event is considered an SAE (see Section 11.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hr for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, ALP, and bilirubin) resolve, stabilize or return to within baseline values.
- In addition, every attempt should be made to carry out the liver event follow-up assessments described in Section 5.4.5.2.

5.4.5.2. Liver Chemistry Testing Procedures

For subjects meeting any of the liver chemistry stopping criteria in Section 5.4.5 make every attempt to carry out the liver event follow-up assessments described below:

- Viral hepatitis serology, including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, then obtain heterophile antibody or monospot testing)
- Serum creatine kinase (CK) and lactate dehydrogenase (LDH). Fractionate bilirubin, if total bilirubin ≥2 X upper limit of normal (ULN). Obtain a complete blood count (CBC) with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms indicative of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE CRF.
- Record the use of concomitant medications, including acetaminophen, herbal remedies or any other over the counter (OTC) medications, or any putative hepatotoxins, on the concomitant medication CRF.

Every attempt should be made to obtain the following assessments for subjects with ALT ≥3 X ULN and bilirubin ≥2X ULN (>35% direct). These assessments are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, MRI or CT) to evaluate liver disease.
- Serum acetaminophen adduct High Performance Liquid Chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week.

5.4.6. Trametinib Dose Modification for Pneumonitis

Pneumonitis has been observed in patients receiving trametinib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms and evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in the tables below.

Pneumonitis Guidelines for Trametinib Monotherapy		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended	• Continue trametinib at current dose
Grade 2	• CT scan (high-resolution with lung windows) recommended. • Work-up for infection • Consult pulmonologist • Pulmonary function tests – if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	• Interrupt trametinib until recovery to Grade ≤1 • Restart treatment with trametinib **dose reduction** (25% dose reduction in patients receiving oral solution or specified dose reduction in patients receiving tablets (See **Appendix II**)) • Escalation to previous dose level after 4 weeks may be considered after consultation with the study chair • If no recovery to Grade ≤1 within 4 weeks, **permanently discontinue trametinib**
Grade 3	• Same as Grade 2	• Interrupt trametinib until recovery to Grade ≤1 • After consultation with the study chair, trametinib may be restarted with a dose reduction (25% dose reduction in patients receiving oral solution or specified dose reduction in patients receiving tablets (See **Appendix II**)) • If no recovery to Grade ≤1 within 4 weeks, **permanently discontinue trametinib**
Grade 4	• Same as Grade 2	• **Permanently discontinue trametinib**

5.4.7 Trametinib Dose Modification for Reduced Left Ventricular Ejection Fraction

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHO/MUGAs must be performed at baseline, at the end of cycle 1 and at the end of cycle 2. Any ECHO/MUGAs thereafter should be done only if clinically indicated. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s).

Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Action and Dose Modification**

Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib and repeat ECHO/MUGA within 2 weeks.[a]
		• If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline):
		  • Consult with the study chair and request approval for restart.
		  • Restart treatment with trametinib at reduced dose by one dose level.[b]
		  • Repeat ECHO/MUGA 2, 4, 8, and 12 weeks after re-start; continue in intervals of 12 weeks thereafter.
		• If LVEF **does not** recover within 4 weeks:
		  • Consult with cardiologist.
		  • **Permanently discontinue trametinib**.
		  • Report as SAE
		  • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.
		  • Consult with the study chair.[c]

Symptomatic[b]	• Grade 3: resting LVEF 39-20% or≥20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue trametinib**. • **Report as SAE**. • **Consult with cardiologist**. • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.
[a] If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later. [b] Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from the study chair is required. [c] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.		

5.4.8. Trametinib Dose Modification for QTc Prolongation

Trametinib Withholding and Stopping Criteria for QTc Prolongation	
QTc Prolongation[a]	**Action and Dose Modification**
• QTcB >500 msec	• Interrupt study treatment until QTcB prolongation resolves to Grade 1 or baseline. • Test serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose.[b] • **If the event recurs after restarting, permanently discontinue study treatment.**
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using Bazett's formula [a] Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued. [b] if the QTc prolongation resolves to Grade 1 or baseline, the subject may resume study treatment if the investigator determines that the subject will benefit from further treatment.	

5.4.9. Trametinib Dose Modification for Hypertension

Increases in blood pressure (BP) have been observed in patients receiving trametinib.

Should initiation of anti-hypertensive therapy be required, single agent therapy (commonly including the calcium channel blockers amlodipine or nifedipine) should be started and the blood pressure should be monitored at least twice weekly until BP is within the 95th percentile for age, height, and gender per Appendix IX.

If patient is already on an anti-hypertensive medication at study enrollment, then their anti-hypertensive therapy should be adjusted (by either adjusting the dose of their current anti-hypertensive medication or by adding another anti-hypertensive agent) according to the algorithm in Section 5.4.9.3.

5.4.9.1. Baseline Blood Pressure

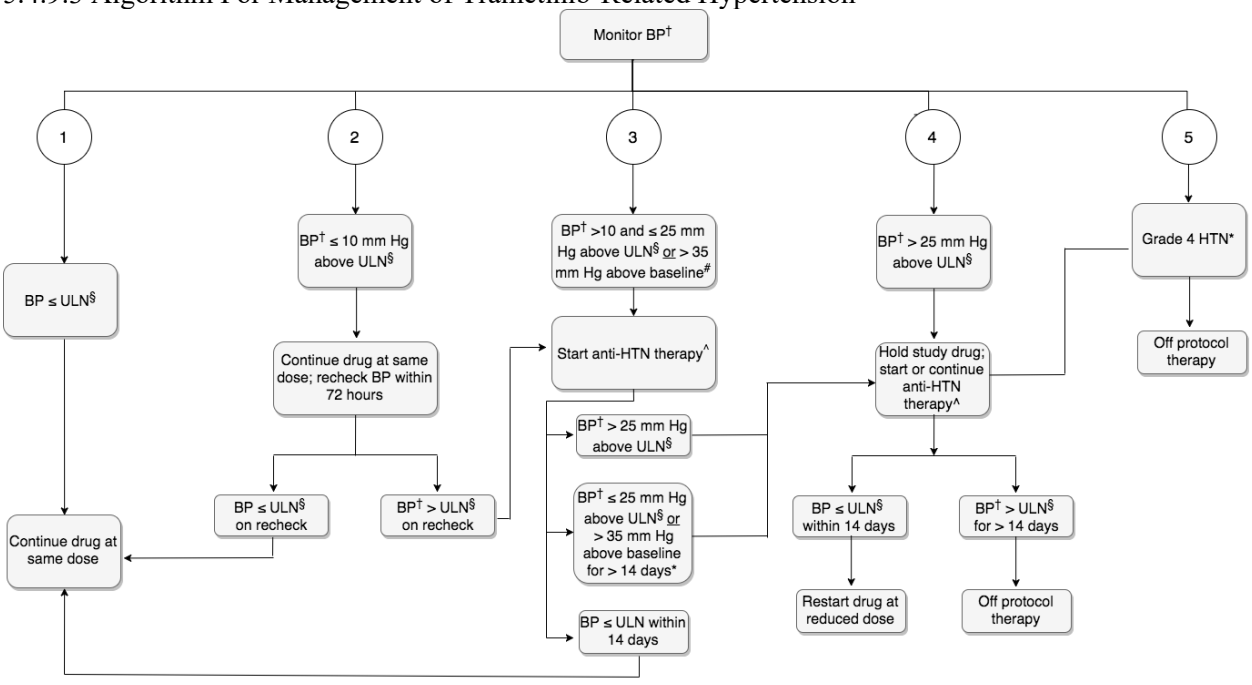
Baseline blood pressure (BP) is defined as the blood pressure obtained at the examination used for study enrollment. This baseline BP should be obtained as follows:

- Obtain 3 serial blood pressures from the same extremity with the patient in the same position that are separated by at least 5 minutes. Avoid using the lower extremity if possible.
- The baseline BP is the mean average of the systolic and the mean average of the diastolic measurements.

5.4.9.2 Management of Hypertension

- The upper limit of normal (ULN) is defined as a BP equal to the 95th percentile for age, height, and gender. (Appendix IX)
- The NCI CTCAE will be utilized to determine the grade of hypertension for reporting purposes.
- Elevated BP measurements should be repeated on the same day to confirm the elevation. Patients with an elevated BP should have BP measurements performed at least twice weekly until BP is ≤ ULN.
- The algorithm below will be used to manage trametinib related hypertension.
- Hypertension should be managed with appropriate anti-hypertensive agent(s) as clinically indicated. It is strongly recommended that nephrology or cardiology be consulted in the evaluation and management of hypertension.

5.4.9.3 Algorithm For Management of Trametinib-Related Hypertension



Elevations in BP are based on systolic or diastolic pressures.
†Elevated blood pressure measurements should be repeated on the same day to confirm the elevation. Patients with elevated BP at any time should have BP measurements performed at least twice weekly until BP is within the ULN.
§ULN is a BP equal to the 95th percentile for age, height, and gender-appropriate normal values (Appendix IX).
*If BP > 25 mm Hg above ULN for age (verified) or Grade 4 hypertension at any time, hold drug. Study drug should also be held for BP ≥ 25 mm Hg above the ULN for 14 days or ≥ 35 mm Hg above baseline for > 14 days. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is held.
^Antihypertensive therapy should be prescribed as clinically indicated, including use of multiple anti-hypertensive agents.
#Baseline BP as defined in Section 5.4.9.1

Arm 1 of algorithm:

- If blood pressure (BP) ≤ 95%ile for age, height, and gender: continue trametinib at the same dose.

Arm 2 of algorithm:

- If BP ≤ 10 mm Hg above the ULN: continue trametinib at the same dose and recheck the BP within 72 hours.
    - If the BP is ≤ ULN on recheck, continue trametinib at the same dose.
    - If the BP remains above the ULN on recheck, then start/adjust antihypertensive therapy and follow Arm 3 of the algorithm from the point that anti-hypertensive therapy is started/adjusted.

Arm 3 of algorithm:

- If BP is 11 to 25 mm Hg above the ULN on ≥ 2 of 3 measurements or > 35 mmHg above baseline on ≥ 2 of 3 measurements, start/adjust anti- hypertensive therapy and continue trametinib at the same dose. Monitor BP at least twice weekly.
    - If the BP returns to ≤ULN within 14 days, continue trametinib at the same dose and continue anti-hypertensive therapy.
    - If the BP remains elevated ≥25 mmHg above the ULN or >35 mmHg above baseline for more than 14 days after the institution/adjustment of anti-hypertensive therapy, **hold trametinib**, monitor BP at least every 3 days, and follow Arm 4 of the algorithm from the point that trametinib is held. The anti-hypertensive therapy should be continued until the BP is less than the ULN.
- If the BP returns to ≤ ULN within 14 days, restart trametinib at reduced dose (25% dose reduction in patients receiving oral solution or at specified dose reduction in patients receiving tablets (See Appendix II).
- If the BP remains > ULN for more than 14 days, patient must be removed from protocol therapy.
    - If the BP increases to > 25 mm Hg above the ULN despite anti-hypertensive therapy, hold trametinib, but continue the anti-hypertensive agent(s). Monitor the BP as clinically indicated and follow Arm 4 of the algorithm from the point that trametinib is held.

Arm 4 of algorithm:

- If BP is > 25 mm Hg above the ULN **hold** trametinib, monitor BP, and administer/adjust anti-hypertensive therapy as clinically indicated.
    - If the BP returns to ≤ ULN within 14 days, trametinib may be restarted at a reduced dose.
    - If the BP is > ULN for >14 days, the patient must be removed from protocol therapy

Arm 5 of algorithm:

If the participant develops Grade 4 hypertension, discontinue trametinib, monitor BP and administer anti-hypertensive therapy as clinically indicated. The patient is Off Protocol Therapy.

6.0 DRUG INFORMATION

6.1 Trametinib (06/09/22)

(Mekinist®, GSK1120212, TMT212-NXA, JTP-74057, JTP-78296, JTP-75303, NSC 763093)

Source and Pharmacology:
Trametinib dimethyl sulfoxide is a kinase inhibitor. The chemical name is acetamide, N-[3-[3-cyclopropyl-5- [(2-fluoro-4- iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-d]pyrimidin-1(2H)- yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1). It has a molecular mass of 693.53. Trametinib dimethyl sulfoxide is a white to almost white powder. It is practically insoluble in the pH range of 2 to 8 in aqueous media.

Trametinib is an orally bioavailable, reversible, highly selective allosteric inhibitor of MEK1/2 that is active in inhibition of pERK and growth of BRAF and Ras mutant cancer cell lines and hematopoietic cancer cells from acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) origins. Tumor cells commonly have hyperactivated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib dimethyl sulfoxide inhibits activation of MEK by RAF kinases and MEK kinases. Through inhibition of MEK 1 and 2 kinase activity, trametinib causes decreased cellular proliferation, Gap-1 (G1) cell cycle arrest, and increased apoptosis in vivo following oral dosing. Trametinib is FDA-approved for the treatment of adults with advanced melanoma with a BRAF V600E or V600K mutation.

Pharmacokinetics (PK):
In patients with solid tumors trametinib is absorbed rapidly with median time to maximum plasma concentration (Tmax) occurring 1.5 hours after single oral administration of trametinib under fasting conditions. It has a moderate to high absolute oral bioavailability (72%) relative to a co-administered intravenous (IV) microdose. Single-dose administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in Cmax, a 24% decrease in area under the concentration-time curve from time zero (pre-dose) to last time point (AUC[0-t]) and a 10% decrease in AUC extrapolated to infinity (AUC[0-∞]) compared to fasted conditions.

Following repeat-dosing the mean AUC [0-t_τ] and Cmax increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing and has a terminal half-life (T1/2) of 5.3 days determined after single dose administration. Steady state appears to be achieved by Day 15, with little difference in pre-dose (trough) concentration at the end of the dosing interval (C-t_τ), Cmax and AUC [0-24]) between Days 15 and 21.

Trametinib is a low extraction ratio drug based on plasma IV clearance of 3.21 L/hr and has a high volume of distribution (Vd) of 1060 L. Following a single dose of [^{14}C]-trametinib, approximately 50% of circulating radioactivity is represented as the parent compound. The fecal route was the major excretion pathway of radioactivity after a single [^{14}C] trametinib oral dose, while urinary excretion accounted for up to 19% of excreted radioactivity recovered.

Potential Drug Interactions:
In vitro and in vivo data suggest that trametinib is unlikely to affect the PK of other drugs and that the PK of trametinib is unlikely to be affected by other drugs. . *In vitro* studies suggest that trametinib is not a substrate of CYP enzymes or of human BCRP, MRP2, OATP1B1, OATP1B3, OATP2B1, OCT1 or MATE1 transporters. It is eliminated predominantly via deacetylation to metabolite M5, which is mediated by caroboxylesterases (CES1b, CES1c, CES2). There is little evidence from clinical studies for drug interactions mediated by carboxylesterases. Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant.

Trametinib dimethyl sulfoxide is an *in vitro* inhibitor of CYP 2C8 and is anticipated to have overall low potential for drug interactions as a perpetrator. It is also a weak CYP 2B6 and 3A4 inducer and expected to have little clinical effect on sensitive substrates. Trametinib is not an inhibitor of CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4 and not an inhibitor of MRP2 or BSEP, but an in vitro inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and MATE1 at systemic concentrations that are not clinically relevant. No clinically relevant inhibition by trametinib is predicted in the liver or kidney and a low risk of intestinal drug-drug interaction is possible with BCRP.

Trametinib is highly bound to plasma proteins (97.3%) and has the potential to interfere with other highly protein-bound drugs. Use caution in patients taking concomitant drugs that are highly protein-bound and have narrow therapeutic ranges.

Pregnancy and lactation:
Trametinib may impair female fertility in humans based on the reduction of corpora lutea in rats. Trametinib is unlikely to affect male fertility. Based on findings from animal studies and its mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of trametinib in pregnant women. Women of childbearing potential should be advised to use effective contraception during treatment with trametinib and for 4 months after the last dose. Male patients must use a condom during intercourse and not to father a child during therapy and for 4 months following discontinuation of trametinib to avoid unnecessary exposure of trametinib to the fetus. It is not known if trametinib is excreted in milk. Women should not breastfeed during treatment with trametinib and for 4 months following the last dose.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1111 patients.* Below is the CAEPR for Trametinib (GSK1120212B).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, October 10, 2019[1]

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[2]		
		Papilledema	
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
Generalized edema[3]			***Generalized edema[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		
INFECTIONS AND INFESTATIONS			
	Folliculitis		***Folliculitis (Gr 2)***
	Lung infection		

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***
		Stevens-Johnson syndrome[6]	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event (venous)	
	Vascular disorders - Other (hemorrhage)[7]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Visual disorders include visual disturbance that can be associated with conjunctival hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, iritis, macular edema, retinal hemorrhage, visual acuity reduced, visual impairment, and vitreous detachment.

[3]Generalized edema includes edema, lymphedema, and edema limbs.

[4]Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

[5]Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, rash acneiform, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.

[6]Stevens-Johnson syndrome has been observed in patients treated with trametinib and dabrafenib combination.

[7]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and fatal intracranial hemorrhages have been reported.

Adverse events reported on trametinib dimethyl sulfoxide (GSK1120212B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trametinib dimethyl sulfoxide (GSK1120212B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia
EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Photophobia
GASTROINTESTINAL DISORDERS - Ascites; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage[7]; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage[7]; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)
INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased;

Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (compression fracture); Myalgia; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage[7]; Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage[7]; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage[7]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage[7]; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension

Note: Trametinib (GSK1120212B) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Formulation and Stability:
Trametinib will be supplied as 0.5 mg and 2 mg (as free base) tablets and powder for oral solution. Tablets may be provided in investigationally-labeled bottles or commercially-labeled bottles.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), colloidal silicon dioxide and sodium lauryl sulfate.

The aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow (0.5 mg tablet), iron oxide red (2 mg tablet) and polysorbate 80 (2 mg tablet).

Each investigationally-labeled bottle contains 32 tablets with a desiccant:

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated.
- 2 mg tablets are pink, round, biconvex and film-coated.

Each commercially-labeled bottle contains 30 tablets with a desiccant:

- 0.5 mg tablets are yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘TFC’ on the opposing face.

2 mg tablets are pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

Trametinib tablets are immediate release for oral administration containing trametinib dimethyl sulfoxide equivalent to 0.5 mg or 2 mg of trametinib as free base.

Trametinib powder for oral solution: each bottle of powder for solution contains 5 mg supplied as a multi-dose formulation in amber glass (USP Type III) bottles with child-resistant, high-density polypropylene closures. The powder for oral solution is uniform white to slightly colored and contains 5 mg of trametinib in addition to beta-cyclodextrin sulfobutylether, sucralose, citric acid, sodium phosphate (dibasic, anhydrous), strawberry flavor, potassium sorbate and methylparaben. The oral solution is stable for 35 days after reconstitution.

Storage:
Store tablets at 2°C -8°C (36° F to 46° F) in the original bottle and dispense unopened bottles. Do not open bottles or repackage tablets or remove desiccant. Bottles should be protected from light and moisture. Refer to the package label for expiration. Stability studies are ongoing. Tablets are only stable for 32 days once bottle has been opened. If multiple bottles are dispensed to a patient in the same visit, please advise the patient to open only one bottle at a time.

Store 5 mg powder for oral solution up to 2°C - 8°C (36°F - 46°F). The oral solution (0.05 mg/mL) is stable for 35 days after reconstitution when stored up to 25°C and protected from light. Do not freeze.

If a storage temperature excursion is identified, promptly return trametinib to 2°C -8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Trametinib should be taken by mouth on an empty stomach, at least 1 hour before or 2 hours after a meal. Trametinib solution can be administered via NG or G-tube, if oral administration is not feasible. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs after taking oral solution formulation, the dose of trametinib should NOT be repeated and the next dose should be administered at the regularly scheduled time. If vomiting occurs within 30 minutes of taking the tablet formulation, the dose of trametinib can be repeated once.

Reconstitution and administration of powder for oral solution:

1. Tap the sides of the Powder-in-Bottle to loosen the powder, and then remove the cap. Add 90 mL room-temperature water for irrigation, bottled still drinking water, Sterile Water for Injection or Purified Water to the bottle. Replace the cap tightly. Reconstituted solution is **0.05 mg/mL.**

2. Shake vigorously by inversion for at least two minutes to ensure complete powder reconstitution to a solution. Then place the bottle on a bench top or flat surface undisturbed for 5-10 minutes for any foam to dissipate.

3. Insert a 28 mm **"Press-In-Bottle Adapter (PIBA®)"** into the neck of the bottle. **Please ensure that the lip of the Adapter fits snugly with the top of the bottle.** Replace the cap tightly.

4. Immediately prior to the removal of dose for administration swirl the bottle of solution gently 2-3 times, if any foam appears allow the bottle to sit for at least 1 minute for the foam to dissipate.

5. Remove the required dose using a suitable graduated syringe:
   a. Ensure that the syringe plunger is fully pushed into the barrel.
   b. Insert the syringe tip into the Adapter, then invert the bottle and dispense at least 5 mL of solution into the syringe and then pump the entire solution back into the bottle to purge the syringe of any air bubbles. Repeat this step until the syringe is free from air bubbles.
   c. Withdraw the required dosing volume. Then re-invert the bottle and remove the syringe from the Adapter and administer the dose to the patient as soon as possible.

Supplier: Trametinib is supplied by Novartis and distributed by CTEP, DCTD, NCI. **Do not use commercial supply.**

Obtaining the Agent

Agent Ordering

NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NIH Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution. Patients must be enrolled prior to ordering study agent since no starter supplies are being provided. If expedited ordering is required, sites should provide express courier information through the Online Agent Order Processing (OAOP) application.

Note: No starter supplies will be provided. Drug orders of trametinib should be placed with CTEP after enrollment on ADVL1521 with consideration for timing of processing and shipping to ensure receipt of drug supply prior to start of protocol therapy. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application. Provide the patient ID number in the comment box when submitting an order request.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, and a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Accountability

Agent Inventory Records:

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: Ibcoordinator@mail.nih.gov

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 End of Therapy& Follow-up

STUDIES TO BE OBTAINED	End of Therapy	Progressive Disease
History	X	
Physical exam with VS	X	
Ht, Wt, BSA	X	

Performance status	X	
Pregnancy test	X	
CBC, differential, platelets	X	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	
Creatinine, SGPT (ALT), bilirubin	X	
Total protein/albumin	X	
Bone marrow evaluation	X	
JMML panel using mutation allele burden	X	X
Genomic, Epigenomic and Functional assays*	X	X

*if the patient consented

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

7.2 Retrospective Central Pathology Review

7.2.1 Requested Materials

Please send the following materials for retrospective pathology review at baseline collection, at the end of Cycles 1 and 2, and when subsequent bone marrows are collected for review:

- Bone marrow biopsy (if unavailable; submit a bone marrow aspirate clot): 1 H& E stained glass slide
- Bone marrow aspirate smear: 1 or 2 stained (e.g. Wright's Giemsa) aspirate smears
- Peripheral blood smear: 1 stained smear
- A copy of the CBC report from the date of marrow collection

7.2.3 Specimen Labeling and Shipping Information

All material submitted for central review should be labeled with the patient's COG I.D., study number (ADVL1521), and the date and time the sample was drawn. Data should be recorded on the Central Pathology Review Specimen Transmittal Form, which must accompany the samples. Please ship within three days of obtaining all samples via FedEx priority overnight to the following address:

FedEx Shipping account number: 331909297

UCSF Hematopathology
Attn: Iryna Yarova & Scott C. Kogan M.D.
505 Parnassus Ave
Room M569, Box 0100
San Francisco, CA 94143

Lab Contact:
Scott C. Kogan M.D.
Phone: (415) 353-1672

7.2.5 Cytologic Slides- Storage/Return

Cytologic slides will be retained at the UCSF Hematopathology lab indefinitely, unless the institution requests their return.

7.3 Mutant Allele Burden Measurement REQUIRED

The mutant allele burden assay encompasses the DNA sequencing of all exons in each of the following genes: *NRAS, KRAS, RRAS2, PTPN11, CBL, NF1, SETBP1, SH2B3, ASXL1,* and *JAK3*. The assay is quantitative and is intended to monitor the allele burden of one or more previously uncovered mutations in a patient to assess for minimal residual disease. See Appendix V for details regarding the determination of pathogenicity.

When a patient enrolls on study, send an email to ADVL1521@ucsf.edu with a copy to the COG assigned Study Research Coordinator, to receive a specimen collection kit.

7.3.1 Sample Collection and Handling Instructions

A peripheral blood sample will be collected at the time points described below. Each sample will be utilized for the purpose of mutant allele burden measurement.

Sampling Schedule and Collection

Peripheral blood samples will be obtained at the following time points:

- A single sample collected at any time between Day -14 through Day 0, before Cycle 1 (if sent as fee-for-service, can be collected up to 30 days prior to treatment)
- Day 28 of Cycle 1
- Day 1 of every odd Cycle (3, 5, 7, etc.…)
- Progressive disease (when applicable)
- End of Treatment

Sample Processing and Labeling

Collect peripheral blood samples of approximately 2-4 mL in Sodium (Na) Heparin green top tubes. Invert 5 times to ensure mixing of the anticoagulant and blood. Peripheral blood should be collected at every Mutant Allele Burden Measurement timepoint listed above.

Collect 4 buccal swabs for each cheek (8 total) by gently rolling the swab along the inside of each cheek 10 times. Place each swab inside a separate tube making sure not to touch the tips. Patient should not have any food inside the mouth at the time of collection. Buccal swabs will only be collected at the initial time point (Day -14 through Day 0, before Cycle 1).

Each tube and swab must be labeled with the patient's COG I.D., study number (ADVL1521), and the date and time the sample was drawn. Data should be recorded on the Mutant Allele Burden Measurement Specimen Transmittal Form, which must accompany the sample(s).

7.3.2 Sample Shipping Instructions

The samples should be shipped to the UCSF Molecular Diagnostics

(CLIA) laboratory. Samples should be shipped between Monday and Thursday for overnight delivery to ensure delivery by Friday. Samples collected on Friday should be shipped on Monday. The sodium heparin tubes and buccal swabs (swabs only collected at first time point) should be shipped at room temperature. Please notify the laboratory prior to shipment, and send tracking information to the following email address:

Erik.Samayoa@ucsf.edu

Samples should be shipped to the following address:

UCSF Clinical Laboratories
Attn: Molecular Diagnostics Lab
185 Berry Street, Suite 100
San Francisco, CA 94107

Lab Contact: Erik Samayoa
Phone: (415) 353-4845

7.4 Correlative Biology Studies

Please note that no more than 3 mL/kg of blood or bone marrow should be drawn on any one day for patients <1 year of age. For patients >1 year of age, no more than 2 mL/kg of blood or bone marrow should be drawn on any one day.

7.4.1 Pharmacodynamic (PD) and Pharmacokinetic (PK) Studies OPTIONAL

For patients who consent, peripheral blood samples will be collected for the purpose of determining trametinib concentration. When a patient is being considered for PD and PK studies, send an email to ADVL1521@ucsf.edu to receive a kit with supplies for blood collection with a copy to the COG assigned Study Research Coordinator.

Pharmacodynamic Studies: Plasma inhibitory assays will be performed to indirectly assess levels of MEK inhibition in patient samples. Phospho-flow cytometry will also be performed on samples to assess changes in intracellular and extracellular signaling after exposure to trametinib.

Pharmacokinetic Studies Trametinib will be extracted from plasma and will be quantified by internal standardization and HPLC-MS/MS methodology. Peak areas will be generated and peak area ratios will be used to calculate trametinib concentrations in each sample.

7.4.1.1 Sample Collection and Handling Instructions

Sampling Schedule and Collection
Blood samples will be obtained at the following time points during Cycle 1:

- Day 1, hours 0 and 4
- Day 15, hours 0 and 4

Sample Processing and Labeling
Collect blood samples of approximately 4 mL in a K2 EDTA Vacutainer and invert to ensure mixing of the anticoagulant and blood. Store the blood samples on wet ice for approximately 10 minutes. Centrifuge (refrigerated centrifuge) at approximately 2000g for 10 minutes at 4˚C. Transfer the plasma immediately after centrifugation to an appropriately labeled 1.8 mL NUNC storage tube and store at -80˚C. Plasma samples on day 1 and 15 can be stored at -80˚C, and batched for shipment on dry ice at the end of cycle 1 on day 28 along with smart tubes (see section 7.4.2.1**)**. Any remaining blood in the EDTA tubes after removing the plasma should be shipped room temperature on the day of collection.

Each tube must be labeled with the patient's COG I.D., study number (ADVL1521), and the date and time the sample was drawn. Data should be recorded on the PD and PK Specimen Transmittal Form, which must accompany the sample(s).

7.4.1.2 Sample Shipping Instructions
Ship samples to the Loh laboratory. Samples should be shipped between Monday and Thursday for overnight delivery to ensure delivery by Friday. Samples collected on Friday should be shipped on Monday. NUNC storage tubes should be shipped on dry ice. The EDTA tubes should be shipped at room temperature.

Please contact the laboratory prior to shipment, and send tracking information to the following email address:

ADVL1521@ucsf.edu with a copy to the COG assigned Study Research Coordinator.

FedEx Shipping account number: 331909297; select priority overnight

Samples should be shipped to the following address:

Elliot Stieglitz, MD
HDFCCC, Loh Lab 1450 3rd St, Room 230
San Francisco, CA 94158

Lab Contact: Alex Chao
Phone: (415) 514-9389
Email: ADVL1521@ucsf.edu

Subsequent Processing by Dr. Jones's Laboratory- Pharmacokinetic Studies
Samples will be processed by the Loh laboratory. A fraction of the plasma will be stored at -80˚C and shipped to Dr. David Jones laboratory at the University of Indiana. Plasma samples will be utilized for pharmacokinetic analysis, and the determination of blood trametinib concentrations.

Specimens will be batched and sent to the Jones laboratory with copies of the completed Specimen Transmittal Forms.

7.4.2 Genomic, Epigenomic and Functional Studies **OPTIONAL**

We will perform exome sequencing, RNA seq, methylation profiling, and CG-CSF hypersensitivity assays at diagnosis, at the end of Cycles 1 and 2, and disease progression (if applicable). We aim to determine whether genomic, transcriptomic, or epigenetic changes occur as a result of treatment with trametinib.

When a patient is being considered for these optional studies, send an email to ADVL1521@ucsf.edu with a copy to the COG assigned Study Research Coordinator, to receive a kit with supplies for bone marrow collection.

7.4.2.1 Sample Collection and Handling Instructions

For patients who consent, bone marrow and peripheral blood samples will be collected at the time points described below. Samples will be used to determine whether genomic, transcriptome, or epigenetic changes occur as a result of trametinib treatment.

If available, please send bone marrow slides (unstained aspirate smears or 5 unstained FFPE recuts) from the original diagnosis of JMML. DNA will be extracted for the purpose of mutation analysis and paired sequencing with relapse samples.

If a patient consents to optional studies, leftover DNA from buccal swabs collected as part of the mandatory Mutant Allele Burden Measurement test will be used as a germline control for next generation sequencing for research.

Sampling Schedule and Collection

Bone marrow and peripheral blood samples will be obtained at each of the following time points:

- Any time point between Day -14 through Day 0 before Cycle 1 therapy
- Day 28 of Cycle 1
- Day 28 of Cycle 2
- Progressive disease (when applicable)

Sample Processing and Labeling

Collect bone marrow samples of approximately 5-10 mL in Sodium (Na) Heparin green top tubes. Invert 5 times to ensure mixing of the anticoagulant and bone marrow.

Collect peripheral blood samples of approximately 5-10 ml in Sodium (Na) Heparin green top tubes and invert to ensure mixing of the anticoagulant and blood. Transfer 1ml from the Sodium Heparin tube(s) into three separate Smart Tubes (1ml in each of the three Smart Tubes). Smart Tubes collected before and during cycle 1 should be stored at -80°C and batched for shipment at the end of cycle 1 on day 28 along with NUNC tubes (see section 7.4.1.1). Any remaining blood in the Sodium Heparin tubes should be shipped same day at room temperature.

Smart tubes collected during cycle 2 and at progression (if applicable) should be stored at -80°C and shipped on dry ice as soon as possible.

Please see the ADVL1521 protocol page for additional Smart Tubes instructions.

Each tube must be labeled with the patient's COG I.D., study number (ADVL1521), and the date and time the sample was drawn. Data should be recorded on the Biologic Studies Specimen Transmittal Form, which must accompany the sample(s).

7.4.2.2 Sample Shipping Instructions

The samples should be shipped to the Loh laboratory. Samples should be shipped between Monday and Thursday for overnight delivery to ensure delivery by Friday. The sodium heparin tubes should be shipped at room temperature. The Smart Tubes should be sent on dry ice. Please contact the laboratory prior to shipment, and send tracking information to the following email address:

ADVL1521@ucsf.edu; with a copy to the COG assigned Study Research Coordinator

FedEx Shipping account number: 331909297; select priority overnight

Samples should be shipped to the following address:

Elliot Stieglitz, MD
HDFCCC, Loh Lab 1450 3rd St, Room 230
San Francisco, CA 94158

Lab Contact: Alex Chao
Phone: (415) 514-9389
Email: ADVL1521@ucsf.edu

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal From Protocol Therapy

a) Progressive disease.
b) Adverse Events requiring removal from protocol therapy, as stated in Section 5.0.
c) Patients who receive concurrent anticancer or investigational therapy, as stated in Section 4.1.4.
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Completion of 12 cycles of therapy.
f) Physician determines it is in patient's best interest.
g) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
h) Patients who develop a second malignant neoplasm.

Patients who are removed from protocol therapy (except for 8.1.g) are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.

b) Lost to follow-up.

c) Entry into another COG study with tumor therapeutic intent (e.g., at recurrence).

d) Withdrawal of consent for any further data submission.

e) The fifth anniversary of the date the patient was enrolled on this study.

f) Patient did not receive protocol treatment after study enrollment

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

COG study AAML0122 (for newly diagnosed JMML) accrued at an average annual rate of 15 patients/year in the US. Assuming roughly half of these newly-diagnosed patients relapse or are refractory to chemotherapy, we can expect an accrual rate of 7.5 relapsed/refractory patients/year. With these entry rates, the probability of accruing 10 patients to complete the initial stage of evaluation within 20 months is 80% and within 24.5 months is 90%. The corresponding probability for enrolling 20 patients in 38 months is 80% and within 43 months is 90%. Allowing for a 20% inevaluability rate, a minimum of 10 patients and a maximum of 24 patients are anticipated. The study will likely require 2.5 to 3.5 years for sufficient patient enrollments to evaluate trametinib in relapsed/refractory JMML.

9.2 Study Design

The primary endpoint will be objective response by the criteria listed in Section 10.2. The following Simon two-stage design will be used.

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 patients	0	Terminate the trial: agent ineffective
	1 or more	Inconclusive result, continue trial (proceed to Stage 2)
Stage 2: Enter 10 additional patients	2 or less	Terminate the trial: agent ineffective
	3 or more	Terminate the trial: agent effective

We will consider trametinib not of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient interest if the true response rate is 25%. If the agent has a true response rate of 5%, the rule described above will identify it of sufficient interest for further study with probability 0.069 (type I error), and the trial will have an expected sample size of 14.01 with 59.9% probability of early termination.

If the agent has a true response rate of 25%, the rule described above will identify it of sufficient interest for further study with probability 0.882 (power against the alternative hypothesis $p = 0.25$). An expanded table of possible true response rates is below:

True response rate	Probability of stopping early for lack of activity	Probability of identifying agent as effective	Expected number of patients accrued
5%	0.599	0.069	14.01
10%	0.349	0.299	16.51
15%	0.197	0.560	18.03
20%	0.107	0.759	18.93
25%	0.056	0.882	19.44
30%	0.028	0.947	19.72
35%	0.013	0.978	19.87

9.3 Methods of Analysis

Response criteria are described in Appendix III. A responder is defined as a patient who achieves a best response (as defined in Section 10.2) of PR or CR on the study prior to having an overall response of PD (as defined in Section 10.2); all others will be considered non-responders. The evaluation period for determination of the best response will be 12 treatment cycles. Response rates will be calculated as the percent of evaluable patients who are responders, and confidence intervals will be constructed accounting for the two-stage design.

Duration of response (Aim 1.2.5) will be defined as the time from first occurrence of PR or CR until the first occurrence of PD, death, or going off study. Patients who progress will be considered to have had an event, patients who die prior to progressing will be considered to have a competing event, and patients who go off study prior to progressing will be censored at time of last contact. The analysis will be done using the method of Gray. [45]

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. A patient will be counted only once for a given toxicity for the worst grade of that toxicity reported for that patient. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen.

The analytic unit for monitoring for protocol-specific toxicities will be the patient-course: Each course where the patient receives the agent and either 1) has a protocol-specific toxicity event, or 2) receives at least 85% of their assigned dose during the cycle will be considered in the analysis. If there is strong evidence (posterior probability of at least 70% with at least 2 observed toxicities) that there is a per course protocol-specific toxicity probability of more than 20%, such information will be presented to the DSMC.

We will use a Bayesian rule to monitor for protocol-specific toxicities. We will assume a beta prior distribution with $\alpha = 0.52$ and $\beta = 2.08$. At least once per month, we will calculate the posterior probability (given the data) that the probability of protocol-specific toxicity exceeds the 20% threshold:

$$P(p_{\text{protocol-specific toxicities}} > 20\% \mid \text{Data}) = \int_{0.2}^{1} \frac{\binom{n}{x} p^x (1-p)^{n-x} \cdot \frac{\Gamma(2.6)}{\Gamma(0.52)\Gamma(2.08)} \cdot p^{-0.48}(1-p)^{1.08}}{\int_0^1 \binom{n}{x} q^x (1-q)^{n-x} \cdot \frac{\Gamma(2.6)}{\Gamma(0.52)\Gamma(2.08)} \cdot q^{-0.48}(1-q)^{1.08} dq} dp$$

Here *n* is the number of protocol-specific toxicity-evaluable cycles and *x* is the number of such cycles on which a protocol-specific toxicity event is observed. Examples of situations in which this rule will indicate protocol-specific toxicities have been noted and are presented below:

Number of failures	Number of patient-cycles
2	6
3	10
4	14
5	19
6	23
7	28
8	32
9	37
10	41
11	46
12	51
13	55
14	60

Protocol-specific toxicities of interest include rash, diarrhea, ejection fraction changes, hypertension, prolonged QTc, pneumonitis, visual changes, ALT increase, AST increase, and bilirubin increase.

If there is strong evidence (posterior probability of at least 70% with at least 2 observed toxicities) that there is a per course protocol-specific toxicity probability of more than 20%, such information will be presented to the DSMC.

9.4 Evaluability for Response

Any patient who is enrolled and receives at least one dose of trametinib will be considered evaluable for response.

9.5 Evaluability for Toxicity

All patients who either (1) receive one dose of trametinib and have a toxicity, or (2) receive at least 85% of the total dose of trametinib according to protocol guidelines during the first cycle of therapy will be considered in the evaluation of toxicity.

9.6 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	1	0	0	**1**
Black or African American	1	1	0	0	**2**
White	4	11	2	2	**19**
More Than One Race	0	0	0	0	**0**
Total	**6**	**14**	**2**	**2**	**24**

This distribution was derived from AAML0122.

9.7 Analysis of the Pharmacokinetic Parameters

A descriptive analysis of pharmacokinetic (PK) parameters of trametinib will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

9.8 Analysis of Biological and Correlative Endpoints

Mutant allele burden (as percentages) and trametinib concentrations as measured by mass spectrometry will be analyzed descriptively. Values will be summarized with means, standard deviations, and 95% confidence intervals.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. The descriptions and grading scales found in the revised CTCAE version 5.0 will be utilized for reporting. All appropriate treatment areas should have

access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Additionally, toxicities are to be reported on the appropriate case report forms.

10.2 Response Criteria

Response and progression will be evaluated using the tables found in Appendix III. These criteria were developed by an international consensus panel. [46]

The overall response will be defined in terms of the genetic and clinical responses defined in Appendix III according to the following table:

Genetic Response	Clinical Response			
	cCR	**cPR**	**cSD**	**cPD**
gCR	CR	CR	CR	PD
gSD	PR	PR	SD	PD
gPD	PD	PD	PD	PD

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting table assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.3 Specific Examples for Expedited Reporting

11.3.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting table in this protocol.

11.3.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered serious AEs.

11.3.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as ***Grade 5 Disease Progression*** under the system organ class (SOC) ***"General disorders and administration site conditions."*** Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.3.4 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.3.5 Second Malignancy

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

11.3.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.3.6.1 Pregnancy

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions – Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.3.6.2 Pregnancy Loss (Fetal Death)

- Pregnancy loss is defined in CTCAE as "Death in utero."
- Any pregnancy loss should be reported expeditiously, as **Grade 4 *"Pregnancy loss"*** under the ***"Pregnancy, puerperium and perinatal conditions"*** **SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.3.6.3 Death Neonatal

- Neonatal death, defined in CTCAE as ***"Newborn deaths occurring during the first 28 days after birth"*** that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

- A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the "General disorders and administration" SOC **when the death is the result of a patient pregnancy or pregnancy in partners of men on study**

- Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

11.4 Reporting Requirements for Specialized AEs

11.4.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.4.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.4.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.5 Exceptions to Expedited Reporting

11.5.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL)).

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.5.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting table for this protocol.

11.6 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.7 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (e.g., H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **(301) 230-0159** (back-up: (301) 897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax# (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.8 Reporting Table for Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	**7 Calendar Days**			**24-Hour Notification 5 Calendar Days**
Not resulting in Hospitalization ≥ 24 hrs	**Not Required**		**7 Calendar Days**	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.9 Protocol Specific Additional Instructions and Reporting Exceptions

- **Grades 1-4 hematologic toxicity (anemia, neutropenia, and thrombocytopenia) do not require expedited reporting.**
- **Grade 1-2 non-hematologic toxicities do not need to be reported unless they otherwise meet criteria for a serious adverse event as defined above.**

11.10 Routine Reporting of Adverse Events

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and Grade 3 and higher Adverse Events.

Hematologic Toxicity: Routine reporting of all grade 1-4 hematologic toxicities is not required in RAVE.

Non-Hematologic Toxicities: Please also report the following via the RAVE AE CRFs:

- All Grade 3 and higher non-hematologic toxicities should be reported.
- The following Grade 1 and 2 events should be reported:
    - Ejection fraction decreased
    - Pneumonitis
    - Eye disorders
    - Paronychia
    - Skin and subcutaneous tissue disorders
    - Palmar-plantar erythrodysesthesia syndrome
    - Diarrhea

Please see section 11.4 for more information regarding routine reporting requirements.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG website with each protocol under “Data Collection/Specimens”. A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children’s Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair’s report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

12.3 CRADA/CTA

NCI/ DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA), a Cooperative Research and Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said

other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

INVESTIGATOR AND RESEARCH ASSOCIATE REGISTRATION WITH CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Downloading Site Registration Documents:
Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *COG*, and protocol number (*insert study number*).
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Protocol-Specific Requirements For Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Data Submission / Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

APPENDIX II: DOSING NOMOGRAM

Consistent with dose levels defined in the pediatric solid tumor study, trametinib dosing will be weight based. The drug is supplied in tablet form or in or solution form, with dosing nomogram for tablet formulation below. **The maximum dose is 2 mg per day.**

Note: If switching from trametinib solution to trametinib tablets or vice versa in patients requiring dose reduction, match up the patient's starting dose to ensure the proper dose reduction is being made.

Dose Level: 0.025 mg/kg/dose PO once daily (age ≥ 6 years)
Subject Weight: ≥ 35 kg
Formulation: **Trametinib Tablets** 0.5 and 2 mg

Actual Weight*(kg)	Dose (mg)	Number of 0.5 mg tablets	Number of 2 mg tablets	Dose Reduction (mg)	Number of 0.5 mg tablets	Number of 2 mg tablets
35 – 50	1 mg	2	0	Oral solution only 0.75 mg (15 mL)		
50.1 – 70	1.5 mg	3	0	1 mg	2	0
≥ 70.1	2 mg	0	1	1.5 mg	3	0

*weight measured within 7 days of the start of the cycle

Dose Level: 0.032 mg/kg/dose PO once daily (age 1 month to < 6 years)
Subject Weight: ≥ 26.6 kg
Formulation: **Trametinib Tablets** 0.5 and 2 mg

Actual Weight*(kg)	Dose (mg)	Number of 0.5 mg tablets	Number of 2 mg tablets	Dose Reduction (mg)	Number of 0.5 mg tablets	Number of 2 mg tablets
26.6 – 39	1 mg	2	0	Oral solution only 0.75 mg (15 mL)		
39.1 – 54.6	1.5 mg	3	0	1 mg	2	0
≥54.7	2 mg	0	1	1.5 mg	3	0

*weight measured within 7 days of the start of the cycle

APPENDIX III: RESPONSE CRITERIA FOR PATIENTS WITH JMML

Table 1: Variables for evaluation of response to therapy in JMML

Variables for Response		Definition of response			Definition of disease progression or relapse (applicable to all patients)
		Assessment of CR and PR is feasible if the following are present before therapy	Requirement for CR for each variable (vCR)	Requirement for PR for each variable (vPR)	Requirement for PD for each variable (vPD)
Clinical variables	1) WBC count	>20 × 10^9/L	3.0 – 15.0 × 10^9/L	Decreased by ≥50% over pretreatment but still >15 × 10^9/L	Increase by ≥50% and ≥20 × 10^9/L
	2) Myeloid and erythroid precursors and blasts in PB*	≥ 5%	0-1%	Decreased by ≥50% over pretreatment but still ≥ 2%	Increase from the baseline: < 5%: ≥ 50% increase and ≥ 5% ≥ 5%: ≥ 50% increase of total % of myeloid and erythroid precursors and blasts
	3) Platelet count	<100 × 10^9/L	>100 × 10^9/L	For patients starting with ≥ 20 × 10^9/L platelets: absolute increase of ≥ 30 × 10^9/L For patients starting with < 20 × 10^9/L platelets: increase by ≥ 100% and > 20 × 10^9/L	Development of transfusion dependency or if patients have the baseline of the platelet count of ≥30 × 10^9/L, decrease by ≥50% and <100 × 10^9/L
	4) BM blasts	≥5%	<5%	Decreased by ≥50% over pre-treatment but still ≥5%	Increase from base line; < 5%: ≥ 50% increase and ≥ 5% ≥ 5%: ≥ 50% increase of BM blasts
	5) Spleen size				
	a) Clinical evaluation or	≥2 cm under the costal margin	No splenomegaly	50% decrease by cm under the costal margin	Increase by ≥100% if baseline <4cm from under the costa margin ≥50% if baseline 5-10cm >30% if baseline >10 cm
	b) Sonography	Length of spleen ≥ 150% of upper limit of normal range	No splenomegaly	>25% decrease by length, but still splenomegaly	Increase by ≥25% of length
	6) Extramedullary disease#	Extramedullary leukemic infiltration	No evidence of extramedullary leukemic infiltration in any organ	-	Worsening or new lesions of extramedullary leukemic infiltration
7) Cytogenetic response		Somatic cytogenetic abnormality detected	Normal karyotype	-	Reappearance or additional acquirement of cytogenetic abnormalities
8) Molecular response		Somatic genetic anomalies detected **	Absence of somatic genetic anomalies	-	Reappearance or additional acquirement of JMML-specific somatic gene abnormalities
9) Chimerism response (only for patients after HSCT)		>15% autologous cells after allo-HSCT	Complete donor chimerism	-	50% increase and >5% increase of autologous cells and >5%

CR: complete response, PR: partial response, PD: progressive disease, WBC: white blood cell, PB: peripheral blood, BM: bone marrow

*Myeloid precursors include promyelocytes, myelocytes, and metamyelocytes. The myeloid and erythroid precursors and blasts in PB are given as % of the total nucleated cells in PB (WBC including erythroblasts).

**in *NF-1, PTPN11, NRAS, KRAS, RRAS2,* or *CBL,* thus the mutation are thought to be initiating. In patients with germ-line *NF-1, PTPN11* or *CBL* mutation, only acquired mutations can be evaluated for response and relapse after therapy. The germ-line mutation remains even if patients achieved complete molecular response. The molecular response will be determined using the "JMML Mutant Allele Burden" assay.

Criteria for progression including WBC, platelet count and spleen size cannot be used in the setting of an active infection.

#Extramedullary disease includes infiltration of skin, lung, and very rarely cranial nerves or central nervous system.

Table 2: Definition of response following therapy other than HSCT in JMML

Clinical remission status: parameter 1-6 of table 1		Genetic remission status: parameter 7-9 of table 1	
Clinical complete remission (cCR)	Patient fulfills the criteria of CR of all applicable clinical variables 1-6 of table 1 The response parameters must be maintained for at least 4 weeks.	**Genetic complete remission (gCR)**	Defined if the patient shows a normal karyotype and absence of acquired mutations in *PTPN11*, *NF-1*, *NRAS*, *KRAS*, or *CBL*.
Clinical partial remission (cPR)	Defined if the patient does not fulfill the criteria of cCR, but vPR was achieved in at least one of clinical variables (1 – 6) and none of clinical variables showed vPD.	-	-
Clinical stable disease (cSD)	Defined if the patient does not fulfill the criteria of cCR and cPR, but none of the parameter showed vPD.	**Genetic stable disease (gSD)**	Defined if the patient does not fulfill the criteria of gCR, but none of the genetic parameters (7-9) showed vPD.
Clinical progressive disease (cPD)	Defined if any of the parameters 1-6 showed vPD.	**Genetic progressive disease (gPD)**	Defined if any of the parameters 7-9 showed vPD.
Clinical relapse (cRel)	Defined if any of the parameters 1 - 6 showed vPD after the achievement of cCR or cPR.	**Genetic relapse (gRel)**	Reappearance of an abnormal karyotype *and/or* mutation of genes related with JMML if previously undetected, *and/or* (only for patients after HSCT) increase in recipient chimerism with at least 10% of autologous cells and >50% increase above the base line.

**In patients with germ-line *NF-1, PTPN11* or *CBL* mutation, the germ-line mutation remains even if patients achieved a genetic complete remission.

APPENDIX IV: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1521
(For children from 7 through 12 years of age)

A study of the drug trametinib in children and young adults with a cancer that has come back after treatment or is difficult to treat

1. We have been talking with you about your cancer. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.

2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have. We will do this by trying a new medicine to treat your cancer.

3. Children who are part of this study will be treated with a cancer-fighting medicine called trametinib. You will also have regular tests and exams done more often while you are in this study. The doctors want to see if trametinib will make children with your type of cancer get better. We don't know if trametinib will work well to get rid of your cancer. That is why we are doing this study.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that trametinib may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from trametinib than other treatments. Other things may happen to you that we don't yet know about.

6. Your family can choose for you to be part of this study or not. Your family can also decide for you to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. As part of your regular care, your doctor may have removed some bone marrow and/or blood to see if you have cancer. If you take part in this study, we will keep some of the tissue that is left over to do special tests. These tests may help us learn more about how trametinib works.

INFORMATION SHEET REGARDING RESEARCH STUDY ADVL1521
(For teens from 13 through 17 years of age)

A study of the drug trametinib in children
with a cancer that has come back after treatment or is difficult to treat

1. We have been talking with you about your cancer. You have been diagnosed with Juvenile Myelomonocytic Leukemia. You have had treatment for the cancer already but the cancer did not go away or it came back after treatment.

2. We are asking you to take part in a research study because other treatments did not get rid of the cancer. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the kind of cancer that you have.

3. Children and teens who are part of this study will be given a cancer-fighting medicine called trametinib. We are using trametinib in this study because it seems to work against certain types of cancer cells in test tubes and animals. Trametinib is considered experimental because the Food and Drug Administration (FDA) has not approved this drug for JMML. The dose of trametinib used in this study was found to be well-tolerated in adults.

4. You will get trametinib by mouth, once a day, on Days 1 through 28 of a 28-day period. This entire 28-day period is called a cycle. You may continue to receive trametinib for up to about 12 months (up to 12 cycles) as long as you do not have bad effects from it and your cancer does not get any worse. You will also have exams and tests done that are part of normal cancer care. But, the exams and tests will be done more often while you are being treated with trametinib. The doctors want to see if trametinib will make children with your type of cancer get better. We don't know if trametinib is better than other medicines. That is why we are doing this study.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that trametinib may cause your cancer to stop growing or to shrink for a period of time but we don't know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you may have more problems, or side effects, from trametinib than other treatments. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

8. As part of your regular care, your doctor may have removed some bone marrow and/or blood to see if you have cancer. If you take part in this study, we will keep some of the tissue that is left over to do special research tests. These tests may help us learn more about how trametinib works. The samples will come from leftover tissue so there would be no extra procedures.

APPENDIX V: DETERMINATION OF PATHOGENICITY

Variants will be determined as pathogenic, likely pathogenic, variants of uncertain significance, likely benign or benign. A combination of assessments are used to determine the classification of each variant in accordance with the "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology". [47]

Single nucleotide polymorphisms (SNPs): Variants are cross referenced in databases including:

dbSNP https://www.ncbi.nlm.nih.gov/projects/SNP/
ExAC http://exac.broadinstitute.org/
1000 genomes project. http://www.internationalgenome.org/

In silico prediction: Variants are assessed for pathogenicity using:
Mutation Assessor http://mutationassessor.org/r3/
SIFT http://sift.jcvi.org/
Polyphen. http://genetics.bwh.harvard.edu/pph/data/

Conservation: Variants are assessed using GERP (http://mendel.stanford.edu/SidowLab/downloads/gerp/) to assess for conservation amongst species.

Cancer Databases: Variants are cross-referenced in COSMIC (http://cancer.sanger.ac.uk/cosmic), and cBioPortal (http://www.cbioportal.org/) and assessed for prior evidence of pathogenicity.

Tumor-Normal: The allelic frequency for each variant is determined in both a tumor and a normal sample.

APPENDIX VI: TRAMETINIB MEDICATION DIARY (TABLET)

COG Patient ID:_____ ACC # : _____ Institution :_____

Please do not write patient names on this form.

Complete each day with the date, time and number of trametinib tablets taken. Make note of other drugs and supplements taken. Your doctor will tell you what foods you should avoid. Trametinib should be taken by mouth on an empty stomach once a day, at least 1 hour before or 2 hours after a meal. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs within 30 minutes of taking the tablet formulation, the dose of trametinib can be repeated once. Return the completed diary to your institution at the end of each treatment cycle. Please return all unused tablets at the end of each cycle. Store tablets in the refrigerator.

Sites will fill out the day of the week and number of prescribed tablets per day according to the dosing nomogram in Appendix II.

EXAMPLE				*Number of Tablets taken*		*Comments*
WEEK 1	*Date*	*Time*		*0.5 mg*	*2 mg*	.
Day 1: Monday	*1/15/12*	*8:30*	*AM*	*# prescribed: 3* *# taken: 3*	*# prescribed: 0* *# taken: 0*	*He felt nauseated an hour after taking the drug but did not vomit*

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

kg _____ Dose: _____mg/kg Total Daily Dose per Nomogram: _____ mg

WEEK 1	Date	Time		0.5 mg	2 mg	Comments
Day 1: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 2: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 3: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 4: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 5: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 6: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 7: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

WEEK 2	Date	Time		0.5 mg	2 mg	Comments
Day 8: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 9: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 10: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 11: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 12: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 13: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 14: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

WEEK 3	Date	Time		0.5 mg	2 mg	Comments
Day 15: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 16: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 17: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 18: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 19: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 20: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 21: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

WEEK 4	Date	Time		0.5 mg	2 mg	Comments
Day 22: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 23: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 24: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 25: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 26: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 27: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	
Day 28: _____			**AM / PM**	# prescribed:_____ # taken: _____	# prescribed:_____ # taken: _____	

Comments:

APPENDIX VII: TRAMETINIB MEDICATION DIARY (ORAL SOLUTION)

COG Patient ID:_____ ACC # : _____ Institution :_____
Please do not write patient names on this form.

Complete each day with the date, time and volume in mL of trametinib oral solution taken. Make note of other drugs and supplements taken. Your doctor will tell you what foods you should avoid. Trametinib should be taken by mouth on an empty stomach once a day, at least 1 hour before or 2 hours after a meal. Do not take a missed dose of trametinib within 12 hours of the next scheduled dose. If vomiting occurs after taking oral solution formulation, the dose should NOT be repeated and the next dose should be administered at the regularly scheduled time. Return the completed diary to your institution at the end of each treatment cycle. Please return all unused solution at the end of each cycle. Store the solution at room temperature (25°C or 77°F).

Immediately prior to the removal of dose for administration swirl the bottle of solution gently 2-3 times, if any foam appears allow the bottle to sit for at least 1 minute for the foam to dissipate. Remove the required dose using a suitable graduated syringe:

a. Ensure that the syringe plunger is fully pushed into the barrel.
b. Insert the syringe tip into the Adapter, then invert the bottle and dispense at least 5 mL of solution into the syringe and then pump the entire solution back into the bottle to purge the syringe of any air bubbles. Repeat this step until the syringe is free from air bubbles.
c. Withdraw the required dosing volume. Then re-invert the bottle and remove the syringe from the Adapter and administer the dose to the patient as soon as possible.

Sites will fill out the day of the week and the volume of prescribed solution per day.

EXAMPLE				***Amount of oral solution taken***	***Comments***
WEEK 1	***Date***	***Time***		***(total mL per dose)***	
Day 1	*1/15/09*	*8:30*	*AM*	*2*	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|
kg: _____ Dose: _____mg/kg Total Daily Dose per Nomogram: _____ mg

WEEK 1	**Date**	**Time**		**Amount of solution taken (total mL per dose)**	**Comments**
Day 1: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 2: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 3: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	

Day 4: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 5: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 6: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 7: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	

WEEK 2	**Date**	**Time**		**Amount of solution taken (total mL per dose)**	**Comments**
Day 8: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 9: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 10: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 11: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 12: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 13: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 14: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	

WEEK 3	**Date**	**Time**		**Amount of solution taken (total mL per dose)**	**Comments**
Day 15: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 16: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	

Day 17: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 18: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 19: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 20: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 21: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	

WEEK 4	**Date**	**Time**		**Amount of solution taken (total mL per dose)**	**Comments**
Day 22: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 23: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 24: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 25: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 26: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 27: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	
Day 28: _____			**AM / PM**	# mL prescribed:_____ # mL taken: _____	

Comments:

APPENDIX VIII: WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: ADV1521

Study Drug(S): Trametinib

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX IX: BLOOD PRESSURE LEVELS FOR CHILDREN BY AGE AND HEIGHT PERCENTILE

Blood pressure (BP) levels for BOYS:

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

Instructions for using this BP Chart:
1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.1.1 for definition of dose limiting hypertension. See Section 5.4.9.2 for management and grading of hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High BloodPressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Note: For patients ≥ 18 yrs, ULN BP is 140/90 mmHg.

Blood pressure (BP) levels for GIRLS:

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Instructions for using this BP Chart:
1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.
4. See Section 5.1.1 for definition of dose limiting hypertension. See Section 5.4.9.2 for management and grading of hypertension.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High BloodPressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

Note: For patients ≥ 18 yrs, ULN BP is 140/90 mmHg.

APPENDIX X: Toxicity-Specific Grading

Bilirubin

Grade 1:	≤ 1.5 x ULN
Grade 2:	> 1.5- 3.0 x ULN
Grade 3:	> 3.0-10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for SGPT is 45 U/L regardless of baseline.

Grade 1:	≤ 135
Grade 2:	136- 225
Grade 3:	226- 900
Grade 4:	> 900

AST: For the purpose of this study, the ULN for SGPT is 50 U/L regardless of baseline.

Grade 1:	≤ 150
Grade 2:	151-250
Grade 3:	251-1000
Grade 4:	> 1000

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5- 5.0 x ULN
Grade 3:	> 5.0-20.0 x ULN
Grade 4:	> 20.0 x ULN

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39. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.,

40. Visual disorders include visual disturbance that can be associated with conjunctival hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, iritis, macular edema, retinal hemorrhage, visual acuity reduced, visual impairment, and vitreous detachment.,
41. Generalized edema includes edema, lymphedema, and edema limbs.,
42. Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.,
43. Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.,
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