To: CTEP Protocol and Information Office

From: Alice Chen, MD, DTC, NCI

Date: January 7, 2019

Re: Amendment to Protocol 9149: Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors

---

With this amendment, we are incorporating recommendations from CTEP's review of protocol version 02/06/2019, and making some administrative changes.

We would also like to update the protocol to allow the sole patient who continues to receive randomized Trametinib DMSO treatment (22+ cycles) to consent to having her mutational status and arm assignment (i.e., experimental or control) disclosed to herself and/or her treating physician now, rather than wait until disease progression, given the new non-randomized study design and statistical analysis plan. We would also like to allow this patient to consent to sample unlinking while she remains on study, in order to enable research-use analysis of her sample in parallel with the other results from the randomized portion of the study. Thank you for your consideration.

I. Recommendations from CTEP review of Amendment #37 (pv 02/06/2019)

#	Section	Comments
1.	12.1	**Please revise the following paragraph as indicated.** Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) ~~(Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator)~~ on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or Rave CRA (Lab Admin) ~~Rave CRA role or CRA Lab Admin~~ role, the user must hold a minimum of an AP registration type. To hold the Rave ~~Site~~ Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. **PI Response:** We have revised the paragraph as indicated.

II. Other Protocol Changes

#	Section	Comments
2.	Cover Page	Updated the protocol version date and letters.

#	Section	Comments
3.	Cover Page	Updated the list of Associate Investigators.
4.	2 5.2	Given the new non-randomized study design and statistical analysis plan, we would like to revise and update the protocol to allow the sole patient who continues to receive randomized Trametinib DMSO treatment (22+ cycles) to consent to having her mutational status and arm assignment (i.e., experimental or control) disclosed to herself and/or her treating physician now, rather than wait until disease progression to find out per the original study plan. The patient, in discussion with the treating physician, will have the same on-study treatment options at progression as before, but because she is unblinded we think she will have better information sooner about her future treatment options.
5.	9.4.1	Revised the sample unlinking procedure to allow sample unlinking for the sole remaining randomized patient to occur while the patient remains on study, in order to enable research-use analysis of her sample in parallel with the other results from the randomized portion of the study.
6.	Appendix F	Replaced the Biopsy Sequencing Results and Analysis Form with an updated form supplied by the MoCha lab. .

Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors

Abbreviated Title: MPACT

Coordinating Center:
LAO-NCI/National Cancer Institute LAO
National Cancer Institute
10 Center Drive, 12N226
Bethesda, MD 20892

Principal Investigator:
A. P. Chen, MD[A-E]
Developmental Therapeutics Clinic (NCI DTC MM)
31 Center Drive, Bldg 31, Room 3A44
Bethesda, MD 20892
Phone: (240) 781-3320
Fax: (240) 541-4515
chenali@mail.nih.gov

NCI Co-Investigators:
James H. Doroshow, MD, DCTD[A-E]
Richard Piekarz, MD, PhD, DCTD[A-E]
Geraldine O'Sullivan Coyne, MD, PhD, DCTD[A-E]
Howard Streicher, MD, DCTD[A-E]
Naoko Takebe, MD, PhD, DCTD[A-E]
Arjun Mittra, MD, DCTD[A-E]
Sheila Prindiville, MD, MPH, DCTD[A-E]
Rafeh Naqash, MD, DCTD/ NCI[A-E]
Jessica Mukherjee, MS, CRNP, DCTD/NCI[A,B,E]

Non-NCI Co-Investigators:
Lamin Juwara CRNP, Leidos Biomed., FNLCR[A,B,E]
P. Mickey Williams, PhD, Leidos Biomed., FNLCR[F]

Referral Contact:
Nancy Moore, RN, DCTD[A,B,E]
Bldg 10/Rm 13N-214
(240) 760-6045
Fax: (301) 451-5625
nancy.moore@nih.gov

Roles: [A]obtains information by intervening or interacting with living individuals for research purposes; [B]obtains identifiable private information about living individuals; [C]obtains the voluntary informed consent of individuals to be subjects; [D]makes decisions about subject eligibility; [E]studies, interprets, or analyzes identifiable private information or data/specimens for research purposes; [F]reviews patient genetic sequencing data but is not involved in clinical care

Participating Organizations:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO

Statisticians:

Larry Rubinstein, PhD[E]
9609 Medical Center Dr.
Rockville, MD 20850
Phone: (240) 276 6026
rubinsteinl@ctep.nci.nih.gov

Jared Foster, PhD
9609 Medical Center Dr.
Rockville, MD 20850
Phone: (240) 276 7385
fosterjc@nih.gov

NCI-supplied Agents:

AZD1775 (NSC 751084)
Veliparib (NSC 737664)
Trametinib DMSO (NSC 763093)
Everolimus (NSC 733504)
Temozolomide (NSC 362856)
Carboplatin (NSC 241240)

IND Number: 116976

Version Date: January 7, 2020 (Amendment Y, iRIS V)

PRÉCIS

Background:

- Targeted therapy based on identifying underlying genetic aberrations within the tumor is the goal of personalized medicine. This pilot trial aims to establish whether advanced cancer patients who have no treatment options with proven benefit, and with tumor mutations in one of 3 genetic pathways (DNA repair, PI3K, or RAS/RAF/MEK) are more likely to derive clinical benefit if treated with agents targeting that pathway than if treated with agents that do not. Each patient will be randomly assigned to receive the recommended Phase II dose of either a study drug identified to work on their tumor's mutation/aberrant pathway, or an agent from the complementary set not identified to work on the mutations of interest. *As of Amendment U, only the DNA repair arm remains open to accrual.*

Objectives:

- Evaluate the proportion of patients with objective response (OR) to targeted study agent(s) in patients with advanced refractory cancers.

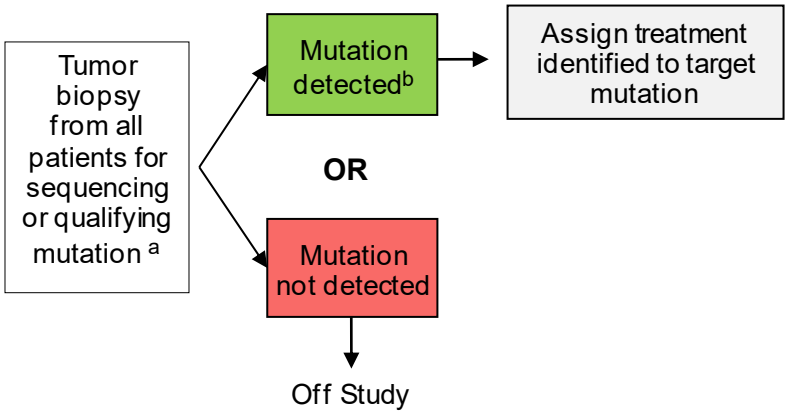
Eligibility:

- Adult patients with histologically documented solid tumors whose disease has progressed following at least one line of standard therapy and/or for which no standard treatment is available that has been shown to improve survival.
- Tumor amenable to percutaneous biopsy, and willingness to undergo tumor biopsy.

Study Design:

- Patients enrolled on study will have a tumor biopsy sequenced in a CLIA-certified lab for specific mutations of interest in DNA repair pathways. If such mutations are not detected, the patient will be taken off study. Eligibility may also be determined from existing CLIA genetic testing reports from a MATCH-designated CLIA lab.
    - Patients who have received PARPi in combination with temozolomide are not eligible.
- Patients in whom a mutation of interest is detected will receive an agent prospectively identified to target that mutation/pathway
- Targeted drugs will be administered at recommended Phase II doses and schedules: (1) Veliparib (PARP inhibitor) with temozolomide for defects in the DNA repair pathway; (2) AZD1775 (Wee1 inhibitor) plus carboplatin for defects in DNA repair pathway; (3) Everolimus (mTOR inhibitor) for mutations in the PI3K pathway; or (4) Trametinib DMSO (MEK inhibitor) for mutations in the RAS/RAF/MEK pathway. *As of Amendment U, only the Veliparib with temozolomide arm remains open to accrual.*
- Given the relative frequencies of the mutations, up to 100 patients will need to be enrolled to acquire 30 evaluable patients per open arm.

SCHEMA

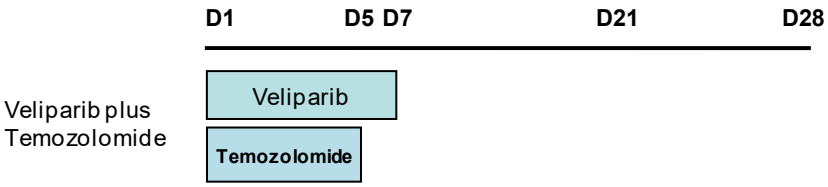


[a] Tumor biopsy (mandatory) will be performed on all patients enrolled on study; tissue will be sequenced for the presence of specific mutations of interest. Patients with qualifying MATCH-designated lab genetic testing reports may also be eligible.

[b] Only patients with specified mutations of interest will be administered targeted drug at recommended Phase II doses and schedules (see page 5).

One additional optional tumor biopsy may be performed at time of disease progression on study to assess for new mutations. (This biopsy may instead be collected on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (per RECIST criteria) if the patient has been on study for at least 4 cycles).

Cycle 1 and Subsequent Cycles



Patients with specified mutations of interest will be assigned to receive the following study drug combination at the assigned dose. Cycle length is +/- 1 day for scheduling:

- **Veliparib** 40 mg orally BID qd days 1-7 plus **temozolomide** 150 mg/m^2 orally qd days 1-5 (no food restrictions) in 28-day cycles

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary

Evaluate the proportion of patients with objective response (OR) to targeted study agent(s) in patients with advanced refractory cancers.

2. BACKGROUND

The initial design of this targeted pilot trial was to establish whether patients with tumor mutations in one of the genetic pathways of interest (DNA repair, PI3K, or RAS/RAF/MEK) are more likely to derive clinical benefit (defined as objective response or progression-free survival) if treated with agents targeting that specific pathway than with agents that do not. The study design was developed in conjunction with experts in clinical trial design, genetic sequencing, molecular oncology, cell biology, and statistics, who developed an algorithm that defines clinical action based on genetic variants reported in the genes of interest (Table 1 and Section 2.2). Aberrations in the PI3K-Akt, KRAS and RAF/MEK/ERK pathways and defects in the DNA repair pathways are common in several cancers. Each of these pathways and the selected targeted agents are discussed below. The genes of interest and mutations to be analyzed have been prospectively defined based on the recommendations of the multidisciplinary Molecular Tumor Board convened for this study (membership list included in Appendix G).

This study was placed on hold in January 2018 for interim futility analysis of the AZD1775 plus carboplatin and Trametinib DMSO arms (see Section 13), at which time a total of 193 patients had biopsies collected for screening and 99 (51%) had an actionable mutation of interest for randomizing to study drug. The major conclusions from this analysis are summarized below; a manuscript describing study results is in progress:

1. No confirmed objective responses were measured among the initial 18 patients of the AZD1775 plus carboplatin cohort; this cohort was terminated in March 2018.
2. One confirmed response was measured among 20 patients starting treatment on the Trametinib DMSO experimental cohort (accrual beyond 12 patients was due to delayed outcome reporting from participating sites); this cohort was terminated in March 2018.
3. There were insufficient numbers of patients treated on the everolimus experimental cohort to assess response rate, but no responses were measured; this cohort was terminated in March 2018.
4. There were insufficient numbers of patients treated on the veliparib plus temozolomide arm to assess response rate, but no responses were measured; however, the study team have revised the eligibility criteria to include BRCA mutations, which is projected to increase the hit rate.
5. Using the percentage of patients who started their assigned treatment as a measure of compliance, the overall percentage of patients assigned to experimental arm B who elected not to receive treatment was 47%, unexpectedly higher than the rate for patients assigned to experimental arm A (23%) (p=.02, 1-sided, by Fisher exact test). Interim analysis therefore suggests that patients at participating sites were choosing not to participate on the assigned

control arm because *a priori* knowledge of their mutations of interest (e.g., from FoundationOne reports) led to expectation of treatment assignment. Our hypothesis, that conducting genetic analysis and choosing targeted therapy based on genomic analysis will result in improved response rate and PFS, cannot be evaluated in light of this—indeed, the utility of the randomized phase 2 design to determine whether targeted therapy based on presence of drug-susceptible tumor mutations will result in improved response rate is clearly in doubt [1]. Based on these data it was determined that the study will reopen without randomization; patients with actionable mutations of interest will be assigned to targeted treatment arm(s) to assess the proportion of patients with objective response. The performance of each individual mutational status cohort will be compared to that of historical controls.

With the current non-randomized study design and statistical analysis plan, there is less of a rationale for blinding randomized patients, treating physicians, and the study team to the actual sequencing data until disease progression. As of Amendment Y (January 7, 2020) one patient who was randomized to the Trametinib DMSO cohort under the original study design remains on treatment with prolonged stable disease (22+ cycles), blinded to sequencing results and arm assignment. Amendment Y allows this patient to consent to having her mutational status and arm assignment (i.e., experimental or control) disclosed to herself and/or her treating physician now, rather than waiting until disease progression. The study team would also be informed. The patient, in discussion with the treating physician, will continue to have the option to receive the other study treatment prospectively identified to work on the identified mutation/pathway per the original study design if she is currently on the control arm. As noted above, the responses in the experimental cohorts were insufficient to indicate that a patient is more likely to derive clinical benefit if treated with agents targeting that pathway than if treated with agents that do not.

The agents and respective pathways being evaluated in this study are:

1. Veliparib (PARP inhibitor) with temozolomide for defects in DNA repair pathways
2. AZD1775 (Wee1 inhibitor) plus carboplatin for defects in DNA repair pathways *(closed March 2018)*
3. Everolimus (mTOR inhibitor) for mutations in the PI3K pathway *(closed March 2018)*
4. Trametinib DMSO (MEK inhibitor) for mutations in the RAS/RAF/MEK pathway *(closed March 2018)*

Genetic sequencing will be performed in the CLIA-certified Molecular Characterization Laboratory at the Frederick National Laboratory for Cancer Research (FNLCR). In view of the complexity of information collected, each patient's data will be reviewed by investigators indicated with an [F] on the cover page or (in their absence), their designees for internal consistency. The genetic variants to be assessed and treatment algorithms have been prospectively defined to proceed with assigning specific treatments to the patients on study. The potential risks associated with obtaining genetic information are discussed in Section 2.5.

Patients with CLIA tumor reports from Foundation Medicine (FoundationOne), CARIS (Molecular Intelligence), or other EAY131 MATCH-Designated Laboratories (https://ecog-acrin.org/nci-match-eay131-designated-labs) may be eligible if they have a study actionable mutation.

At the NCI only, every attempt will be made to collect standard-of-care images (CT or MRI) that qualified the patient for inclusion in this trial, along with the images taken during image-guided biopsy, and any follow up imaging studies during restaging (optional), will be collected to allow research into correlation of the image phenotypic features with the genomic analyses, an area of active research in radiology [2] [3]. All images will be de-identified of personal health information at the CCR Molecular Imaging Program before leaving the NIH Clinical Center site and will be stored in The Cancer Imaging Archive (http://www.cancerimagingarchive.net/), an NIH policy-compliant internet-accessible collection, with controlled access. The process is defined in Appendix L.

2.1 Targeted Mutations and Pathways

2.1.1 Mutations in DNA Repair Pathways and PARP Inhibitors

DNA damage by traditional chemotherapeutic agents does not always result in cell death due to complex DNA repair pathways. Recent research has suggested that directly targeting DNA repair pathways may result in effective killing of tumor cells, particularly in patients with pre-existing defects in DNA repair pathways. There are 6 major DNA repair pathways: direct repair (DR), base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end-joining (NHEJ) [4]. Each pathway consists of a complex interaction of different molecular characteristics (Figure 1).

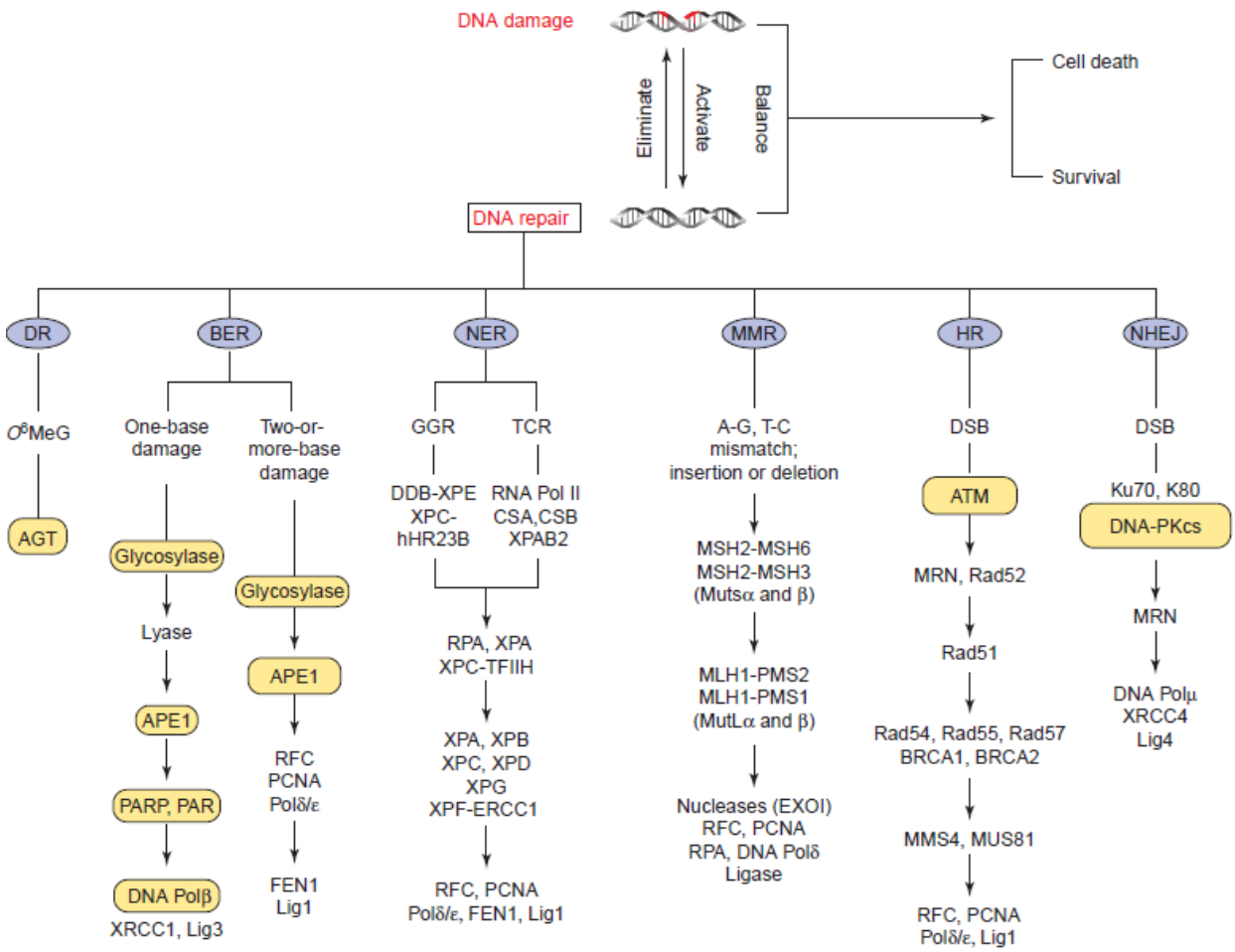


Figure 1. DNA repair pathways and potential analytes for assessment of DNA repair [4].

The BER pathway exerts its biological role by removing bases that have been damaged and plays a vital role in repairing DNA single-strand breaks (SSBs) caused by DNA-damaging factors such as anticancer agents [5]. This pathway includes the poly(ADP-ribose) polymerase (PARP) family of enzymes. PARP-1 and -2 are the most abundant of the PARPs and are essential nuclear enzymes that play a role in recognition of DNA damage and facilitation of DNA repair [6, 7]. PARP-1 and -2 bind rapidly to sites of DNA SSBs, which leads to the separation of PARP from DNA. This leads to modulation of DNA damage response proteins (XRCC1/ligase III complex, Polβ) that bind to sites of DNA damage. Double-strand breaks (DSBs) are also strong activators of PARP-1, resulting in PARP-1–mediated activation of DNA-PK and Ku80, important components of NHEJ repair pathway [8, 9]. Inhibition of PARP sensitizes tumor cells to cytotoxic agents (e.g., temozolomide) which induce DNA damage that would normally be repaired through the BER system. PARP inhibitors do not potentiate agents that do not cause DNA damage.

Expression of PARP is higher in tumor cells than normal cells. This overexpression has been linked to drug resistance and the ability of tumor cells to withstand genotoxic stress. In knockout mouse models, deletion of PARP-1 is sufficient to impair DNA repair [10-12]. Hence, it is anticipated that PARP inhibitors will function as sensitizing agents for

chemotherapy and radiation therapy administered to induce DNA damage. Recent data preclinical data that isocitrate dehydrogenase 1 (IDH1) and IDH2 mutations induce a homologous recombination defect and a sensitivity to PARP inhibition suggest that these targets may have may have therapeutic relevance [13].

Wee1 is a tyrosine kinase implicated in the inhibitory phosphorylation of CDK1/CDC2-bound cyclin B complex responsible for G2 arrest [14]. Originally identified in fission yeast [15], wee 1 deficiency resulted in premature mitotic entry and replication of smaller-sized yeast. Wee1 belongs to a family of protein kinases involved in the terminal phosphorylation and inactivation of (CDK1/CDC2)-bound cyclin B via phosphorylation of its Tyr15 residue near the ATP-binding pocket, resulting in G2 cell cycle arrest in response to DNA damage. Wee1 overexpression has been demonstrated in hepatocellular carcinoma [16], luminal and HER-2 positive breast cancers [17], colon, lung carcinoma, and seminoma tumor samples [18].

2.1.2 Mutations in the RAS Pathway: KRAS, NRAS, BRAF

MEK is a critical kinase in the mitogen-activated protein (MAP) kinase signal transduction pathway for many growth factor receptors that provide growth signals to cancer cells, including epidermal growth factor receptor (EGFR), insulin-like growth factor-1 receptor (IGFR1), and platelet-derived growth factor receptor. Cell signaling through growth factor receptors and protein kinases plays an essential role in cell survival, proliferation, and differentiation. The RAS/RAF kinase pathway is one of the most important and best understood MAP kinase pathways involved in normal and uncontrolled cell growth. In proliferative diseases, genetic mutations and/or over expression of growth factor receptors, downstream signaling proteins, or protein kinases involved in the RAS/RAF MAP kinase pathway lead to uncontrolled cell proliferation and, eventually, tumor formation.

RAS:RAF association promotes translocation of the normally cytoplasmic RAF protein to the plasma membrane, resulting in activation of its kinase function. Constitutive activation of the RAS pathways occurs through mutation activation of the RAS oncogene or of downstream effectors of RAS [19]. Mutated, oncogenic forms of RAS are found in 50% of colon and >90% of pancreatic cancers [20], as well as many others types of cancers [21], including 15 to 30% of non-small cell lung cancer (NSCLC) [22].

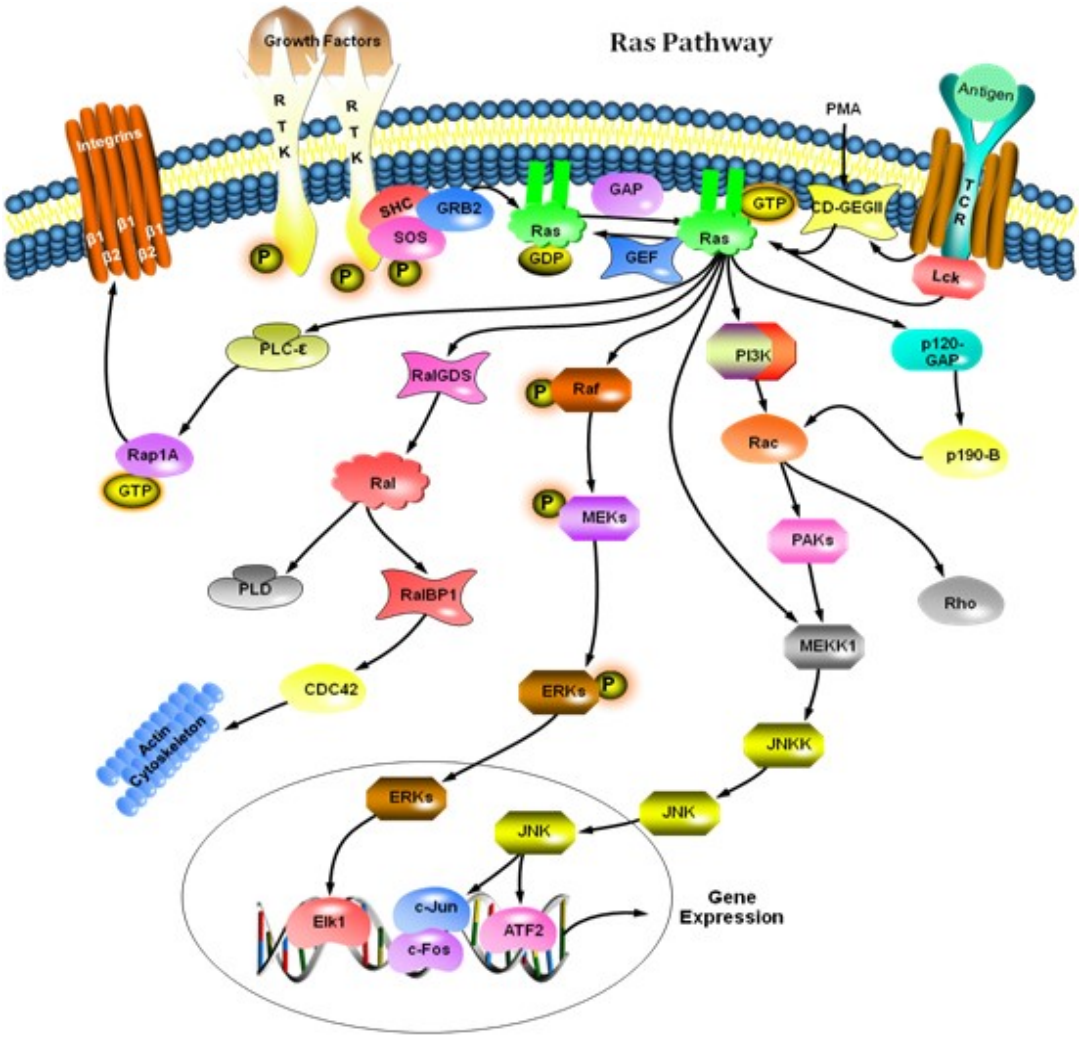


Figure 2: RAS Pathway (Figure from SABiosciences.com)

KRAS mutations, specifically in codon 12, have been shown to be important for cancer progression and may predispose to more aggressive biological behavior in patients with advanced colorectal cancer [23]. Recently, BRAF (a member of the RAF kinase family) gene mutations, which result in a constitutively active MAP kinase cascade, have been identified in more than 60% of malignant melanomas [24]. Studies of primary tumor samples and cell lines have also shown constitutive activation or overactivation of the MAP kinase pathway in cancers of the pancreas, colon, lung, ovary, and kidney [25]. Thus, there is a strong correlation between cancers and an overactive MAP kinase pathway resulting from genetic mutations.

Because activation of the RAS/RAF MAP kinase cascade plays a pivotal role in cell proliferation, inhibition of this pathway is believed to be beneficial in hyperproliferative diseases. It is anticipated that inhibition of MEK activity should inhibit transduction of the mitogenic signals from multiple pathways, resulting in an effect on tumor proliferation, differentiation, and survival. Inhibition of MEK has been shown to have potential therapeutic benefit in several studies [26, 27].

2.1.3 Mutations in the PI3K-AKT-mTOR Pathway

The phosphatidylinositol 3-kinase (PI3K) family of lipid kinases converts phosphatidylinositol-4,5-bisphosphate to phosphatidylinositol-3,4,5-trisphosphate, which initiates a signaling cascade that promotes cell growth, proliferation, motility, and survival [28]. PI3 kinases activate AKT. The PI3K-AKT pathway is downstream of the common growth factor receptor tyrosine kinases (RTKs), including EGFR, HER2, and IGFR, and is a likely driver of tumor progression in most carcinomas [29-31]. AKT promotes cell survival, growth, proliferation, migration; as well as angiogenesis and invasion by acting on multiple downstream pathways.

AKT protein kinase is activated in a substantial proportion of human solid tumors, including breast, endometrial, ovarian, prostate, pancreatic, colon, gastric, and NSCLC. Upregulation of AKT can be caused by direct amplification/mutation of AKT, or by overexpression of RTKs, PI3K, and RAS, and/or by inactivation of the tumor suppressor PTEN [32, 33]. AKT activates and/or inhibits other proteins including BAD, FOXO, and mTOR [34].

Activation of AKT is an important mechanism of chemotherapy/radiotherapy resistance, and is therefore of great interest as a potential pathway to overcome resistance. Numerous references provide support for AKT inhibitors in the treatment of various malignancies [29-31, 35-65]. AKT phosphorylation as a pharmacodynamic (PD) marker has also been explored in early phase clinical trials [34].

Inactivation or hypoactivation of PTEN causes overactivation of the PI3K-AKT pathway [34]. PTEN inactivation is caused by a variety of mechanisms including somatic mutations, deletions, promoter methylation, and/or loss of heterozygosity. These changes are commonly found in many cancers including prostate cancer, endometrial cancer, and glioblastoma and are often associated with advanced disease stage. mTOR is a serine/threonine kinase that is structurally related to PI3K. When mTOR binds to other intracellular proteins; there are two distinct complexes formed known as mTORC1 and mTORC2 [34]. The currently approved mTOR inhibitors: rapamycin (sirolimus), everolimus, and temsirolimus only block mTORC1. mTORC1 is made up of mTOR, regulatory-associated protein of mTOR (raptor), and mLST8/GβL. Results from a recent Phase I study of doxorubicin, bevacizumab, and temsirolimus in patients with advanced gynecologic and breast malignancies indicated that a high percentage of responders had PI3K aberrations [66].

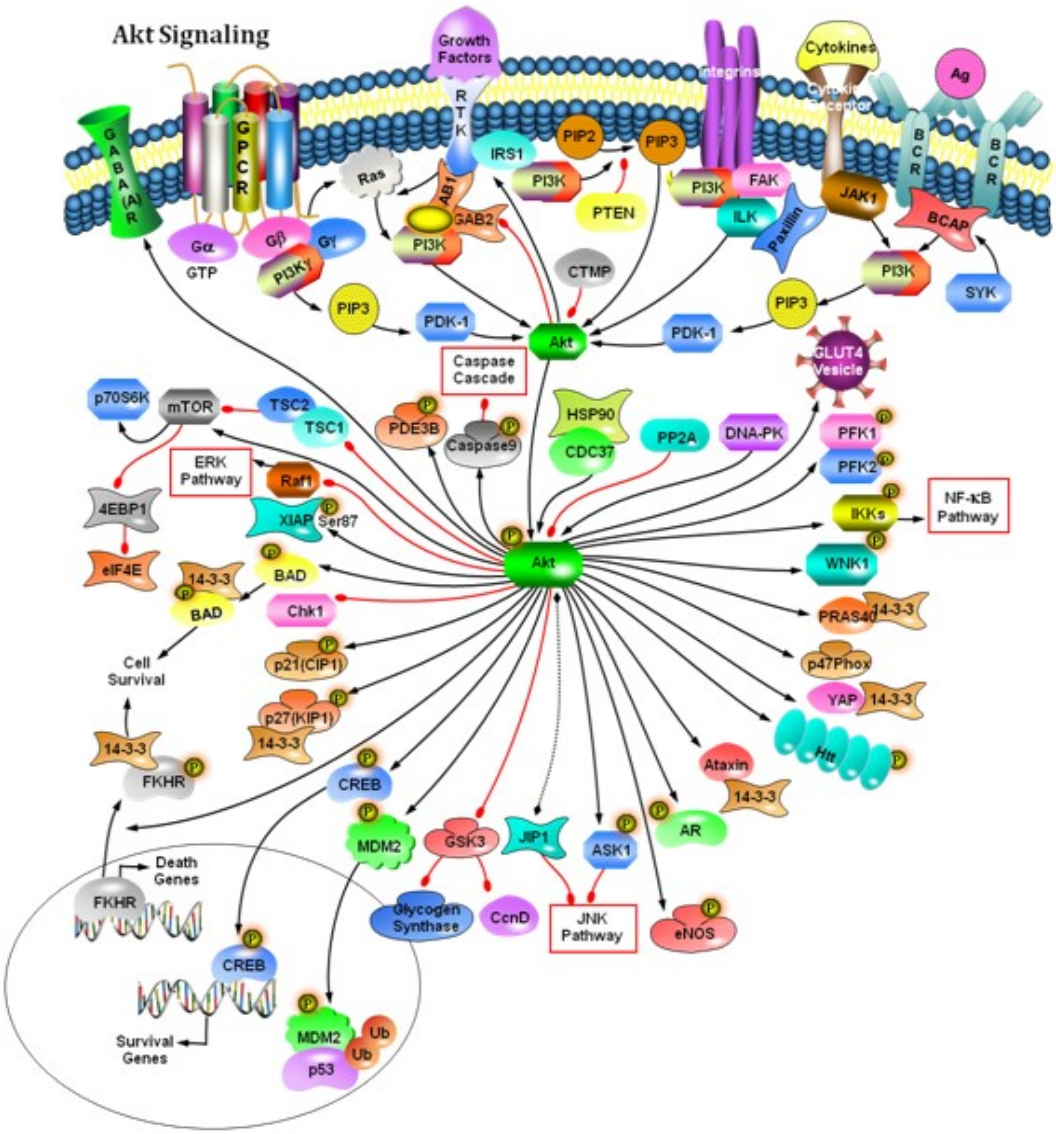


Figure 3: AKT/PI3K signaling cascade (SABiosciences.com).

2.2 Targeted Genes/Locus Selection

Patients enrolled on study will have a tumor biopsy sequenced for one or more of the specific mutations of interest listed in Table 1. This sequencing may be performed prior to enrollment, to determine eligibility, or once the patient has started treatment, to confirm the results from previous CLIA sequencing.

A minimum of two biopsy specimens will be shipped directly to the Laboratory of Molecular Characterization (MoCha), located at FNLCR. Biopsy samples (FFPE blocks) collected as part of another study or from a procedure performed due to medical necessity may be acceptable if the samples were collected within 6 months prior to registration on MPACT and the patient has not received any investigational or targeted treatment since that time. Upon receipt of specimens, a visual examination will be performed for acceptance. If all acceptance criteria are met, the specimen will be logged into the laboratory database for processing. Biopsy cores will

be processed and embedded in paraffin using routine histological procedures. A tissue section will be stained for histological examination for tumor content. Samples with a tumor content of at least 50% (with minimal necrosis and stromal tissue) will be subjected to nucleic acid extraction using Qiagen's AllPrep FFPET nucleic acid extraction methodology. Samples with tumor content less than 50% will undergo tumor enrichment (described below). Resultant DNA and RNA will be quantified by, but not limited to, NanoDrop spectroscopy. If sufficient DNA is obtained, 20 ng will be used for library preparation using a custom AmpliSeq kit, "MATCHv3" (until Amendment P, the assay used MPACTv2.0). This custom panel was designed and developed by MoCha to support this clinical study. The panel employs AmpliSeq multiplex PCR technology to amplify and prepare clinical specimens for sequencing of genetic loci (targets) used for therapy selection in this trial. The panel currently includes 13 DNA damage repair actionable genes (Table 1). The genes were selected using several criteria:

- Genes within the DNA damage repair pathway were selected based on demonstrating a minimum frequency (5%) of somatic variants as listed in the COSMIC [catalogue of somatic mutation in cancer] database[1] version #86.
- Additional genes were added, including the targets of the study drugs.
- The Molecular Tumor Board further assessed the genes selected and agreed upon a final reportable variant protocol based on reported frequency as well as preclinical and clinical literature associated with a given gene and its variant.

All sequencing will be performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. All of the DNA damage repair genes covered by the panel are tumor suppressor genes and will be assessed for loss of function mutations (Table 1). These loss of function mutations have been previously reported in the COSMIC database (version 86) or ClinVar. In addition to the hotspot aMOIs, the panel will also report on novel loss of function mutations that create a frameshift of premature stop codon in the predicted protein.

The sequencing data for these genes will be shared with the patient (Appendix H) once the results are available. Targeted analysis will not include analyzing for known mutations in receptor tyrosine kinases or TP53.

The clinical specimen will be sequenced using the Ion Torrent Personal Genome Machine. A variety of specimen and assay quality checks are built into the assay process and detailed in the SOPs. MoCha has prepared an analytical validation plan with assay performance testing, validation, and quality control metrics. These metrics include DNA yield and quality, minimum percentage tumor nuclei per specimen, read depth, and positive and negative controls (see summary below) to ensure valid assay performance and result reporting.

[1] http://www.sanger.ac.uk/genetics/CGP/cosmic/

Table 1. Genes and Pathways of Interest (DNA repair genes only after Amendment U)

Gene Name	*Pathways/Function*	*Gain or Loss of Function?*
ATM	DNA repair pathway	Loss
NBN	DNA repair pathway	Loss
RAD51	DNA repair pathway	Loss
RAD51B	DNA repair pathway	Loss
RAD51C	DNA repair pathway	Loss
RAD51D	DNA repair pathway	Loss
PALB2	DNA repair pathway	Loss
BRCA1	DNA repair pathway	Loss
BRCA2	DNA repair pathway	Loss
CHEK1	DNA repair pathway	Loss
CHEK2	DNA repair pathway	Loss
FANCA	DNA repair pathway	Loss
MRE11A	DNA repair pathway	Loss
IDH1	DNA repair pathway	Loss
IDH2	DNA repair pathway	Loss

Quality Metrics	*Threshold*
Tissue Specimen Review	>50% non-necrotic tumor nuclei present in section
DNA Recovery	> 20 ng
Library Yield	> 10 pM
Testing Fragments	TF-A/D > 80% AQ17, Read Length Histogram >90 bp
Reads per Sample	>350,000
Amplicon Coverage	≥ 80% of amplicons coverage >450x
Positive (CPSC) Control	Detect and call all plasmid variants
Negative Control CEPH	Detect no false-positive aMOIs
LibNTC Sequence Data	Total reads < 2% read libraries OR <120 bp mean read length

After a clinical specimen has completed sequencing and passed all quality checks and filters, the data will be analyzed. The report will be reviewed (by investigators indicated with an [F] on the cover page) and treatment assignments made based on the locked down algorithm defined in the protocol. All delinked RNA and DNA will be stored under appropriate conditions until further sample studies are indicated. Delinking of patient identifiers will be performed in a secure manner prior to use performing, but not limited to, whole exome sequencing and circulating tumor DNA (ctDNA) for research purposes.

Mutations will be reported based on their presence in tumor cells and the percent of cells demonstrating the predefined mutation.

An adequate tumor biopsy sample will contain at least 50% tumor with minimal necrosis and stromal tissue; samples with less than 50% tumor will be reflexed for tumor enrichment using a standardized macrodissection protocol. In case of samples with insufficient tumor content or DNA yield, the patient will be given the option to undergo a repeat tumor biopsy to obtain more

tissue. Patients from whom sufficient tumor DNA material cannot be obtained for targeted analysis will be taken off-study.

2.3 Study Agents

Proprietary information about each of the study agents is included in this protocol document as an appendix. Veliparib will be administered with temozolomide.

2.3.1 Veliparib

Veliparib is an orally available, small molecule inhibitor of PARP. Preclinical and clinical data show that inhibition of PARP potentiates the effects of DNA-damaging chemotherapeutic drugs such as the alkylating agent temozolomide [67]. In this study, Veliparib and temozolomide will be administered to patients with defects in DNA repair pathways. Please refer to Appendix I for more information.

2.3.2 Temozolomide

Temozolomide is an oral alkylating agent approved by the FDA for the treatment of certain cancerous tumors in the brain of adult patients. Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species.

2.3.3 Trametinib dimethyl sulfoxide (GSK1120212) (*This arm was closed to new accrual with Amendment U*)

Trametinib DMSO is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. The safety, pharmacokinetic (PK), and pharmacodynamic (PD) profiles, and activity of trametinib DMSO are currently being evaluated in 13 ongoing monotherapy and combination therapy clinical trials involving subjects with a variety of cancers. Trametinib DMSO was recently approved for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations based on a statistically significant prolongation of progression free survival over chemotherapy (4.8 months vs. 1.5 months) in 322 patients on a randomized active-control trial.

2.3.4 AZD1775 (*This arm was closed to new accrual with Amendment U*)

AZD1775 is a selective, adenosine-triphosphate (ATP) competitive, small molecule inhibitor of Wee1 kinase that directly inhibits phosphorylation of CDC2. In vitro experiments have demonstrated that AZD1775 has synergistic antitumor effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action. In this study, AZD1775 will be administered with carboplatin. Results from preclinical and clinical studies suggest that the combination of AZD1775 with carboplatin has antitumor efficacy and is well tolerated; refer to Appendix J for more information.

2.3.5 Carboplatin (*This arm was closed to new accrual with Amendment U*)

The alkylating agent carboplatin acts by binding DNA to form interstrand DNA cross-

links that interrupt cell division. It is approved by the FDA for the treatment of patients with ovarian cancer and non-small cell lung cancer, and is also used for the treatment of patients with small cell lung cancer, head and neck cancer, endometrial cancer, metastatic seminoma, and breast cancer. Carboplatin is eliminated by renal excretion; clearance is related to the glomerular filtration rate (GFR), therefore the drug is dosed based on the GFR and the target area under the concentration versus time curve (AUC). The main side effects of carboplatin are myelosuppression, nausea, vomiting, renal toxicity, and neurotoxicity.

2.3.6 **Everolimus** (*This arm was closed to new accrual with Amendment U*)

The mTOR inhibitor everolimus was approved by the FDA for patients with advanced renal cell carcinoma (RCC) based on results from a multicenter, randomized, double-blind Phase III trial comparing everolimus (10 mg daily) and placebo in 416 patients with metastatic RCC whose disease had progressed despite prior treatment with vascular endothelial growth factor-targeted therapy (sunitinib, sorafenib, or both sequentially) [68, 69]. Median progression-free survival was 4.9 months in the everolimus arm and 1.9 months in the placebo arm; objective response rates were 2% and 0%, respectively. As described in Section 2.1.3, the serine-threonine kinase mTOR is an essential component of the multiprotein mTOR complex 1 (mTORC1), along with regulatory-associated protein of mTOR (raptor). Once activated through PI3K activation of AKT, mTORC1 functions as a key regulator of cell growth by phosphorylating 4E-binding protein 1 (4E-BP1) and p70S6K (S6K), translation initiation factors required for protein synthesis [70, 71]. Everolimus binds to the intracellular protein, FKBP-12, which in turn binds mTOR, impairing its activity and inhibiting translation of proteins essential for cell cycle progression and survival. The main side effects of everolimus reported in patients with RCC are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The recommended dose of everolimus for the treatment of patients with advanced RCC is 10 mg, to be taken once daily; this dose will be administered on this trial.

2.4 Study Disease

Patients with histologically documented solid tumors whose disease has progressed following at least one line of standard therapy and/or there are no standard therapies available that are known to prolong survival will be enrolled on study and undergo mandatory tumor biopsy. This tumor biopsy will be sequenced for presence of specific mutations of interest in a CLIA-certified laboratory. The following specific mutations in pathways will be assessed:

1. Mutations in DNA repair pathways
2. Mutations in the PI3K pathway (Not currently accruing)
3. Mutations in the RAS/RAF/MEK pathway (Not currently accruing)

2.5 Genetic Sequencing Research Ethics and NIH Genomic Data Sharing Policy

This trial will collect identifiable genetic data from all patients enrolled to determine whether or not their tumors have a mutation(s) in one or more of the pathway of interest. We will screen for pre-defined variations in genes in a CLIA-certified laboratory for assignment of patient treatment on study. As treatment options and data analyses will be based on this information, de-identifying the samples is not feasible. Designing the study therefore poses challenging

questions about informed consent, the privacy of the patient and the patient's family, the researchers' obligation to disclose genetic information to the patient, and the use and storage of research data, as well as of the selection and interpretation of gene variants [72-74]. In the vast majority of cases we do not know the medical significance of genetic variants [75, 76]. These challenges will continue to be evaluated to maintain the rigor and integrity of the study and the wellbeing of our patients. A Certificate of Confidentiality has been obtained from the NIH to help protect the privacy of all study participants.

The protocol includes separate informed consent forms for the screening biopsy and treatment parts of the study; each patient will know whether or not their tumor has a variation in a gene of interest. Patients with actionable mutations that may establish eligibility for other clinical trials or targeted agents, including MATCH (*Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma*, NCT02465060), which uses the same custom AmpliSeq screening panel as MPACT, will be informed that they may have other treatment options. Information on tumor gene variants that form the basis of treatment assignment will be stored in the patient's medical records.

Whole exome sequencing (performed for research purposes) of tumor and blood can detect nonambiguous germline variants, which may raise health and privacy implications for the patient and his or her family. Whole exome sequencing will not be validated for clinical use and no clinical decisions can be made based on its results. In addition, given the uncertain clinical significance of some of these variants and the ethical implications, we will perform such research analysis on de-identified samples only. Once each patient has completed treatment on study and is taken off study, patient identifiers will be de-linked and we will perform whole exome sequencing on the de-identified samples. No genetic data will be shared with the patient other than the data from the targeted sequencing panel. All other analysis will be performed on de-identified samples. The process for de-identifying the samples is described in Section 9.4.1.

This study affords a unique opportunity to collect information about the prevalence of mutations in genes associated with cancer, as well as how patients' tumors respond to targeted therapy in the refractory tumor setting; DNA variants and changes in RNA expression from tumors collected when patients progress on study drugs is anticipated to illuminate resistance mechanisms that will inform subsequent studies and improve patient outcomes.

2.5.1 NIH Genomic Data Sharing Policy

The NIH Genomic Data Sharing (GDS) Policy ensures broad and responsible sharing of genomic research data from all NIH-funded research[2]. Providing that patient consent has been obtained, whole-exome sequencing data generated for research purposes from samples unlinked from patient identifiers will be submitted to the Database of Genotypes and Phenotypes (dbGaP) for controlled-access use within a time frame consistent with study CRADAs and data publication. The identities of research participants will not be disclosed to dbGaP or to secondary users of the data. Genomic data generated from

[2] https://gds.nih.gov/index.html

patients before this trial became a multicenter study will not be subject to GDS policy as adequate consent was not obtained from these individuals.

2.6 Rationale for the Study

The original proposal was designed to address, in a randomized trial, whether patients with underlying mutations in a given pathway in their tumor are more likely to derive clinical benefit if treated with agents that target that pathway than if treated with agents that do not, as well as to address this question, in a non-randomized fashion, for each separate cohort defined by mutation status. Randomization was taken out of the study design with Amendment U.

Patients will receive one of the agents/regimens defined to work on one of their identified mutations. In the absence of a randomized control arm, the performance of each individual mutational status cohort will be compared to that of historical controls. If no objective responses are observed among the initial 12 patients of a 30-patient Arm A agent cohort, the cohort will be terminated early. An optional tumor biopsy will be performed at the time of disease progression to assess for new acquired mutations; this biopsy may, if feasible, be collected on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (per RECIST criteria) if the patient has been on study for at least 4 cycles.

The treatment regimens and number of treatment regimens may change over time as long as the same set of regimens is offered to a given set of patients. The doses that will be administered are Phase II-recommended doses.

2.6.1 Veliparib plus Temozolomide arm

As of Amendment U, this is the only arm open to accrual. Seven patients had been assigned to this arm prior to the study being placed on hold for futility analysis (targeted plus control arms).

The combination of veliparib with temozolomide in patients with DNA damage mutations is supported by preclinical data in patient-derived xenograft (PDX) mouse models. Overall, 32 PDX models have been treated with this combination; 8 have demonstrated delayed tumor growth (unpublished data). Complete or partial response, as well as an increase in relative median event-free survival, has been observed with veliparib plus temozolomide in tumors with a range of DNA damage mutations. Based on these data, we have revised the list of actionable mutations of interest for the veliparib plus temozolomide arm. We expect that the new eligibility criteria, including variants in DNA repair genes BRCA1, BRCA2, CHK2, and ATM, will allow more patients with potential to benefit from this combination to enroll on this treatment arm.

3. PATIENT SELECTION (TUMOR SEQUENCING/DRUG TREATMENT)

Patients meeting the criteria defined below will be enrolled on study, then undergo a tumor biopsy. The tumor will be sequenced for specific mutations of interest defined in Section 2.2; only if such mutations are detected will the patient continue on study to the randomization/treatment part of this protocol. The eligibility criteria for both the tumor

sequencing and treatment parts of this protocol are similar, such that in general, a patient eligible for tumor sequencing will be eligible for the subsequent treatment part of the protocol if his/her tumor contains a mutation of interest. **Additional agent-specific treatment exclusions are listed in Section 3.4; agent-specific exclusions are to ensure patient safety.**

3.1 Eligibility Criteria: Tumor Biopsy Sequencing

3.1.1 Patients with histologically documented solid tumors whose disease has progressed following at least one line of standard therapy and/or no standard of treatment exists that has been shown to prolong survival.

3.1.2 Patient must have tumor amenable to percutaneous or excisional skin biopsy and be willing to undergo a tumor biopsy, or

Biopsy samples (FFPE blocks) collected on another study or from a procedure performed due to medical necessity may be acceptable if collected within 6 months prior to registration on MPACT and providing that the patient has not received any investigational or targeted treatment since that time, or

A report from an MATCH study designated CLIA laboratory (see https://ecog-acrin.org/nci-match-eay131-designated-labs) that a patient has a variant in the genes of interest.

3.1.3 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.

3.1.4 Patients with bone metastases or hypercalcemia on intravenous bisphosphonate treatment, denosumab, or similar agents are eligible to participate and may continue this treatment. Patients with prostate cancer may continue LHRH agonists or antagonists.

3.1.5 Age ≥ 18 years. Children are excluded from this study, but may be eligible for future pediatric trials.

3.1.6 Karnofsky performance status ≥ 70%, see Appendix A.

3.1.7 Life expectancy > 3 months.

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

– absolute neutrophil count	≥1,000/µL (mcL)
– platelets	≥100,000/µL (mcL)
– total bilirubin	< 1.5 X institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤ 3 X institutional upper limit of normal
– creatinine	< 1.5 X institutional upper limit of normal
OR	

– creatinine clearance	≥ 60 mL/min for patients with creatinine levels ≥1.5 X institutional upper limit of normal.

3.1.9 The effects of these targeted agents on the developing human fetus are unknown or anticipated to cause fetal harm based on their mechanism of action. For this reason, women of childbearing potential and men must agree to use highly effective contraception prior to study entry, for the duration of study participation, and for 3 months after completion of study. Because there may be a risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued while the patient is on this trial and for 30 days following last dose of study drug.

3.1.10 Patients with history of CNS metastases who have received treatment and who either have not had seizures or have been on stable doses of anti-seizure medicine and had no seizures for 4 weeks will be eligible. Enzyme-inducing anticonvulsants are contraindicated.

3.1.11 Ability to understand and the willingness to sign a written informed consent document (subjects with impaired decision-making capacity are not eligible).

3.2 Exclusion Criteria: Tumor Biopsy Sequencing

3.2.1 Women who are pregnant or breastfeeding.

3.2.2 Patients who are receiving any other investigational agents. Patients on other trials will be eligible as long as they are no longer receiving study treatment.

3.2.3 Patients with uncontrolled intercurrent illness including, but not limited to psychiatric illness/social situations that would limit compliance with study requirements, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, myocardial infarction in the past 6 months, invasive fungal infections, or active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and active and chronic hepatitis (i.e., quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA) are not eligible to participate. Testing for hepatitis B or other infections for eligibility will be performed only if clinically indicated.

3.2.4 Patients with gastrointestinal conditions that might predispose for drug intolerability or poor drug absorption (e.g., inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, malabsorption syndrome, and active peptic ulcer disease) are excluded. Subjects with Crohn's disease or a partial or complete small bowel obstruction are also excluded, as are any patients who cannot swallow tablets or capsules whole. Tablets or capsules must not be crushed or chewed; nasogastric or G-tube administration is not allowed.

3.2.5 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for PK interactions.

3.2.6 Patients who require use of coumarin-derivative anticoagulants such as warfarin are excluded. Low molecular weight heparin is permitted for prophylactic or therapeutic use.

3.2.7 Patients who have previously been treated with the combination of temozolomide plus a PARP inhibitor should not be considered eligible for a biopsy given that these patients would not be eligible for the active Veliparib plus temozolomide arm.

Patients who meet the screening criteria and have a tumor biopsy determined to have one of the specific mutations of interest (defined in Section 2.2) will be eligible to participate in the treatment part of this protocol. **If the patient does not meet the criteria in Section 3.3 or the patient has any of the conditions listed in Section 3.4, the patient is not eligible for this trial.**

3.3 Eligibility Criteria: Targeted Treatment

3.3.1 Patient must have predefined targeted mutation in tumor biopsy as defined in Section 2.2.

3.3.2 Patients with histologically documented solid tumors whose disease has progressed following at least one line of standard therapy or for which no standard therapy exists that has been shown to prolong survival.

3.3.3 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.

3.3.4 Any prior therapy, radiotherapy, or major surgery must have been completed ≥ 3 weeks (> 6 weeks for nitrosoureas or mitomycin C) or 5 half-lives of the agent (whichever is shorter) prior to enrollment on protocol, and the participant must have recovered to eligibility levels from prior toxicity. RFA of localized lesions should have been performed ≥ 2 weeks prior to starting treatment.

3.3.5 Patients with bone metastases or hypercalcemia on intravenous bisphosphonate treatment, denosumab, or similar agents are eligible to participate and may continue this treatment. Patients with prostate cancer may continue LHRH agonists or antagonists.

3.3.6 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of study investigational agents in patients < 18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

3.3.7 Karnofsky performance status ≥ 70%, see Appendix A.

3.3.8 Adequate organ and marrow function as defined in Section **3.1.8**

3.3.9 Life expectancy > 3 months.

3.3.10 The effects of these targeted agents on the developing human fetus are unknown or anticipated to cause fetal harm based on their mechanism of action. For this reason, women of childbearing potential and men must agree to use highly effective contraception (see list below) prior to study entry, for the duration of study participation, and for 3 months after completion of study.

Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).

Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female subjects on the study, the vasectomised male partner should be the sole partner for that subject).

Use of a combination of any two of the following (a+b or a+c or b+c):

a. Use of oral, injected, implanted or other hormonal methods of contraception

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.

Sexually active males must use a condom during intercourse

3.3.11 Because there may be a risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued while the patient is on this trial and for 30 days following last dose of study drug.

3.3.12 Patients with ovarian cancer or metastatic breast cancer and BRCA mutations must have received approved PARP inhibitor therapy; these patients are eligible for the Veliparib plus temozolomide arm unless the PARP inhibitor was administered with temozolomide.

3.3.13 Patients with a history of seizures are not eligible to receive Veliparib,

3.3.14 Patients who have had prior treatment with any PARP inhibitor in combination with temozolomide are not eligible to receive treatment with Veliparib on this study. Patients who have received prior temozolomide or PARP inhibitor with or without other chemotherapy/targeted agent should not be excluded.

3.3.15 Patients must have ≥10.0 g/dL Hb and no blood transfusion in the past 28 days to

receive Veliparib.

3.4 Exclusion Criteria: Targeted Treatment

3.4.1 Women who are pregnant or breastfeeding.

3.4.2 Patients who are receiving any other investigational agents. Patients on other trials will be eligible as long as they are no longer receiving study treatment.

3.4.3 Patients with active brain metastases or carcinomatous meningitis are excluded from this clinical trial. Patients who have a history of seizures are not eligible to receive Veliparib

3.4.4 Patients with uncontrolled intercurrent illness including, but not limited to psychiatric illness/social situations that would limit compliance with study requirements, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, myocardial infarction in the past 6 months, invasive fungal infections, or active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and active and chronic hepatitis (i.e., quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA) are not eligible to participate. Testing for hepatitis B or other infections for eligibility will be performed only if clinically indicated.

3.4.5 Patients with gastrointestinal conditions that might predispose for drug intolerability or poor drug absorption (e.g., inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, malabsorption syndrome, and active peptic ulcer disease) are excluded. Subjects with Crohn's disease or a partial or complete small bowel obstruction are also excluded, as are any patients who cannot swallow tablets or capsules whole. Tablets or capsules must not be crushed or chewed; nasogastric or G-tube administration is not allowed.

3.4.6 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for PK interactions.

3.4.7 Eligibility of subjects receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics (i.e., CYP450, PgP) of any of the study drugs will be determined following review of their cases by the PI. Patients on strong and moderate cytochrome P450 system inducers or inhibitors (Appendix B) are ineligible. Every effort would be made to switch patients off medications that are known substrates of CYP450; if it is medically important for the patient to remain on such medications, these patients can still be eligible to participate based on PI discretion. Refer to Section 8 for more detailed information.

3.4.8 Patients who require use of coumarin-derivative anticoagulants such as warfarin are excluded. Low molecular weight heparin is permitted for prophylactic or therapeutic use.

3.4.9 Patients who have a history of another primary malignancy, with the exceptions of: non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for > 3 years.

3.4.10 Patients with treatment-related AML (t-AML)/MDS, or with features suggestive of AML/MDS, or who have had prior allogeneic bone marrow transplant or double umbilical cord blood transplantation, should not receive Veliparib due to reports of MDS and leukemia secondary to oncology therapy on CTEP-sponsored studies utilizing Veliparib.

3.5 Evaluation for Enrollment for Tumor Biopsy Screening

3.5.1 Histologic confirmation of solid malignancy.

3.5.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, performance score, EKG) will be conducted within 8 days prior to enrollment.

3.5.3 Imaging Studies (Baseline): Imaging studies to determine biopsiable disease.

3.5.4 Laboratory Evaluation: Baseline laboratory data are to be obtained within 8 days prior to enrollment (fasting blood preferred):

- Hematological Profile: CBC with differential
- Biochemical Profile: albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, phosphorus, total protein, SGOT[AST], SGPT[ALT], magnesium, potassium, and sodium
- Serum or urine pregnancy test for female participants of childbearing potential

3.6 Evaluation for Treatment on Study

3.6.1 History and physical examination: complete history and physical examination (including weight, vital signs, performance score, EKG) will be conducted within 8 days prior to enrollment. If the patient's condition deteriorates prior to initiation of treatment, evaluations should be repeated within 48 hours prior to initiating treatment.

3.6.2 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to starting study drugs. MRI or CT scan with contrast of the brain, MRI liver, MRI for other disease sites, ECHO/MUGA or bone scan may be done as clinically indicated before starting study drugs (ECHO/ MUGA required for patients receiving trametinib or everolimus).

3.6.3 Laboratory Evaluation: Baseline laboratory data are to be obtained within 8 days prior to enrollment and within 3 days prior to starting study drugs. If the patient's condition deteriorates prior to initiation of treatment, laboratory evaluations should be repeated within 48 hours prior to initiating treatment:

a. Hematological Profile: CBC with differential.
b. Biochemical Profile: albumin, alkaline phosphatase, total bilirubin, BUN, calcium, creatinine, glucose, phosphorus, total protein, SGOT[AST], SGPT[ALT], magnesium, potassium, and sodium.
c. Serum or urine pregnancy test for female participants of childbearing potential.

4. REGISTRATION PROCEDURES

4.1 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 (https://ctepcore.nci.nih.gov/iam).

In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	
HSP/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 CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found 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.

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol PI must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. For the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Regulatory Documents

Site registration forms may be downloaded from the *9149* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, and then select *LAO-NCI*, and protocol #9149.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

Requirements for 9149 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)
- Local informed consent document

- Study chair approval

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000, Philadelphia, PA 19103

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.

Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.2.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

As this trial has a slot reservation requirement, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment. Slots can be reserved for a maximum of 14 calendar days.

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

OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (i.e., CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: website http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11 This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.3 General Guidelines

Following registration, patients should be assigned to protocol treatment as specified in Section 5.1. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible. Please make every effort not to schedule biopsy collections on a Friday as FNLCR cannot accept courier deliveries at weekends.

4.4 Randomization Procedures (N/A)

5. TREATMENT PLAN

5.1 Study Design

After signing the consent form and enrolling on the study, patients will undergo mandatory tumor biopsy as described in Section 9 unless a CLIA-certified tumor mutation report from an

MATCH study designated lab (see https://ecog-acrin.org/nci-match-eay131-designated-labs) indicating a study aMOI is provided. Reports from other academic, clinical, or commercial testing organizations will not be accepted due to the level of evidence needed for this research protocol. Genetic sequencing at the NCI will be performed in the CLIA-certified laboratory of Dr. Mickey Williams, Director, Molecular Characterization and Clinical Assay Development Laboratory (MoCha), to assess for the presence of specific, pre-defined mutations of interest.

The laboratory will return notification of whether a mutation of interest has been detected in approximately 2 weeks, including details about the specific mutation/pathway for assignment to the treatment arm based on predefined criteria. Patients in whom mutations of interest are not detected will be taken off study. Patients considered eligible for the study due to results from a MATCH-designated lab will have a biopsy collected during cycle 1 for confirmatory testing with the MPACT Oncominev3 assay; patients who do not have their actionable mutation confirmed can choose to continue treatment but will not count towards evaluable patients and will be replaced for futility analysis.

All treatment will be open-label in this trial. Drugs will be administered at the recommended Phase II doses and schedules. A new cycle may begin 1 day earlier or 1 day later than it would otherwise be scheduled to allow for flexibility for days the clinic is closed and other unexpected events. CT scans will be performed at baseline, and repeat imaging scans will be performed every 2 cycles (8 weeks for 28-day schedules, 6 weeks for 21-day schedules). Once a patient has been on a treatment for more than 1 year, the CT scans will be performed every 3 cycles for 28-day cycles or every 4 cycles for 21-day cycles.

History and physical exam, labs (CBC with differential; serum chemistries, including fasting glucose) will be performed at the start of each cycle (within 3 days prior to start of new cycles). Additional evaluations will be conducted as clinically indicated at the investigator's discretion, or more frequently for patients on certain treatment arms as specified in Section 10.

Lipid monitoring (triglycerides and cholesterol) will be performed at restaging (every 2 cycles or as defined above) and urinary protein the start of each cycle for patients on everolimus only.

Patients will be asked to maintain a Study Medication Diary (Appendix D) and record each dose of medication. Patients will be given instructions for completing the medication diary and will be asked to return it to the clinic staff at the end of each cycle. All patients will be carefully monitored for side effects while on study. Appropriate dose modifications are described in Section 6.

5.2 Targeted Therapy Arms

Treatment assignment is made by GeneMed, an informatics system that performs treatment assignments based on the locked down algorithm defined in the protocol. The assignment will be sent to the treating physician once it is verified within 24-48 hours. The treating physician and the patient will not be blinded to the sequencing data.

Patients with tumor mutations of interest will receive an agent prospectively identified to work on that mutation/pathway (see below). As long as the same set of protocols are offered to a given set of patients, the number and actual treatments regimens can vary over time.

At the time of Amendment Y, the last patient randomized to the Trametinib DMSO cohort under the original study design remains on treatment with the option that she and/or her physician may now be informed prior to, rather than at, disease progression about her mutational status and arm assignment. The study team would also be informed. The patient, in discussion with the treating physician, may still crossover to a study treatment prospectively identified to work on the identified mutation/pathway per the original study design (see list below). The patient may not switch to another treatment and then back to Trametinib DMSO.

The treatment regimens are as follows:

- Veliparib plus temozolomide for defects in DNA repair pathways
- AZD1775 (Wee1 inhibitor) plus carboplatin for defects in DNA repair pathways *(no longer an active study drug as of March 2018)*
- Everolimus (mTOR inhibitor) for mutations in the PI3K pathway *(no longer an active study drug as of March 2018)*
- Trametinib DMSO (MEK inhibitor) for mutations in the RAS/RAF/MEK pathway *(no longer an active study drug as of March 2018)*

Treatment exceptions are also listed in Section 3.3. The following patients will **not** receive certain treatments on this protocol:

1) Patients with ovarian cancer and BRCA mutations must have received specific PARP inhibitor therapy.

2) Patients with treatment-related AML (t-AML)/MDS, or with features suggestive of AML/MDS, or who have had prior allogeneic bone marrow transplant or double umbilical cord blood transplantation, should not receive Veliparib due to reports of MDS and leukemia secondary to oncology therapy on CTEP-sponsored studies utilizing Veliparib.

Information on whether a mutation(s) of interest was detected for a given patient as well as what drugs are allowed for assignment of a treatment regimen will be provided to the study team; the Biopsy Sequencing Results and Analysis Form (Appendix F) will be provided to the clinician.

Arm A: Targeted treatment based on the detected genetic mutation will be assigned. Mutations will be reported based on their presence in tumor cells and the percent of cells demonstrating the pre-defined mutation (as allele frequency).

At the time of disease progression for all targeted therapy patients, an optional tumor biopsy may be collected to assess for new acquired mutations; this biopsy may instead be collected on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (per RECIST criteria) if the patient has been on study for at least 4 cycles.

No more than 3 tumor biopsy procedures will be performed: one mandatory at baseline, one

optional repeat biopsy if sufficient tumor DNA cannot be isolated at baseline, and one optional biopsy at or near time of disease progression to assess for new acquired mutations.

5.3 Agent Administration

5.3.1 Veliparib plus Temozolomide

The Veliparib dose of 40 mg BID on days 1-7 with temozolomide administered 150 mg/m^2 po QD days 1-5 in 28-day cycles was selected based on clinical results presented at ASCO [77] [78]. The dose of temozolomide is based on BSA then rounded off to the nearest 5 mg. Patients who receive temozolomide will have an evaluation of their LFTs at the time of coming off-treatment.

5.3.2 Everolimus

Everolimus will be administered once a day at a dose of 10 mg each day in 28-day cycles. Tablets should not be crushed or chewed and should be swallowed whole with a glass of water. If patients miss a dose of everolimus, they may still take it up to 6 hours after the time they would normally take it. If more than 6 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take everolimus at the usual time; patients should not take 2 doses to make up for the one that they missed. If vomiting occurs, no attempt should be made to replace the vomited dose. Caregivers should be advised to wash their hands thoroughly after touching the tablets. Patients on everolimus should also avoid close contact with others who have received live, attenuated vaccines (e.g., intranasal influenza).

5.3.3 Trametinib DMSO

Trametinib DMSO will be administered at 2 mg each day in 28-day cycles. Drug must be taken while fasting (water is permitted) 1 hour before or 2 hours after a meal.

5.3.4 AZD1775 plus carboplatin

AZD1775 will be administered orally at a dose of 225 mg BID for 5 doses starting on day 1 of every cycle. Drug must be taken at least two hours before or two hours after a meal. Carboplatin (AUC 5) will be administered IV on day 1 of every cycle over 30-60 minutes concomitantly with AZD1775; the cycle length is 21 days. All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO BID or granisetron (Kytril) 1 mg PO BID prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given with each AZD1775 dose as a minimum on the first day of dosing AZD1775 of every 3-5 days dosing period, unless contraindicated or not well-tolerated. Dexamethasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV as needed. Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy. Please note: aprepitant (Emend) and fosaprepitant are not permitted due to known DDIs.

5.4 General Concomitant Medication and Supportive Care Guidelines:

All patients will be provided with the best available supportive care. All concurrent medications should be documented prior to initiation of treatment and be periodically reviewed with the patient. Particular attention must be paid to medications which may prolong the QTc interval (Appendix C) and agents that interact with CYP450 isoenzymes or are PgP inhibitors (Appendix B).

Nausea/Vomiting: Nausea and vomiting will be considered refractory if they do not resolve to ≤ Grade 1 with treatment with a combination of at least 2 antiemetics. Concomitant treatment with aprepitant is not allowed for patients receiving AZD1775 because of potential drug-drug interaction.

Diarrhea: If diarrhea develops and does not have an identifiable cause other than study drug administration, loperamide 4 mg po will be given after the first unformed stool with 2 mg po every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep). This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours to ≤ Grade 1 with the above regimen (total of 16 mg of loperamide a day). If the patient develops blood or mucus in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, loperamide will be discontinued and the patient will be treated with IV fluids and antibiotics as medically indicated.

Seizures: Seizures were seen in some animal toxicology studies with Veliparib, although at doses much higher than those anticipated for this study. Seizures in animals were successfully treated with lorazepam. Therefore, lorazepam should be considered as a possible first choice for controlling seizures, should they occur on this study. All patients experiencing a seizure on study need to be evaluated (e.g., imaging of the brain) to determine the cause.

Anemia: Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 mg/dL. Use of erythropoietin is allowed per accepted guidelines.

Thrombocytopenia: Thrombocytopenia will be treated conservatively. In the absence of bleeding, fever, or a necessary invasive procedure, platelet transfusions should be given for a platelet count below 10,000/µL (mcL). If the patient is febrile, platelet transfusions should be given for a platelet count below 20,000/µL (mcL). If an invasive procedure is planned or the patient develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count above 50,000/µL (mcL).

Neutropenia: Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. If clinically indicated, filgastrim may be initiated for Grade 4 neutropenia at the study investigator's discretion. Study medications will not be reinitiated until at least 24 hours after filgastrim administration.

Reflux/Gastritis: Antacids and other anti-ulcer medications such as histamine H2-receptor antagonists may be used if clinically indicated. To avoid significantly altering gastric pH, when needed, these medications should be used 4 hours after study drug administration.

Skin Rash: Appropriate clinical management of skin rash may be utilized as clinically indicated. Patients will be allowed to use topical emollients, topical steroids, antihistamine agents, and topical or oral antibiotics. A suggested step-wise approach follows:

- Grade 1 rash: Start with topical steroids (e.g., hydrocortisone, triamcinolone acetonide), topical antibiotics such as clindamycin gel, or no treatment if the patient is asymptomatic. Use of topical steroid cream with higher potency or oral antibiotic may be considered early in patients with moderate rash on the face.
- Grade 2 rash: Topical steroid cream, consider addition of an oral antibiotic (e.g., minocycline 100 mg PO BID) or a similar agent.
- Grade 3 rash that does not respond to our measures: Dose interruption and/or dose reduction, in addition to supportive care as above.
- Pruritus of any grade may be treated with an antihistamine, such as diphenhydramine or hydroxyzine hydrochloride.
- Xerosis can be treated with classical emollients.

Hyperglycemia: Blood glucose home monitoring will be initiated in patients with persistently elevated fasting glucose (> 160 mg/dL, CTCAE Grade ≥ 2). Appropriate clinical management including oral anti-hyperglycemic medication or insulin, and supportive care (e.g., electrolyte management and hydration) will be provided as clinically indicated.

5.5 Definition of Off-Study Parameters

In the absence of treatment delays due to adverse events, treatment may continue per protocol until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment,
- Patient requires more than 2 dose reductions (see Section 6.0)

At which point, the patient is taken off that particular treatment.

Duration of Therapy on MPACT Study:

- Pre-defined mutation is not identified
- Disease progression
- All treatment regimens on study specific for the patient's mutation(s) of interest have been exhausted
- Intercurrent illness that prevents further administration of treatment,
- Patient receives any other investigational agent or anticancer therapy
- Patient decides to withdraw from the study.

At which point, the patient is taken off the MPACT study.

5.6 Duration of Follow-Up

Patients in whom a pre-defined mutation is not identified will be taken off study, and no study-specific follow up will be performed. Patients who receive study drug will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Unacceptable toxicities (i.e., AEs related to the intervention) that have not resolved by Day 30 post-treatment will be followed via biweekly phone calls until stabilization or resolution.

5.7 Criteria for Removal From Study

Patients will be removed from the MPACT study for one of the following reasons:

- mutation of interest not detected on pre-treatment biopsy
- inability to obtain pre-treatment biopsy on study
- completion of 30-day follow-up period
- toxicities are unresolved but stabilized
- patient enrolls on another protocol
- patient receives standard of care
- pregnancy
- death

The reason for study removal and the date the patient was removed must be documented in the medical record.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications

Non-hematologic toxicities should have resolved to ≤ Grade 1 (except electrolyte abnormalities, which should resolve to ≤ Grade 2) and hematologic toxicities to ≤ Grade 2 (except lymphopenia) prior to starting the next cycle. Doses of study drugs will not be held or reduced for any grade of lymphopenia. The treatment day count will continue through days when doses are held. A new cycle will not start until the patient starts dosing on the next cycle. Treatment may be delayed for toxicity a maximum of 2 weeks beyond the actual cycle length; in case toxicities do not resolve as defined above, the patient will not receive further treatment with that regimen and will receive no further therapy on this protocol and will be followed for resolution of toxicities. Patients will be allowed up to 2 dose reductions before being taken off a treatment regimen.

For the purposes of dose reduction, the following dose levels will be used:

Drug	Dose and Schedule	Dose Level -1	Dose Level -2
Veliparib: Temozolomide:	40 mg po BID d1-7 150 mg/m^2 po qd d1-5	20 mg po BID d1-7 150 mg/m^2 po qd d1-5	20 mg po BID d1-7 100 mg/m^2 po qd d1-5

Drug	Dose and Schedule	Dose Level -1	Dose Level -2
AZD1775: Carboplatin:	225 mg po BID x5 doses AUC5 IV d1	175 mg po BID x5 doses AUC 5 IV d1	175 mg po BID x5 doses AUC 4 IV d1
Everolimus:	10 mg po qd	5 mg po qd	2.5 mg po qd
Trametinib DMSO:	2 mg qd x28	1.5 mg qd x28	1 mg qd x28

Dose modifications will only be made for adverse events that are felt to be related to study drug. Non-hematologic toxicities should have resolved to Grade ≤ 1 (except electrolyte abnormalities, which should resolve to Grade ≤ 2) and hematologic toxicities should have resolved to grade 2 or less prior to starting the next cycle. Doses will not be held or changed for alopecia, any grade lymphopenia, leucopenia in the absence of neutropenia, nausea/vomiting/diarrhea (unless it is refractory to palliative treatment), or electrolyte abnormalities. Patients receiving Veliparib who have persistent myelosuppression should be evaluated for the possible development of AML/MDS using a bone marrow aspirate with cytogenetics (Section 6.4).

6.1.1 Grade 2 Drug-Related Toxicity: No changes will be made to the study treatment for Grade 2 toxicities.

6.1.2 Grade 3-4 Drug-Related Non-Hematologic Toxicities: Doses will be held until toxicities recover to Grade ≤ 1 (with the exception of electrolyte abnormalities which should resolve to grade 2 or less; no dose adjustments will be made for electrolyte abnormalities) prior to re-initiating therapy at the next lower dose level.

6.1.3 Grade 3 Drug-Related Hematologic Toxicities: Doses will be held until hematologic toxicities (except lymphopenia, leucopenia in the absence of neutropenia) have resolved to Grade ≤ 2 or baseline prior to re-starting study treatment. Therapy will be re-initiated at the same dose level.

6.1.4 Grade 4 Drug-Related Hematologic Toxicities: Doses will be held until hematologic toxicities (except lymphopenia, leucopenia in the absence of neutropenia) have resolved to ≤ Grade 2 or baseline prior to re-starting study treatment. Therapy will be re-initiated at the next lower dose level.

6.2 Agent-specific Dose Modifications: Trametinib DMSO

6.2.1 Ocular toxicities

Visual changes have been observed in patients receiving trametinib, and can be caused by retinal pigment epithelial detachments (RPED) or Retinal Vein Occlusion (RVO). Patients are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline, at the start of cycle 2, and any time patients report visual disturbance. The exam will include best corrected visual acuity, visual field examination, tonometry, slit lamp biomicroscopic examination, and indirect fundoscopy. Optical coherence tomography may be performed at scheduled visits and 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. Special attention should be given to retinal (e.g., RPED) or retinal vein abnormalities (e.g., RVO).

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**
Grade 1*	• 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 level. • 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**.
Grade 2 and Grade 3	• Consult ophthalmologist immediately.	• Hold trametinib • If RPED or RVO excluded, restart trametinib at same dose level after visual AE is < grade 1. If no recovery within 3 weeks, discontinue trametinib • If RPED diagnosed: See RPED dose modification table below; **report as SAE**. • If RVO: **Permanently discontinue trametinib and report as SAE**.
Grade 4	• Consult ophthalmologist immediately. • Report as SAE.	• Hold Trametinib • If RPED/RVO excluded, may restart trametinib at same or reduced dose after discussion with the CTEP Medical Monitor. • **If RVO or RPED, permanently discontinue trametinib**.
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**
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.
Grade 2-3 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 one dose level reduction (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

6.2.2 Rash

Rash is a frequent AE observed in patients receiving trametinib DMSO (Investigator's Brochure, 2012). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors [79, 80].

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight. • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily, starting on Day 1 of study treatment, to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID).
Symptomatic Care[b]	• Pruritic lesions: Cool compresses and oral antihistamine therapies. • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream. • Desquamation: Thick emollients and mild soap. • Paronychia: Antiseptic bath, local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon. • Infected lesions: Appropriate bacterial/fungal culture-driven systemic or topical antibiotics.
[a] Rash prophylaxis is recommended for the first 6 weeks of study treatment. [b] Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.	

Trametinib DMSO Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue trametinib. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib DMSO by one dose level**.[3]
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce trametinib by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase dose to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt trametinib until recovery to ≤ grade 1. • **Restart trametinib at reduced dose level.**[3]
Grade ≥3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt trametinib until rash recovers to ≤ grade 1. • **Restart with trametinib reduced by one dose level.**[3,4] • If no recovery to ≤ grade 2 within 4 weeks, **permanently discontinue trametinib**.
1. Rash prophylaxis is recommended for the first 6 weeks of study treatment. 2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone priopionate 0.5% cream. 3. Approval of CTEP Medical Monitor is required to restart study treatment after >4 weeks of interruption. 4. Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

6.2.3 Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib DMSO (Investigator's Brochure, 2012). Other frequent causes may include concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *C. difficile* or other pathogens, or partial bowel obstruction. Those conditions should be excluded. Guidelines regarding management and dose modification for diarrhea considered related to trametinib are provided in the table below.

Management and Trametinib DMSO Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth). • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics.	• Continue trametinib DMSO. • If diarrhea is grade 2 for > 48 h, interrupt trametinib until diarrhea resolves to grade ≤1. • Restart trametinib at the same dose level • If treatment delay is > 14 days, discontinue trametinib.
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt trametinib until diarrhea resolves to ≤ grade 1. • Restart with trametinib reduced by one dose level.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib DMSO**. • If treatment delay is >21 days, discontinue trametinib.
1. **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 2. **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. 3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea. 4. Escalation of trametinib to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.		

6.2.4 Liver Chemistry Changes

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
ALT ≥3x ULN but <5x ULN and TB <2x ULN, without symptoms considered related to liver injury or hypersensitivity and who can be monitored weekly for 4 weeks	May continue study drug. Report as SAE if CTEP-AERS reporting criteria are met. If liver chemistry stopping criteria are met any time, proceed as described below. MONITORING: Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT <3x ULN and TB <2 ULN).
Criteria for discontinuing study drug: When any of the liver stopping criteria below is met, discontinue trametinib ALT ≥3xULN and bilirubin ≥2x ULN or >35% direct bilirubin [1, 2] ALT ≥ 3xULN and INR >1.5, if INR measured[2] (INR threshold does not apply if subject is on anticoagulant) ALT ≥5x ULN ALT ≥3x ULN persists for ≥4 weeks ALT ≥3x ULN and cannot be monitored weekly for 4 weeks ALT ≥3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	Immediately discontinue study treatment. Do not restart/rechallenge unless approved by CTEP trametinib medical monitor. Report as SAE if: 1) CTEP-AERS reporting criteria are met, or 2) patients meet criteria 1-2. Perform liver event ASSESSMENT AND WORKUP (see below). Monitor the subject until liver chemistries resolve, stabilize, or return to baseline (see MONITORING below). *If applicable, provide details on required follow up assessments (e.g., follow up for overall survival or disease recurrence or progression).* MONITORING: *In patients stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities):* Repeat liver chemistries (ALT, AST, ALK, bilirubin) and perform liver event follow-up assessments within 24 hours. Monitor subjects twice weekly until LFT return to normal/baseline or stabilize. A specialist or hepatology consultation is recommended. *In patients stopping for criteria 2-6:* Repeat LFT and perform liver event follow up assessments within 24-72 hrs Monitor subjects weekly until LFTs return to normal/baseline or stabilize. ASSESSMENT and WORKUP: Viral hepatitis serology.[4] If possible, obtain blood sample for PK analysis.[5] Serum CPK and LDH. Fractionate bilirubin, if total bilirubin ≥2x ULN. CBC with differential to assess eosinophilia. Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). Record alcohol use.

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
	Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities): Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). Serum acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[6] Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.
Footnotes: 1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, which indicates direct bilirubin elevations and suggesting liver injury. 2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3x ULN and INR >1.5 (if INR measured) may indicate severe liver injury (possible "Hy's Law"). INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants. 3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia) 4. Includes: 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, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody 5. PK sample is desired if feasible. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. 6. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al.*, 2005).	

6.2.5 Pneumonitis

Pneumonitis has been observed in patients receiving trametinib DMSO. 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). 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 reduced by one dose level Escalation to previous dose level after 4 weeks may be considered after consultation with medical monitor 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 medical monitor, trametinib may be restarted reduced by one dose level If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib
Grade 4	Same as grade 2	Permanently discontinue trametinib.
Abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography.		

6.2.6 Reduced Left Ventricular Ejection Fraction (LVEF)

Decreases of LVEF have been observed in patients receiving trametinib DMSO. Therefore, ECHOs must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline, every three cycles, and as clinically indicated.

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 CTEP trametinib medical monitor and request approval for restart. – Restart treatment with trametinib at reduced dose by one dose level. – Repeat ECHO/MUGA 2, 4, 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. – Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution. – Consult with the CTEP trametinib medical monitor.[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 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 CTEP trametinib medical monitor is required. [c] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema		

6.2.7 QTc Prolongation

Trametinib Withholding and Stopping Criteria for QTc Prolongation	
QTc Prolongation[a]	**Action and Dose Modification**
• QTcB ≥501 msec, or • Uncorrected QT >600 msec, or • QTcB >530 msec for subjects with bundle branch block	• 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 level.[b] • **If the event does not resolve or 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 and the CTEP trametinib medical monitor agree that the subject will benefit from further treatment.	

6.2.8 Hypertension

Increases in blood pressure (BP) have been observed in patients receiving trametinib DMSO. Recommendations for BP monitoring and management are provided below.

Monitoring: All BP assessments should be performed under the following optimal conditions:

- The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
- The subject is relaxed comfortably for at least 5 minutes.
- Restrictive clothing has been removed from the cuff area, and the right cuff has been selected.
- The subject's arm is supported so that the middle of the cuff is at heart level.
- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
- Persistent hypertension is defined as an increase of systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg in three consecutive visits with blood pressure assessments from two readings as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: – Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. – Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. – Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension) that resolve after the blood pressure is controlled within the normal range. – Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		
(Scenario A) • Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario C) • Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of trametinib	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	**Permanently discontinue trametinib**.
a. Escalation of trametinib to previous dose level can be considered if BPs remain well controlled for 4 weeks after restarting of trametinib. Approval from Medical Monitor is required.		

6.3 Agent-specific Dose Modifications: Everolimus

6.3.1 Hyperglycemia: Grade 2 or higher elevations in blood glucose with the patient non-fasting should be confirmed by obtaining fasting values prior to making any treatment decisions. Grade 3 will result in temporary dose reduction, management with appropriate therapy, and re-initiation at a lower dose.

6.3.2 Hyperlipidemia and Hypertriglyceridemia: Grade 3 (measured by cholesterol and triglycerides) will result in holding study drug until resolution of toxicity to Grade 2 or less, at which point study drug administration will be reinstituted at the next lowest dose level. Grade 4 elevation in either serum cholesterol or triglyceride levels will result in study drug discontinuation.

6.3.3 Skin Toxicity: For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

6.3.4 Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors: Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment).

Dosing Guidelines for > Grade 3 toxicities associated with Everolimus

Everolimus will be discontinued for all grade 4 hematologic and non-hematologic toxicities. Patients with reactivated Hepatitis B or C will have everolimus treatment discontinued and will be taken off study.

Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus as specified in Section 6.0. If the inhibitor is discontinued, the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.

Dosing guidelines for Grade 3 Everolimus-related non-hematologic toxicities

AST or ALT elevation Grade 3	Interrupt Everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, Everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold Everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce Everolimus at one dose level lower, if available.

Intolerable grade 2 mucositis, or grade 3 AE	Interrupt Everolimus administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, Everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold Everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce Everolimus at one dose level lower, if available. Drug will be discontinued if patients fail to recover to ≤ grade 1 or baseline grade / value within 28 days.
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. If toxicity recurs at Grade 3, consider discontinuation
Grade 3 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue Everolimus
Any non-hematologic toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus

Dosing guidelines for Grade 3 Everolimus-related hematologic toxicities

Grade 3 thrombocytopenia	Interrupt Everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce Everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce Everolimus at one dose level lower, if available.
Grade 3 neutropenia or anemia	Interrupt Everolimus until resolution to grade ≤1 or baseline value. If AE resolution occurs ≤ 7 days, reintroduce Everolimus at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce Everolimus at one dose level lower, if available.
Grade 4 neutropenia or anemia	Interrupt Everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce Everolimus at one dose level lower, if available*
Febrile neutropenia	Interrupt Everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce Everolimus at one dose level lower, if available*
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available.
Any hematologic toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa such as gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Management of stomatitis/oral mucositis/mouth ulcers

Grade 1 (Minimal symptoms, normal diet)	Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
Grade 2 (Symptomatic but can eat and swallow modified diet)	Temporary dose interruption until recovery to grade ≤1. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e., triamcinolone oral paste 0.1%)*. Re-initiate everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate everolimus at a lower dose.
Grade 3 (Symptomatic and unable to adequately eat or hydrate orally)	Temporary dose interruption until recovery to grade ≤1. Manage with topical analgesic mouth treatments (i.e., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e., triamcinolone oral paste 0.1%)* Re-initiate everolimus at lower dose.

*Do not use agents containing alcohol, hydrogen peroxide, iodine, or thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Everolimus.

Management of non-infectious pneumonitis

Worst grade	Suggested investigations	Management of pneumonitis
Grade 1	CT scans with lung windows.	No specific therapy is required; initiate appropriate monitoring
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome. Rule out infection and consider interruption of Everolimus until symptoms improve to Grade ≤ 1. Re-initiate Everolimus at one dose level lower. Discontinue Everolimus if failure to recover within ≤ 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated. Interrupt Everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating Everolimus at one dose level lower. Discontinue Everolimus if failure to recover within ≤ 28 days. If toxicity recurs at Grade 3, consider discontinuation.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O_2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated. Discontinue everolimus.

Note: Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment).

6.4 Agent-specific Dose Modifications: Veliparib

If a patient taking Veliparib in combination with temozolomide develops bone marrow findings consistent with AML/MDS or severe persistent anemia, he or she may be allowed to continue the other therapy if they are experiencing clinical benefit and the toxicity is not related to the other therapy, based on the opinion of the Principal Investigator.

Hematologic toxicities should have resolved to ≤ Grade 2 (except lymphopenia) prior to starting the next cycle. Doses of study drugs will not be held or reduced for any grade of lymphopenia. Treatment may be delayed for toxicity a maximum of 2 weeks beyond the actual cycle length per Section 6.1.

Use of hematopoietic agents

Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. Aranesp, Epogen and Procrit may not alleviate fatigue or increase energy and should not be used in patients with uncontrolled hypertension. The package inserts for these agents should be consulted.

If a patient develops febrile neutropenia, Veliparib should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of veliparib unless absolutely necessary. Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Dose modifications for hematologic toxicity

Patients who have veliparib held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery; these data should be recorded in eCRF as extra laboratory examinations. If counts do not improve to CTCAE Grade 2 or better despite drug cessation for 2 weeks, patients should be referred to a hematological oncologist for further assessment. A bone marrow analysis should be considered.

Management of anemia

Anemia is a common adverse drug reaction related to Veliparib; management of anemia is in accordance with the table below:

CTCAE Grade	Definition	Dose
3	Hb <8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt veliparib until improved to ≥ Grade 2 or baseline. Upon recovery, therapy will be re-initiated at the same dose level.

CTCAE Grade	Definition	Dose
4	Hb <8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt veliparib until improved to ≥ Grade 2 or baseline. Upon recovery, dose reduce veliparib to 20 mg BID.

BID = twice daily; Hb = hemoglobin

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. Any subsequently required dose interruptions related to development of anemia, or coexistent with newly developed neutropenia, and/or thrombocytopenia, will require veliparib dose reductions to 20 mg twice daily (BID).

If Hb drops to <8 g/dL despite the dose reduction or more than one blood transfusion is required to recover Hb levels with no alternative explanation for the anemia, veliparib should be permanently discontinued.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in veliparib due to CTCAE Grade ≥3 anemia (Hb <8 g/dL) and/or development of blood transfusion dependence
- ≥2-week interruption/delay in veliparib due to CTCAE Grade ≥3 neutropenia (ANC <1 x 10^9/L)
- ≥2-week interruption/delay in veliparib due to CTCAE Grade ≥3 thrombocytopenia and/or development of platelet transfusion dependence (Platelets <50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 2 weeks of dose interruption, the patient should be referred to a hematological oncologist for further investigations. Bone marrow for evaluation and cytogenetics should be considered at this stage according to standard hematological oncology practice.

Patients who develop MDS/AML on treatment should discontinue veliparib treatment and be managed appropriately.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will

determine whether the event requires expedited (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.1 Adverse Event List(s) for Commercial Agents

Please refer to Sections 8.1 and 8.2 for adverse events related to carboplatin and temozolomide.

7.1.2 CAEPR for Veliparib (NSC 737664)

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 2310 patients.* Below is the CAEPR for ABT-888 (Veliparib).

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 2.4, May 13, 2018

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			**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)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***

Adverse Events with Possible Relationship to ABT-888 (Veliparib) (CTCAE 5.0 Term) [n= 2310]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
		Treatment related secondary malignancy	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event[2]	

[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]Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.

Adverse events reported on ABT-888 (Veliparib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ABT-888 (Veliparib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Cardiac disorders - Other (Takotsubo cardiomyopathy); Heart failure; Left ventricular systolic dysfunction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Colonic obstruction; Dental caries; Dry mouth; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Lower gastrointestinal hemorrhage; Mucositis oral; Obstruction gastric; Rectal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Flu like symptoms; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (cirrhosis)

INFECTIONS AND INFESTATIONS - Appendicitis; Catheter related infection; Infections and infestations - Other (peritonsillar abscess); Lung infection; Lymph gland infection; Mucosal infection; Sepsis; Shingles; Skin infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Radiation recall reaction (dermatologic)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Generalized muscle weakness; Muscle cramp; Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Extrapyramidal disorder; Intracranial hemorrhage; Lethargy; Memory impairment; Movements involuntary; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Psychiatric disorders - Other (emotional instability); Psychosis; Restlessness
RENAL AND URINARY DISORDERS - Dysuria; Hematuria; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail changes; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Vascular disorders - Other (brainstem infarction)

Note: Veliparib (ABT-888) 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.

7.1.3 CAEPR for AZD1775 (NSC 751084)

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 299 patients.* Below is the CAEPR for AZD1775 (MK-1775, NSC 751084).

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.

NOTE: Many adverse events on this CAEPR are treatment-emergent events that have been observed in trials of AZD1775 in combination with chemotherapy including carboplatin, cisplatin,

gemcitabine, 5-fluorouracil, paclitaxel, or topotecan. There are limited adverse event data reported with monotherapy of AZD1775 at this time.

Version 2.4, August 3, 2016

Adverse Events with Possible Relationship to AZD1775 (CTCAE 4.0 Term) [n= 299]			**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)***
	Febrile neutropenia		
CARDIAC DISORDERS			
		Atrial fibrillation	
		Supraventricular tachycardia	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
	Tinnitus		
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
Abdominal pain			***Abdominal pain (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
	Flatulence		
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Oral pain		
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
Fever			***Fever (Gr 2)***
	Flu like symptoms		
	Malaise		
	Non-cardiac chest pain		
	Pain		
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatitis)	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
INFECTIONS AND INFESTATIONS			
Infection (2)			***Infection[81] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		

Adverse Events with Possible Relationship to AZD1775 (CTCAE 4.0 Term) [n= 299]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Blood bilirubin increased		
	Creatinine increased		
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		
	Hyperglycemia		
	Hypoalbuminemia		
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
	Paresthesia		
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
	Acute kidney injury (3)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		
	Hiccups		
		Hypoxia	
	Voice alteration		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		

Adverse Events with Possible Relationship to AZD1775 (CTCAE 4.0 Term) [n= 299]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hyperhidrosis		
	Pruritus		
	Rash (4)		***Rash[82] (Gr 2)***
VASCULAR DISORDERS			
		Phlebitis	
	Thromboembolic event		

[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]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.
[3]Acute kidney injury includes renal impairment and acute renal insufficiency.
[4]Rash may include rash, erythema, eczema, and rash maculo-papular.
[5]Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy.

Adverse events reported on AZD1775 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD1775 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (thrombocytosis); Leukocytosis
CARDIAC DISORDERS - Acute coronary syndrome; Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Blurred vision; Cataract; Conjunctivitis; Eye disorders - Other (eye swelling); Eye disorders - Other (visual impairment); Eye pain; Keratitis; Photophobia; Scleral disorder; Watering eyes
GASTROINTESTINAL DISORDERS - Anal pain; Ascites; Bloating; Cheilitis; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (duodenitis); Gastrointestinal disorders - Other (eructation); Hemorrhoids; Lower gastrointestinal hemorrhage; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Gait disturbance; General disorders and administration site conditions - Other (catheter site pain); Infusion site extravasation
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (excoriation); Injury, poisoning and procedural complications - Other (ligament sprain)
INVESTIGATIONS - Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood urea increased); Lymphocyte count increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperkalemia; Hyperuricemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (groin pain); Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoid tumor); Tumor pain

NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Dysesthesia; Encephalopathy; Lethargy; Nervous system disorders - Other (hemiparesis); Peripheral neuropathy[83]; Presyncope; Somnolence; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression
RENAL AND URINARY DISORDERS - Hematuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Female genital tract fistula; Genital edema
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Nasal congestion; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (diaphragmalgia); Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Purpura; Rash acneiform; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension

Note: AZD1775 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.

7.1.4 CAEPR for Trametinib DMSO (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		

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%)**	
		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		
	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)***

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%)**	
	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.

7.1.5 CAEPR for Everolimus (RAD-001, NSC 733504)

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 3033 patients.* Below is the CAEPR for Everolimus (RAD-001).

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 2.5, July 3, 2018

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 5.0 Term) [n= 3033]			**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)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea[2]			***Diarrhea[2] (Gr 3)***
Mucositis oral[3]			***Mucositis oral[3] (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 3)***

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 5.0 Term) [n= 3033]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication[5]	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Cholesterol high		***Cholesterol high (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia[6]		***Hyperglycemia[6] (Gr 3)***
	Hypertriglyceridemia		***Hypertriglyceridemia (Gr 4)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache		***Headache (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
	Pneumonitis[7]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Pruritus		
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (angioedema)[8]	

[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]Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

[3]Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.
[4]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
[5]Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma.
[6]Hyperglycemia may result in either exacerbation of or development of new onset diabetes mellitus.
[7]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease.
[8]Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.
[9]Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

Adverse events reported on everolimus (RAD-001) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that everolimus (RAD-001) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (myocardial abnormality); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
ENDOCRINE DISORDERS - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels); Hypothyroidism; Testosterone deficiency
EYE DISORDERS - Blurred vision; Keratitis
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Hemorrhoids; Intra-abdominal hemorrhage; Oral pain; Pancreatitis; Periodontal disease; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly)
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bicarbonate decreased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; GGT increased; INR increased; Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia).
METABOLISM AND NUTRITION DISORDERS - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hyperlipidemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts)
NERVOUS SYSTEM DISORDERS - Dizziness; Encephalopathy; Hydrocephalus; Lethargy; Paresthesia
PSYCHIATRIC DISORDERS - Agitation; Anxiety[76]; Delirium; Depression; Insomnia; Irritability; Mania
RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dysmenorrhea; Genital edema; Irregular menstruation; Menorrhagia; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (rales); Rhinorrhea; Sore throat; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail disorder); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration
VASCULAR DISORDERS - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; Vascular disorders - Other (acute bowel ischemia); Vascular disorders - Other (hemorrhage)

Note: Everolimus (RAD-001) 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.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. 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).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. Specific Protocol Exceptions to Expedited Reporting (SPEER) appears as ***bold and italicized*** text in the CAEPR (Section 7.1).

- **Attribution** of the AE: Definite – The AE *is clearly related* to the study treatment; Probable – The AE *is likely related* to the study treatment; Possible – The AE *may be related* to the study treatment; Unlikely – The AE *is doubtfully related* to the study treatment; Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.2).

In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: (301) 897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, lead organization study research nurses, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.2 Phase 1 and Early Phase 2 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 [1,2]

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:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- 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 electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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.

Expedited AE reporting timelines are defined as:

1) "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
2) "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events 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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.3 Protocol-specific expedited AE reporting exclusions.

Lymphopenia (any grade), alopecia (any grade), anemia (grade 2), electrolytes (grade 2: sodium, potassium, phosphorous, and magnesium), albumin (grade 2), hyperuricemia (grade 3), INR (grade 2), and PTT (grade 2) will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

7.3.4 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and faxed along with any additional medical information to **301-230-0159.** 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.

7.3.4.1 Pregnancy

- Because patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, DCTD/DCP is requesting that pregnancy should 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.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report

7.3.4.2 Pregnancy loss

- 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.
- A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

7.3.4.3 Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" 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.
- Neonatal death should NOT be reported as Grade 5 "Death neonatal" under the General disorders and administration SOC. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event 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. AEs are reported in a routine manner at scheduled times

during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 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 secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP 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:

1. Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2. Myelodysplastic syndrome (MDS)
3. Treatment-related secondary malignancy

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

7.6 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.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with these agents can be found in Section 7.1.

8.1 Temozolomide (NSC 362856)

Availability: Please refer to the FDA-approved package insert for complete product information. Commercial supplies of temozolomide will be purchased by the DCTD, NCI and distributed by the Pharmaceutical Management Branch, CTEP.

Toxicities: The most common adverse events across the cumulative temozolomide experience were alopecia, nausea, vomiting, anorexia, headache, and constipation. Forty-nine percent (49%) of patients treated with temozolomide reported one or more severe or life-threatening events, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%). Myelosuppression (neutropenia and thrombocytopenia), which is a known DLT for most cytotoxic agents, was observed, as were Grade 3 or Grade 4 neutrophil abnormalities including neutropenic events, and Grade 3 or Grade 4 platelet abnormalities, including thrombocytopenic events.

Chemical Name: 3,4-dihydro-3-11 methyl-4-oxoimidazo(5,1-d)-*a*s-tetrazine-8-carboxamide.

Other Names: Temodar®, Temodal, Temcad

CAS Registry Number: 85622-93-1

Molecular Formula: $C_6H_6N_6O_2$ **M.W.:** 194.15

Mode of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions of guanine.

How Supplied: PMB, CTEP, DCTD distributes commercially labeled Temozolomide as 5 mg, 20 mg, 100 mg and 250 mg capsules for oral administration. Each bottle contains 5 capsules. The dose of temozolomide is to be rounded to the nearest 5 mg. The manufacturer of the NCI-purchased supplies may vary throughout the course of the trial. Temozolomide capsules contain the following inactive ingredients: lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid in varying quantities per capsule strength. Refer to the approved package insert for complete product information and physical description of the supplied product.

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

Stability: Refer to the package label for shelf life.

Route of Administration: Oral.

Method of Administration: Take each day's dose of capsules at one time, with a full glass of water. They should be swallowed whole and **never chewed**. If capsules are vomited do not take a second dose. New capsules should not be taken until the next planned dose. The incidence of nausea and vomiting is decreased when temozolomide is taken on an empty stomach.

8.2 Carboplatin (NSC 241240)

Availability: Please refer to the FDA-approved package insert for complete product information. Commercial supplies of Carboplatin will be purchased by the DCTD, NCI and distributed by the Pharmaceutical Management Branch, CTEP.

How supplied: PMB, CTEP, DCTD distributes commercially-labeled supplies of Carboplatin aqueous solution Injection as 450 mg/45 mL (10 mg/mL in Water for Injection) multi-dose vials. The manufacturer of the NCI-purchased supplies may vary throughout the course of the trial. Refer to the approved package insert for complete product information and description of the supplied product.

Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

Storage and Stability: Unopened vials of Carboplatin aqueous solution are stable to the date indicated on the package when stored at 25°C (77°F); excursions permitted from 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.
Carboplatin aqueous solution multi-dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following initial vial entry. When prepared as directed, carboplatin solutions for infusion are stable for 8 hours at room temperature (25°C). Prepared solutions for infusion are to be discarded 8 hours after preparation.

NOTE: Aluminum reacts with carboplatin, causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Dosing and Administration: Carboplatin will be administered concomitantly with AZD1775 as an i.v. infusion over 30-70 minutes. The dose will be calculated based on the patient's actual body weight at each treatment visit and the AUC (area under curve) dosing according to the formula provided below.

The calculated GFR for the carboplatin dose will be based on the calculated creatinine clearance using the Cockroff-Gault formula.

Calvert Formula for carboplatin dose: AUC Dose = 5.0 x (GFR + 25)

Where GFR (Cockroff-Gault):

$$\text{GFR} = \frac{(140 - \text{pt. age in years}) \text{ (weight in Kg)} \times 0.85 \text{ (females) or } 1.0 \text{ (males)}}{\text{serum creatinine} \times 72}$$

The GFR (calculated by Cockcroft-Gault or any other means using creatinine) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min under any circumstance. By definition, this results in the following upper limits on the dose to be administered, by AUC target:

AUC target (mg•min/mL)	Maximum carboplatin dose (mg)
4	600
5	750

Questions about this calculation should be directed at the study investigator.

Toxicities: Some of the expected adverse events from carboplatin are listed below. For further description of adverse events, see Package Insert.

Hematologic: Myelosuppression

Gastrointestinal: Nausea, vomiting, diarrhea, weight loss, constipation, gastrointestinal pain

Metabolic: Electrolyte imbalances, hypomagnesemia, hypocalcemia, hyponatremia, hyperuremia, hypokalemia

Hepatic: Elevated alkaline phosphatase, AST, and total bilirubin

CNS: Peripheral neuropathies (mild paresthesias, clinical ototoxicity and other sensory abnormalities are rare)

Genitourinary: Renal tubular damage, renal insufficiency, impotence, sterility, amenorrhea, gynecomastia

Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritis, and rarely hypotension or bronchospasm

Other: Alopecia, pain, asthenia, and mucosal side effects

Patient Care Implications: Patients taking carboplatin should avoid the use of live vaccines and close contact with those who have received live vaccines. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

8.3 Everolimus (NSC 733504)

Chemical Name: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-((1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl)-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo(30.3.1.04,9)hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone

Other Names: RAD001, Afinitor

Classification: mTOR inhibitor

CAS Registry Number: 159351-69-6

Molecular Formula: $C_{53}H_{83}NO_{14}$ **M.W.:** 958.2

Mode of Action: Everolimus is an inhibitor of selective mammalian target of rapamycin (mTOR), the effects of which specifically target the mTOR-raptor signal transduction complex 1 (mTORC1). Inhibition of mTORC1, an essential regulator of global protein synthesis downstream on the PI3K/AKT/mTOR pathway, reduces tumor cell proliferation, glycolysis, and angiogenesis. The PI3K/AKT/mTOR pathway is dysregulated in the majority of human cancers and is the object of many targeted agents.

Description: White to faintly yellow powder

How Supplied: Novartis supplies and PMB, CTEP, DCTD distributes commercially labeled Everolimus as 2.5 mg, 5 mg, and 10 mg tablets for oral administration. Each box of 28 tablets contains 4 blistercards of 7 tablets each. The white to slightly yellow, elongated tablets are distinguished as follows:

- 2.5 mg tablet is engraved with "LCL" on one site and "NVR" on the other
- 5 mg tablet is engraved with "5" on one side and "NVR" on the other
- 10 mg tablet is engraved with "UHE" on one side and "NVR" on the other

Tablet excipients include drug substance, 0.2% butylated hydroxytoluene (BHT), magnesium stearate, lactose anhydrous/anhydrous lactose, lactose monohydrate, hypromellose/hydroxypropyl methylcellulose, and crospovidone.

Storage: Store at 25°C (77°F) [excursions permitted between 15 to 30°C (59 to 85°F].

Stability: Refer to the package label for shelf life. Store tablets in the original container and protect from light and moisture.

Route and Method of Administration: Oral administration. Tablets should be swallowed whole with a glass of water. They can be taken with or without food but should be taken consistently the same time every day. If a dose is missed, it can still be taken up to 6 hours after the usual time of administration. Missed doses more than 6 hours late should be skipped for that day.

Potential Drug Interactions: Everolimus is a substrate of CYP3A4 and P-glycoprotein (PgP). Concomitant treatment with strong inhibitors or inducers of CYP3A4 or PgP should be avoided. Use caution when everolimus is given concomitantly with moderate inhibitors or inducers of CYP3A4 and PgP. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro, everolimus is a competitive inhibitor of CYP3A4, a mixed inhibitor of CYP2D6, an inhibitor of transport proteins, OATP1B1 and OATP1B3 and a moderate inhibitor of P-gp. Exercise caution when everolimus is taken in combination with orally administered substrates of these enzymes and transporters, in particular, CYP3A4 substrates with a narrow therapeutic index.

Co-administration with angiotensin-converting enzyme (ACE) inhibitors may increase the risk for angioedema based on results of a pooled analysis of randomized, double blind studies.

Patient Care Implications: Patients taking everolimus should avoid the use of live vaccines and close contact with those who have received live vaccines. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

8.4 Veliparib (NSC 737664)

Chemical Name: 1*H*-Benzimidazole-7-carboxamide, 2-[(2*R*)-2-methyl-2-pyrrolidinyl]-

Other Names:ABT-888, A-861695.0

Classification: Poly (ADP-ribosome) polymerase (PARP) Inhibitor

CAS Registry Number: 912444-00-9

Molecular Formula: $C_{13}H_{16}N_4O$ **M.W.:** 244.29

Approximate Solubility: Freely soluble at pH < 6.9, soluble at pH 6.9 to 7.1, and slightly soluble at pH > 7.1.

Mode of Action: Veliparib inhibits the formation of poly (ADP-ribose) (PAR) polymers in vitro and in vivo. It inhibits the repair of DNA when the DNA is damaged by cytotoxic agents.

Veliparib increases antitumor efficacy when added to DNA-damaging therapies such as temozolomide.

Description: White to light yellow solid.

How Supplied: Veliparib capsules are available in 10 mg, 20 mg, 40 mg, and 50 mg immediate release capsules. The inactive ingredients are microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, FD&C yellow #5, and titanium dioxide. The capsules are packaged in HDPE bottles, and each HDPE bottle contains 16 capsules or 64 capsules.

Veliparib capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. Expiration will be 30 days from the repackaging date (or the original retest date, whichever is earlier) when stored at 15°C to 25°C (59°F to 77°F).

Storage: Store the original bottle at 15º to 25º C (59º to 77º F).
Stability: Shelf-life stability studies for Veliparib capsules are ongoing.

Route(s) **of Administration:** Oral

Method of Administration: Administer Veliparib orally without regards to meals.

Potential Drug Interactions: Clinical studies evaluating the metabolism of Veliparib have not been conducted. However, results from the in vitro analysis reveal that this agent is metabolized by multiple isoenzymes – CYP1A1, 2D6, 2C19, and 3A4. Veliparib is neither a potent inhibitor nor a potent inducer of the CYP-450 isoenzymes. Use caution when concomitantly administering with drugs that are substrate, inhibitor, or inducers of CYP1A1, 2D6, 2C19 and 3A4. Veliparib clears primarily in the urine as intact parent drug along with metabolites suggesting that renal function plays an important role in the drug clearance and its metabolites.

Patient Care Implications: Patients may feel fatigue or tiredness. Loss of appetite and losing weight are common. Provide appropriate supportive care for diarrhea. Avoid long-sun exposure as it might exacerbate skin rash.

Availability: Veliparib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Veliparib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI.

8.5 AZD1775 (NSC 751084)

Chemical Name: 2-Allyl-1-[6-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-6-[4-(4-methylpiperazin-1-yl)anilino] pyrazolo[3,4-d]pyrimidin-3-one hemihydrate

Classification: Inhibitor of Wee1-kinase

CAS: 277170-60-1

Molecular Formula: $C_{27}H_{32}N_8O_2 \cdot 0.5H_2O$ **M.W.:** 518.623

Approximate Solubility*:* Aqueous solubility is 0.02 mg/mL.

Mode of Action: AZD1775 is an inhibitor of the Wee1-kinase. Wee1 is a tyrosine kinase upstream of CDC2 thereby involved in regulation of cell cycle checkpoints, particularly the G2 checkpoint. As the majority of human cancers harbor abnormalities in the p53 pathway, they become more dependent on S- and G2-phase checkpoints. In preclinical models, AZD1775 selectively enhanced chemotherapy-induced death of cells deficient in p53 signaling.

Description: AZD1775 is a crystalline, non-hygroscopic, monohydrate of the neutral drug. It dehydrates upon heating leading to formation of a crystalline anhydrate.

How Supplied: AZD1775 is supplied by AstraZeneca and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as capsules available in 25 mg (yellow color, size 2 gelatin capsule) and 100 mg (orange color, size 2 gelatin capsule) strengths. Due to no further manufacturing, the 200 mg (light brown color, size 0 gelatin capsule) strength is available only as inventory allows until the shelf life is reached. The capsules consist of a roller compacted granule of agent, lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Each high-density polyethylene (HDPE) bottle contains 20 capsules.

Storage: Store bottles at controlled room temperature, not to exceed 30° C.

Stability: Shelf life studies of AZD1775 are on-going.

Route of Administration: Oral administration. Take AZD1775 at least two hours before or two hours after a meal.

Potential Drug Interactions: AZD1775 is primarily metabolized by CYP3A4 and is a weak, time-dependent inhibitor of CYP3A4. Avoid concomitant CYP3A4 moderate or strong inhibitors/inducers, and sensitive substrates with a narrow therapeutic index. AZD1775 is also a weak inhibitor of CYP2C19. Caution should be exercised with concomitant administration of sensitive substrates or substrates with a narrow therapeutic index.

In vitro transporter studies have shown that AZD1775 was an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and a substrate for P-gp and BCRP. The PK parameters of AZD1775 could be altered if AZD1775 is co-administered with P-gp and BCRP inhibitors/inducers, and there is potential for drug-drug interactions when co-administered with OATP1B1, OATP1B3, MATE1, MATE2K, P-gp and BCRP substrates. This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of atorvastatin when co-administered with AZD1775 and the use of atorvastatin is therefore prohibited.

Contraindications: Treatment with AZD1775 is contraindicated in subjects with hypersensitivity to any component of the drug. Developmental and reproductive toxicity studies of AZD1775 have not been performed. AZD1775 is not to be given to women who are pregnant or breast feeding.

Availability AZD1775 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. AZD1775 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and DCTD, NCI.

8.6 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)

Chemical Name (IUPAC): equimolecular combination of acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro6,8-dimethyl- 2,4,7-trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl] with 1,1'-sulfinylbis[methane]

Other Names: trametinib, GSK1120212, JTP-74057, JTP-78296, JTP-75303, Mekinist

CAS Registry Number: 1187431-43-1

Classification: MEK inhibitor

Molecular Formula: $C_{26}H_{23}FIN_5O_4 . C_2H_6OS$ **M.W.:** 693.53

Approximate Solubility: Trametinib dimethyl sulfoxide is almost insoluble in water (<0.0001 mg/mL at 25° C)

Mode of Action: Trametinib dimethyl sulfoxide is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. 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.

Description: Trametinib dimethyl sulfoxide is a white to almost white powder.

How Supplied: Novartis supplies and CTEP, NCI, DCTD distributes 0.5 mg and 2 mg (as free base) tablets. Each commercially-labeled bottle contains 30 tablets with a desiccant.

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

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated with 'GS' debossed on one face and 'TFC' on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow.
- 2 mg tablets are pink, round, biconvex and film-coated with 'GS' debossed on one face and 'HMJ' on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

Storage: Store tablets at 2°C -8°C in the original bottle. Do not repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

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.

Stability: Refer to the package label for expiration.

Route of Administration: Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal. If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

Potential Drug Interactions: *In vitro* studies suggest that trametinib dimethyl sulfoxide is not a substrate of CYP enzymes or of human BCRP, MRP2, OATP1B1, OATP1B3, OATP2B1, OCT1, or MATE1 transporters. Trametinib elimination by deacetylation to metabolite M5 is dependent on carboxylesterases (CES1b, CES1c, and CES2). M5 is eliminated by CYP3A4 and other pathways, presenting the clinically relevant, albeit low, potential for drug-drug interaction. Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant due to trametinib's high permeability.

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 CYP3A4 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 P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 MRP2 and MATE1.

Patient Care Implications: Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib. Refer to the protocol document for specific guidance.

8.7 Agent Ordering

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment arm prior to submitting the clinical drug request to PMB.

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI 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.

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, 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 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 Everolimus, Veliparib, AZD1775, and Trametinib dimethyl sulfoxide will be accessible to site investigators and research staff through the PMB 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://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.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)

9. GENETIC ANALYSIS

9.1 Tumor Biopsies

A mandatory pre-treatment tumor biopsy (2 cores) will be obtained from all patients after signing the consent and enrolling on the study to determine whether the tumor has a mutation in one of the pathways of interest, unless an FFPE block that meets Eligibility Criterion 3.1.2 is provided or a CLIA genetic testing report from a MATCH-designated lab is available and indicates an actionable mutation of interest. Patients entered on trial based on outside reports from MATCH-designated labs will be biopsied during their first week on study for confirmatory screening with the Oncominev3 (MATCHv3) assay. Biopsy samples will be fixed in formalin and shipped as described in Section 9.3.

Additionally, an optional tumor biopsy (2-5 cores) may be taken at or near the time of disease progression to assess for new acquired mutations.

There is increasing awareness that biopsies lacking tumor of sufficient quantity or quality for analysis are a barrier to clinical research in both trials for which genetic sequencing establishes eligibility and in trials where paired pre- and post-treatment biopsies are collected to quantify

target modulation. In a retrospective analysis, we found that only 70% of the 18-gauge needle biopsies collected met pharmacodynamic assay quality control criteria due to necrosis, fibrosis, no or insufficient tumor content, and/or poor morphology; the success rate is only 50% when both pre- and post- treatment (paired) biopsies are required (Ferry-Galow et al., manuscript in preparation). The NCI is currently promoting efforts and providing resources to improve research biopsy quality given that insufficient tumor tissue samples compromise the scientific value of the study, the patients' contribution to research, and the staff resources devoted to clinical trials.

Based on our experience, immediate and significant improvements in biopsy quality can be achieved simply from better communication with the interventional radiologists performing the biopsy procedures. We therefore recommend that participating site PIs invite their site's radiologists to join the research team and to review and discuss this protocol and the biopsy and specimen handling requirements. We recognize that these individuals are not always compensated for the additional time required to participate nor recognized for their effort, but at a minimum, communicating that research biopsies present requirements beyond those of biopsies collected for diagnostic purposes is of considerable value. Collecting multiple cores from each patient during each biopsy procedure increases the probability of obtaining sufficient samples for analysis, and the radiologist is best placed to determine how many cores are safe and feasible and evaluate patient willingness to continue donation. In the absence of a reliable and rapid method for "real-time" tumor content evaluation and given the need to preserve the tissue rapidly to ensure optimal sample quality, the interventional radiologist's judgment and experience are critical to procuring and preserving quality material.

An adequate tumor biopsy sample will contain at least 50% tumor cells with minimal necrosis and stromal tissue; samples with less than 50% tumor cells will undergo tumor enrichment using a standardized macrodissection protocol. In case of samples with insufficient tumor content or DNA yield for analysis, the patient will be given the option to undergo a repeat tumor biopsy to obtain more tissue. Patients from whom sufficient tumor DNA material cannot be obtained for targeted analysis will be taken off-study.

9.1.1 Biopsy Procedure

No more than three serial tumor biopsies will be obtained through Interventional Radiology by a percutaneous approach: one mandatory at screening baseline; one optional repeat biopsy if sufficient tumor DNA cannot be isolated at baseline; and one optional biopsy at time of disease progression (this biopsy may instead be collected on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed, per RECIST criteria, if the patient has been on study for at least 4 cycles).

For eligibility determination, it is preferred that up to three core biopsies18-gauge in diameter and at least 1 cm in length are obtained. Only percutaneous biopsies will be performed on patients with solid tumors. However, excisional biopsy is allowed if indicated and can be used for analysis. Biopsies will be sent for analyses as defined in the protocol. It is estimated that there will be between 2-5 million cells from each biopsy. If a site is deemed appropriate for biopsy with minimal risk to the participant by

agreement between the investigators and Interventional Radiology, an attempt at biopsy will be made.

The biopsy procedure to be used in this protocol is described below; local anesthesia will be administered. Such biopsies can be safely performed as evidenced by literature reports [93] as well as our experience at the Clinical Center. Risks of the procedure include, but are not limited to, bleeding, infection, pain, and scarring. Each site will follow local Interventional Radiology SOPs for coagulant panel and platelets.

- All biopsies will be by percutaneous approach unless excisional biopsy is indicated.
- No biopsy by an invasive (endoscopic, laparoscopic, or surgical) procedure will be performed.

The use of imaging to facilitate biopsies will be decided by members of the Interventional Radiology team and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant as determined by the investigators and Interventional Radiology.

If an initial attempt at percutaneous biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt at percutaneous biopsy. If a pre-treatment biopsy sample is unable to be obtained for a given patient, or the patient chooses not to undergo the pre-treatment tumor biopsy, he/she must be taken off study because the genetic data from the tumor biopsy are essential to the primary objective of the trial.

9.2 Screening Eligibility Sample Collection and Processing

At the NCI, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10 at least 24 hours prior to sample collection (E-mail: NCIPK-PDsupportgroup@mail.nih.gov; Pager: 102-12798; Phone: 301-451-1169; Fax: 301-480-5871). The lab staff will be paged for sample pick-up. At the NCI only, 2-3 additional cores may be collected and snap frozen (see NCI Supplementary Appendix).

Other participating sites should follow the sample collection instructions in Appendix E.

Formalin jars (prefilled 30 mL) pre-labeled with the participant ID, biopsy date, protocol number, and site of tissue biopsy will be used for biopsy collection. Surgical tumor tissue and needle core biopsies (collected by 16-18-gauge needles) collected in neutral buffered formalin (one core per jar) will be shipped via overnight courier at ambient temperature on the day of biopsy collection to Dr. Mickey Williams' laboratory (MoCha) at the Frederick National Laboratory for Cancer Research (FNLCR) as defined in Appendix E.

9.3 Shipping for Genetic Analysis

9.3.1 Tumor Samples

For all patients, formalin-fixed tumor tissue or suitable FFPE block will be submitted for the genetic analyses described below. Genetic analysis will be done by the MoCha Laboratory. Samples labeled with unique patient IDs **only** will be sent directly to Dr. Mickey Williams' laboratory. **Do NOT include patient identifiers (e.g., medical record number, patient name, or initials) with the samples.**

Please e-mail NCI-FrederickMPACTCLIA@mail.nih.gov if you have any questions about sample shipping. A sample shipping manifest is included in Appendix E.

Following processing and paraffin embedding, one tissue section will be stained with H&E for histopathological examination by a designated pathologist. Tumor cellular content must be at least 50% and estimated tumor content will be recorded. The remaining biopsy will be extracted for nucleic acids using the Qiagen FFPET All-Prep procedure. DNA will be assessed for quantity and quality by spectroscopy (OD 260/280) and a PCR-based amplification quality assessment test. All specimens that meet necessary quantity and quality will be sequenced using a targeted sequencing assay. This assay will identify those mutations that are used for treatment assignment.

If sufficient DNA is available from the tumor biopsy, whole-exome sequencing will be performed retrospectively for research purposes on samples unlinked from patient identifiers.

9.3.2 Blood Samples for Genetic Analysis

Whole blood samples will be collected to obtain plasma and mononuclear cells. All sequencing analysis from the plasma and mononuclear cells will be performed only after the samples are unlinked and stripped of the patient identifiers for retrospective research sequencing. The nucleic acid extracted from the unlinked patient's mononuclear cells will be sequenced to compare somatic mutational status to the tumor biopsy specimen. Plasma collected in this process will be delinked and used in exploratory research protocol to study (but not limited to), circulating tumor DNA.

Two 10-mL cell-free DNA BCT (Streck) tubes should be collected on the same day as the screening eligibility biopsy (collection time can be either pre- or post-biopsy) and shipped at ambient temperature as described in Appendix E. The samples should be labeled with only the unique patient ID. **Do NOT include patient identifiers (e.g., medical record number, patient name, or initials) with the samples.**

Please e-mail NCI-FrederickMPACTCLIA@mail.nih.gov if you have any questions about sample shipping. A sample shipping manifest is included in Appendix E.

Upon receipt at the service laboratory, genomic DNA will be extracted for clinical targeted sequencing.

9.4 Sample Handling and Unlinking Procedures

Biospecimens will be collected and processed using locked SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions.

Using a computerized inventory system, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers. Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number 9149, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
300 series: blood for pharmacodynamics
500 series: tumor biopsies
800 series: blood for research (Streck tubes)

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Samples which are unlinked cannot be traced to the individual patients, and the patient's request cannot be met. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (e.g., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

9.4.1 Sample Unlinking

Clinical information linked to the unique patient IDs will be stored in a bioinformatics database along with the targeted sequencing panel. Once patient has completed treatment on study and has been taken off study, the unique patient ID will be deleted and a new random ID generated (arbitrary or random alphanumeric code) in the database by the bioinformatics team, thereby delinking the patient identifier from the information in the database. Patient consent to allow research use of his/her samples will be confirmed at this time. The Bioinformatics team will inform Dr. Mickey Williams' laboratory of the new random ID, all samples from a given patient will be transferred to the new ID, and Dr. Williams' lab will also break the link to the unique patient ID. The unique patient IDs will be discarded so there is no possibility of linking the samples to the sources. Dr. Williams' lab will proceed with (but not limited to) whole exome sequencing on de-identified samples for research purposes only. Data reports sent to the clinical site will be summary reports with no identifiable patient IDs whatsoever.

When the study was re-opened with a new non-randomized design, a singular patient continued to receive randomized first-line study treatment. As of Amendment Y (January 7, 2020), sample unlinking (as described above) may occur while this patient remains on study treatment, if the patient consents to this change, in order to enable research-use analysis of samples in parallel with the other results from the randomized phase of the study.

10. STUDY CALENDAR:

Baseline evaluations are to be conducted within 8 days prior to start of protocol therapy. If the patient's condition deteriorates prior to initiation of treatment, evaluations should be repeated within 48 hours prior to initiating treatment. Scans and x-rays must be done within 28 days prior to the start of therapy. The start of the next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. Treatments within a cycle may be delayed up to +/- 1 day to accommodate scheduling conflicts. Cycles may be continued until a patient meets one of the criteria in Section 5.6. Additional evaluations will be conducted as clinically indicated at the investigator's discretion.

	Pre-Study	Cycle 1 Week 1	Cycle 1 Week 2	Cycle 1 Week 3	Cycle 1 Week 4	Cycle 2 onwards Week 1
Informed consent	X					
Tumor biopsy and blood sample for genetic analysis	X					
Study Drug[a]		X[a]	X[a]	X[a]	X[a]	X[a]
Demographics	X					
Medical history[b]	X	X				
Concurrent meds	X	X……...……...……...……...X				
Physical exam[b]	X	X				X
Vital signs[b]	X	X				X
Height	X					
Weight[b]	X	X				X
Performance status	X	X				X
CBC w/diff, plts[c]	X	X	X	X	X	X
Serum chemistry[c]	X	X	X	X	X	X
EKG[i]	X					X
Adverse event evaluation	X	X……..……..……..……..……X				
Radiologic evaluation	X	Tumor measurements are repeated every *2 cycles** Documentation (radiologic) must be provided for patients removed from study for progressive disease.				
β-HCG[d]	X					X
Ophthalmologic exam[e]	X					X
ECHO/MUGA[f]	X					
Lipid monitoring[g]	X	*Lipid monitoring every 2 cycles*				
Urinary Protein[h]	X					X

a: Patients will be assigned to receive **one** of the following study drugs or drug combinations at the assigned dose (cycles +/- 1 day for scheduling):

- **Veliparib:** 40 mg orally BID qd days 1-7 plus temozolomide 150 mg/m^2 orally qd days 1-5 (no food restrictions) in 28-day cycles. Patients who receive temozolomide will have an evaluation of their LFTs at the time of coming off-treatment.
- **Everolimus:** 10 mg orally each day (no food restrictions) in 28-day cycles.
- **Trametinib DMSO**: 2 mg orally each day either one hour before or two hours after a meal in 28-day cycles.
- **AZD1775**: 225 mg orally BID x 5 doses either at least two hours before or two hours after a meal plus carboplatin (AUC 5) IV on day 1 of every 21-day cycle.

b: History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium prior to treatment (up to 8 days prior) and as indicated. CBC w/diff, platelets and serum chemistries should be performed prior to cycle 1 treatment (up to 8 days prior), weekly throughout cycle 1, and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3.

d: Urine or serum pregnancy test (women of childbearing potential) pre-study. Repeat pregnancy test at the start of each subsequent cycle (up to 3 days before start of new cycle) for patients on AZD1775 only.

e: Complete ophthalmologic examination at baseline for patients on MEK inhibitors only (within 6 months prior to start of therapy), and at the start of the second cycle. Additional ophthalmologic exams may be performed as clinically indicated.

f: Repeat echocardiograms for patients on trametinib DMSO or everolimus only, every 3 cycles. Additional echocardiograms may be performed as clinically indicated. The same modality (either ECHO or MUGA) should be used at baseline and at follow-up.

g: Repeat lipid monitoring for patients on everolimus only (within 1 week prior to enrollment), and every 2 cycles.

h: Repeat urinary protein at baseline for patients on everolimus only (within 1 week prior to enrollment), and at the start of each subsequent cycle (up to 3 days before start of new cycle).

i: Repeat EKGs at the start of each subsequent cycle (up to 3 days before start of new cycle) for patients on AZD1775 only.

* CT scans can be performed every 4 cycles (for both the 21-day and 28-day cycles) for patients on study more than one year; it the patient changes therapy, CT scans will be performed once every 2 cycles for 1 year.

Baseline evaluations are to be conducted within 8 days prior to start of protocol therapy. If the patient's condition deteriorates prior to initiation of treatment, evaluations should be repeated within 48 hours prior to initiating treatment. Scans and x-rays must be done within 28 days prior to the start of therapy. The start of the next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. Treatments within a cycle may be delayed up to +/- 1 day to accommodate scheduling conflicts. Cycles may be continued until a patient meets one of the criteria in Section 5.4.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated every 2 cycles (every 4 cycles for patients on study more than one year). Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [94]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm by chest x-ray, as $\geq$ 10 mm with CT scan, or $\geq$ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with $\geq$ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast

disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered

in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [95-97]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [98].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or

	non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the

progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

Safety Monitoring Committee

Because this is a multi-institutional protocol for which the NCI DTC is the coordinating center, it will be monitored by the DTC Safety Monitoring Committee (SMC).

12.1 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in 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 users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users 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.

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

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by e-mail at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.1.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS are reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with

regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.2 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

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/industry) 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 investigational 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 investigational 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 NIH, 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 investigational 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 investigational 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 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 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: E-mail: 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.

12.3 Publication Policy

Recognizing the need to make clinical trial outcomes rapidly available to the cancer clinical trials community [99], publication of the results from this study will be a priority following completion of accrual, follow up, and data analyses.

Authorship of this group-wide study will include the Coordinating Center PI, the study statistician, and one representative from each participating institution listed on the cover page of the protocol that contributed more than 10% of the eligible, evaluable cases. The first author, last author, corresponding author(s), and study statistician, will all be NCI investigators. The CTEP medical monitor will also be listed as an author. Lead investigators from laboratories involved in conducting correlative studies will be listed as authors if data from their laboratories are included in the clinical results manuscript.

If several investigators were responsible for a participating institution's accrual, the designated representative from that institution ordinarily will be the PI. When an individual other than the PI is largely responsible for a participating institution's accrual, the PI is expected to substitute that individual as an author in place of himself/herself. The intent is to offer recognition to the individuals who have been most directly involved in the study. Because the Coordinating Center PI will often be unaware of the relative contributions of investigators at each institution, the PIs at participating institutions accruing more than 10% of cases will be solicited routinely to determine whether another individual should be substituted for them in authorship. There will be only one author from each of the participating institutions listed on the cover page of the protocol. If the PI is already an author, based on scientific contribution to the study, a second person from that PI's institution will not automatically be accepted for authorship based on institutional accrual.

This protocol includes several correlative studies that may be published with the group-wide clinical results paper or as separate, stand-alone scientific papers. The decision to publish correlative study papers separately will be made by the Coordinating Center PI and relevant correlative study investigators, and will be subject to the Collaborative Agreement for study publications described in Section 12.3. Authorship of the correlative results paper will include the Coordinating Center PI, the correlative study lead investigators, and researchers from the correlative studies laboratories nominated by the correlative study lead investigators. Correlative study lead investigators may also nominate authors who have contributed to the feasibility of the study and/or the development of assays and procedures that supported evaluation of study samples. The final decision on the authorship of any manuscripts related to this trial will be made by the Coordinating Center PI.

13. STATISTICAL CONSIDERATIONS

This is a multi-histology pilot trial with patients enrolled into multiple cohorts. Up to 30 patients will be treated within each of the targeted agent cohorts.

All eligible patients who have initiated treatment will be included in the OR and PFS analyses within each agent cohort in which objective response rate and PFS (as a secondary endpoint) will be assessed against the historical standards of 5% response rate and 25% 4-month PFS. We will allow patients to be entered on trial and begin treatment based on CLIA genetic testing reports from MATCH-designated labs indicating actionable mutations of interest in study DNA damage repair genes. On-study biopsies will be collected from these patients for study confirmatory screening with the Oncominev3 (MATCHv3) assay. Those whose aMOIs cannot be confirmed can choose to remain on study and receive study drugs but will not be counted as eligible or included in the primary efficacy analysis or the futility analysis.

1. Within each agent cohort, up to 30 eligible patients will be accrued, to discriminate between tumor response rates of 20% vs. 5%. If at least 4 objective responses (at least 13%) are observed among the 30 patients, this agent will be considered promising for this mutation category. If no objective responses are observed among the initial 12 eligible patients, beginning, for the veliparib plus temozolomide arm, with Amendment U), the cohort will be terminated early. Accrual to the cohort will be paused after accrual of the initial 12 eligible patients until at least 1 objective response is observed. This design yields at least 88% power to detect a true objective response rate of at least 20%. It yields at least .94 probability of a negative result if the true objective response rate is no more than 5%. As a secondary endpoint, 4-month PFS will be evaluated. If at least 12 instances of 4-month PFS (at least 40%) are observed among the 30 patients, 4-month PFS will be considered promising. This will occur with 90% likelihood if the true 4-month PFS rate is 50% (median PFS of 4 months) and with 5% likelihood if the true 4-month PFS rate is 25% (median PFS of 2 months).

13.1 Sample Size/Accrual Rate

Given the relative frequencies of mutations it is anticipated that we will need to enroll up to 100 patients until we have 30 evaluable patients on each open agent cohort. Once all sites are open, we hope to accrue 150-200 patients a year. It is anticipated that accrual will require at least 1.5 - 3 years.

13.2 Analysis of Additional Endpoints

All molecular and other secondary evaluations will be considered for exploratory analyses. In general, it is anticipated that non-parametric analyses will be used for these evaluations. In view of the exploratory nature of these analyses, any p-values reported will not be adjusted for multiple comparisons, and any such analyses will be stated carefully as being hypothesis-generating. All eligible patients who have initiated treatment will be included in the toxicity assessments.

14. HUMAN SUBJECTS PROTECTIONS

14.1 Rationale for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, pregnant women and children are excluded from this study. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). Participants should realize that there is no guarantee of benefit to them from participation in this trial. The results of this trial may benefit future cancer patients. To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

14.1.1 Inclusion of Women and Minorities

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met.

Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	18		18		36
Not Hispanic or Latino	72		72		144
Ethnic Category: Total of all subjects	90 (A1)	+	90 (B1)	=	180 (C1)
Racial Category					
American Indian or Alaskan Native	1		1		2
Asian	8		8		16
Black or African American	8		8		16
Native Hawaiian or other Pacific Islander	1		1		2
White	72		72		144
Racial Category: Total of all subjects	90 (A2)	+	90 (B2)	=	180 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 2-3 pts/month **Total Expected Accrual:** 45 Min 700 Max

Projected Start Date of study: 10/20/12

14.2 Justification for Exclusions

Because the effects of study investigational agents on the developing human fetus are unknown, pregnant women will be excluded from this trial. Nursing women are also excluded, as there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with study medications.

Participants with unstable or serious medical conditions (ongoing or active infection, symptomatic congestive heart failure [AHA Class II or worse], unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements) are excluded due to the possibility that the underlying condition may obscure the attribution of effect and adverse events with respect to study drugs and may limit study compliance.

14.2.1 Participation of Children

Because no dosing or adverse event data are currently available on the use of many of these investigational agents in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric Phase I/II trials.

14.3 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document, as well as the risks associated with the acquisition and disclosure of information about germline variants relevant to a patient's hereditary risk of disease.

The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in the Study Calendar (Section 10). To minimize the risk of disclosing information about potential nonambiguous germline variants from whole exome sequencing, samples will be de-identified once the patient has completed treatment and is taken off study. No genetic data will be shared with the patient other than the data from the targeted sequencing panel. A Certificate of Confidentiality has been obtained for this study.

The research component of this study (2 CT tumor biopsies, with the possibility of a third optional biopsy should a baseline tumor biopsy sample contain insufficient DNA) confers radiation exposure at an effective dose of 1.6 rem at the NIH Clinical Center. This dose is below NIH RSC guidelines for adults of 5.0 rem per year and represents a slightly greater than minimal risk to patients.

14.4 Consent and Assent Process and Documentation

This protocol includes separate informed consent forms for tumor biopsy collection and treatment. An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided IRB-approved consent(s) for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained

from the patient. The original signed consent(s) go to Medical Records; a copy is placed in the research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

14.5 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication and from undergoing blood sampling procedures. If patients suffer any physical injury as a result of the participation in this study at the NCI, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

15. REFERENCES

1. Le Tourneau, C., et al., *Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial.* The Lancet Oncology, 2015. **16**(13): p. 1324-1334.
2. Jaffe, C.C., *Imaging and Genomics: Is There a Synergy?* Radiology, 2012. **264**(2): p. 329-331.
3. Gevaert, O., et al., *Non–Small Cell Lung Cancer: Identifying Prognostic Imaging Biomarkers by Leveraging Public Gene Expression Microarray Data—Methods and Preliminary Results.* Radiology, 2012. **264**(2): p. 387-396.
4. Ding, J., et al., *Emerging cancer therapeutic opportunities target DNA-repair systems.* Trends Pharmacol Sci, 2006. **27**(6): p. 338-44.
5. Pallis, A.G. and M.V. Karamouzis, *DNA repair pathways and their implication in cancer treatment.* Cancer Metastasis Rev, 2010. **29**(4): p. 677-85.
6. Schreiber, V., et al., *Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1.* J Biol Chem, 2002. **277**(25): p. 23028-36.
7. Memisoglu, A. and L. Samson, *Base excision repair in yeast and mammals.* Mutat Res, 2000. **451**(1-2): p. 39-51.
8. Ruscetti, T., et al., *Stimulation of the DNA-dependent protein kinase by poly(ADP-ribose) polymerase.* J Biol Chem, 1998. **273**(23): p. 14461-7.
9. Galande, S. and T. Kohwi-Shigematsu, *Poly(ADP-ribose) polymerase and Ku autoantigen form a complex and synergistically bind to matrix attachment sequences.* J Biol Chem, 1999. **274**(29): p. 20521-8.
10. Fernet, M., et al., *Poly(ADP-ribose) polymerase, a major determinant of early cell response to ionizing radiation.* Int J Radiat Biol, 2000. **76**(12): p. 1621-9.
11. Shall, S. and G. de Murcia, *Poly(ADP-ribose) polymerase-1: what have we learned from the deficient mouse model?* Mutat Res, 2000. **460**(1): p. 1-15.
12. Masutani, M., et al., *The response of Parp knockout mice against DNA damaging agents.* Mutat Res, 2000. **462**(2-3): p. 159-66.
13. Sulkowski, P.L., et al., *2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity.* Sci Transl Med, 2017. **9**(375).
14. Watanbe, E., *Regulation of the human WEE1 Hu cdk tyrosine 15-kinase during the cell cycle.* Embo J, 1995. **14**: p. 1878-1891.
15. Russell, P. and P. Nurse, *Negative regulation of mitosis by wee1+, a gene encoding a protein kinase homolog.* Cell, 1987. **49**(4): p. 559-567.
16. Masaki, T., et al., *Cyclins and cyclin-dependent kinases: Comparative study of hepatocellular carcinoma versus cirrhosis.* Hepatology, 2003. **37**(3): p. 534-543.
17. Iorns, E., et al., *Integrated Functional, Gene Expression and Genomic Analysis for the Identification of Cancer Targets.* PLoS ONE, 2009. **4**(4): p. e5120.
18. Mir, S.E., et al., *In Silico Analysis of Kinase Expression Identifies WEE1 as a Gatekeeper against Mitotic Catastrophe in Glioblastoma.* Cancer Cell, 2010. **18**(3): p. 244-257.
19. Marshall, C.J., *MAP kinase kinase kinase, MAP kinase kinase and MAP kinase.* Curr Opin Genet Dev, 1994. **4**(1): p. 82-9.
20. Deramaudt, T. and A.K. Rustgi, *Mutant KRAS in the initiation of pancreatic cancer.* Biochim Biophys Acta, 2005. **1756**(2): p. 97-101.
21. Kohl, N.E., et al., *Selective inhibition of ras-dependent transformation by a farnesyltransferase inhibitor.* Science, 1993. **260**(5116): p. 1934-7.
22. Eberhard, D.A., et al., *Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib.* J Clin Oncol, 2005. **23**(25): p. 5900-9.

23. Andreyev, H.J., et al., *Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study.* Br J Cancer, 2001. **85**(5): p. 692-6.
24. Davies, H., et al., *Mutations of the BRAF gene in human cancer.* Nature, 2002. **417**(6892): p. 949-54.
25. Hoshino, R., et al., *Constitutive activation of the 41-/43-kDa mitogen-activated protein kinase signaling pathway in human tumors.* Oncogene, 1999. **18**(3): p. 813-22.
26. Sebolt-Leopold, J.S., et al., *Blockade of the MAP kinase pathway suppresses growth of colon tumors in vivo.* Nat Med, 1999. **5**(7): p. 810-6.
27. Milella, M., et al., *Therapeutic targeting of the MEK/MAPK signal transduction module in acute myeloid leukemia.* J Clin Invest, 2001. **108**(6): p. 851-9.
28. Wee, S., et al., *PTEN-deficient cancers depend on PIK3CB.* Proc Natl Acad Sci U S A, 2008. **105**(35): p. 13057-62.
29. Altomare, D.A. and J.R. Testa, *Perturbations of the AKT signaling pathway in human cancer.* Oncogene, 2005. **24**(50): p. 7455-64.
30. Hennessy, B.T., et al., *Exploiting the PI3K/AKT Pathway for Cancer Drug Discovery.* Nat Rev Drug Discov, 2005. **4**(12): p. 988-1004.
31. Steelman, L.S., et al., *Akt as a therapeutic target in cancer.* Expert Opinion on Therapeutic Targets, 2008. **12**(9): p. 1139-1165.
32. Samuels, Y., et al., *Mutant PIK3CA promotes cell growth and invasion of human cancer cells.* Cancer Cell, 2005. **7**(6): p. 561-73.
33. Cantley, L.C. and B.G. Neel, *New insights into tumor suppression: PTEN suppresses tumor formation by restraining the phosphoinositide 3-kinase/AKT pathway.* Proc Natl Acad Sci U S A, 1999. **96**(8): p. 4240-5.
34. Ogita, S. and P. Lorusso, *Targeting phosphatidylinositol 3 kinase (PI3K)-Akt beyond rapalogs.* Target Oncol, 2011. **6**(2): p. 103-17.
35. Cejka, D., et al., *Everolimus (RAD001) and anti-angiogenic cyclophosphamide show long-term control of gastric cancer growth in vivo.* Cancer Biol Ther, 2008. **7**(9): p. 1377-85.
36. Testa, J.R. and A. Bellacosa, *AKT plays a central role in tumorigenesis.* Proc Natl Acad Sci U S A, 2001. **98**(20): p. 10983-5.
37. Han, Z., et al., *Akt1/protein Kinase Bα is Involved in Gastric Cancer Progression and Cell Proliferation.* Digestive Diseases and Sciences, 2008. **53**(7): p. 1801-1810.
38. Vestey, S.B., et al., *Activated Akt expression in breast cancer: correlation with p53, Hdm2 and patient outcome.* Eur J Cancer, 2005. **41**(7): p. 1017-25.
39. Saal, L.H., et al., *PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma.* Cancer Res, 2005. **65**(7): p. 2554-9.
40. Shayesteh, L., et al., *PIK3CA is implicated as an oncogene in ovarian cancer.* Nat Genet, 1999. **21**(1): p. 99-102.
41. Shoman, N., et al., *Reduced PTEN expression predicts relapse in patients with breast carcinoma treated by tamoxifen.* Mod Pathol, 2005. **18**(2): p. 250-9.
42. Nakayama, K., et al., *Sequence mutations and amplification of PIK3CA and AKT2 genes in purified ovarian serous neoplasms.* Cancer Biol Ther, 2006. **5**(7): p. 779-85.
43. Hu, L., et al., *Inhibition of phosphatidylinositol 3'-kinase increases efficacy of paclitaxel in in vitro and in vivo ovarian cancer models.* Cancer Res, 2002. **62**(4): p. 1087-92.
44. *MK-2206.* Merck & Co., Inc, 2008.
45. Barnett, S.F., et al., *Identification and characterization of pleckstrin-homology-domain-dependent and isoenzyme-specific Akt inhibitors.* Biochem J, 2005. **385**(Pt 2): p. 399-408.
46. Engelman, J.A., et al., *Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers.* Nat Med, 2008. **14**(12): p. 1351-1356.
47. Fry, M.J., *Phosphoinositide 3-kinase signalling in breast cancer: how big a role might it play?* Breast Cancer Research, 2001. **3**(5): p. 304-312.

48. Kawauchi, K., et al., *The PI3K/Akt pathway as a target in the treatment of hematologic malignancies.* Anti-cancer agents in medicinal chemistry, 2009. **9**(5): p. 550.
49. Kinkade, C.W., et al., *Targeting AKT/mTOR and ERK MAPK signaling inhibits hormone-refractory prostate cancer in a preclinical mouse model.* The Journal of clinical investigation, 2008. **118**(9): p. 3051.
50. Kirkegaard, T., et al., *AKT activation predicts outcome in breast cancer patients treated with tamoxifen.* The Journal of Pathology, 2005. **207**(2): p. 139-146.
51. Konecny, G.E., et al., *Activity of the Dual Kinase Inhibitor Lapatinib (GW572016) against HER-2-Overexpressing and Trastuzumab-Treated Breast Cancer Cells.* Cancer Res, 2006. **66**(3): p. 1630-1639.
52. Kornblau, S.M., et al., *Simultaneous activation of multiple signal transduction pathways confers poor prognosis in acute myelogenous leukemia.* Blood, 2006. **108**(7): p. 2358-2365.
53. Lee, J.W., et al., *PIK3CA gene is frequently mutated in breast carcinomas and hepatocellular carcinomas.* Oncogene, 2004. **24**(8): p. 1477-1480.
54. Min, Y.H., et al., *Constitutive phosphorylation of Akt//PKB protein in acute myeloid leukemia: its significance as a prognostic variable.* Leukemia, 2003. **17**(5): p. 995-997.
55. Nakanishi, K., et al., *Akt phosphorylation is a risk factor for early disease recurrence and poor prognosis in hepatocellular carcinoma.* Cancer, 2005. **103**(2): p. 307-312.
56. Oki, E., et al., *Akt phosphorylation associates with LOH of PTEN and leads to chemoresistance for gastric cancer.* International Journal of Cancer, 2005. **117**(3): p. 376-380.
57. Oza, A.M., *Molecular correlates associated with a phase II study of temsirolimus (CCI-779) in patients with metastatic or recurrent endometrial cancer–NCIC IND 160.* J Clin Oncol, 2006. **24**: p. A3003.
58. Rahman, M.A., et al., *Impact of PTEN expression on the outcome of hepatitis C virus-positive cirrhotic hepatocellular carcinoma patients: Possible relationship with COX II and inducible nitric oxide synthase.* International Journal of Cancer, 2002. **100**(2): p. 152-157.
59. Salvesen, H.B., et al., *Integrated genomic profiling of endometrial carcinoma associates aggressive tumors with indicators of PI3 kinase activation.* Proceedings of the National Academy of Sciences, 2009. **106**(12): p. 4834-4839.
60. Sosman, J.A., I. Puzanov, and M.B. Atkins, *Opportunities and Obstacles to Combination Targeted Therapy in Renal Cell Cancer.* Clin Cancer Res, 2007. **13**(2): p. 764s-769.
61. Staal, S.P., *Molecular cloning of the akt oncogene and its human homologues AKT1 and AKT2: amplification of AKT1 in a primary human gastric adenocarcinoma.* Proceedings of the National Academy of Sciences of the United States of America, 1987. **84**(14): p. 5034-5037.
62. St-Germain, M.-E., et al., *Regulation of COX-2 protein expression by Akt in endometrial cancer cells is mediated through NF-kappaB/IkappaB pathway.* Molecular Cancer, 2004. **3**(1): p. 7.
63. Tanno, S., et al., *AKT activation up-regulates insulin-like growth factor I receptor expression and promotes invasiveness of human pancreatic cancer cells.* Cancer Res, 2001. **61**(2): p. 589-93.
64. Uddin, S., et al., *Role of phosphatidylinositol 3'-kinase/AKT pathway in diffuse large B-cell lymphoma survival.* Blood, 2006. **108**(13): p. 4178-4186.
65. Wolf, J. and B.M. Slomovitz, *Novel biologic therapies for the treatment of endometrial cancer.* International Journal of Gynecological Cancer, 2005. **15**(2): p. 411-411.
66. Moroney, J.W., et al., *A Phase I Trial of Liposomal Doxorubicin, Bevacizumab, and Temsirolimus in Patients with Advanced Gynecologic and Breast Malignancies.* Clinical Cancer Research, 2011. **17**(21): p. 6840-6846.
67. Donawho, C.K., et al., *ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models.* Clin Cancer Res, 2007. **13**(9): p. 2728-2737.
68. Motzer, R.J., et al., *Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.* The Lancet. **372**(9637): p. 449-456.

69. Grunwald, V., et al., *An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy.* European Journal of Cancer, 2012. **48**(3): p. 324-332.
70. Kim, D.-H., et al., *mTOR Interacts with Raptor to Form a Nutrient-Sensitive Complex that Signals to the Cell Growth Machinery.* Cell, 2002. **110**(2): p. 163-175.
71. Gibbons, J.J., R.T. Abraham, and K. Yu, *Mammalian Target of Rapamycin: Discovery of Rapamycin Reveals a Signaling Pathway Important for Normal and Cancer Cell Growth.* Seminars in Oncology, 2009. **36, Supplement 3**(0): p. S3-S17.
72. Tabor, H.K., et al., *Genomics really gets personal: How exome and whole genome sequencing challenge the ethical framework of human genetics research.* American Journal of Medical Genetics Part A, 2012. **155**(12): p. 2916-2924.
73. Kass, N.E., et al., *Medical privacy and the disclosure of personal medical information: The beliefs and experiences of those with genetic and other clinical conditions.* American Journal of Medical Genetics Part A, 2004. **128A**(3): p. 261-270.
74. Dressler, L.G. and S.F. Terry, *How Will GINA Influence Participation in Pharmacogenomics Research and Clinical Testing?* Clin Pharmacol Ther, 2009. **86**(5): p. 472-475.
75. Caulfield, T., et al., *Research Ethics Recommendations for Whole-Genome Research: Consensus Statement.* PLoS Biol, 2008. **6**(3): p. e73.
76. Berg, J.S., M.J. Khoury, and J.P. Evans, *Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time.* Genet Med, 2011. **13**(6): p. 499-504.
77. Hussain, M., et al., *Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).* J Clin Oncol 30, 2012. **30**(suppl 5; abstr 224).
78. Isakoff, S.J., et al., *A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer.* ASCO Meeting Abstracts, 2010. **28**(15_suppl): p. 1019.
79. Balagula, Y., et al., *Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886).* Investigational New Drugs, 2011. **29**(5): p. 1114-1121.
80. Lacouture, M., et al., *Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities.* Supportive Care in Cancer, 2011. **19**(8): p. 1079-1095.
81. Puls, L.N., M. Eadens, and W. Messersmith, *Current Status of Src Inhibitors in Solid Tumor Malignancies.* The Oncologist, 2011. **16**(5): p. 566-578.
82. Bruce, D. and P.H. Tan, *Blocking the interaction of vascular endothelial growth factor receptors with their ligands and their effector signaling as a novel therapeutic target for cancer: time for a new look?* Expert Opinion on Investigational Drugs, 2011. **20**(10): p. 1413-1434.
83. Seymour, L., et al., *iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics.* The Lancet Oncology, 2017. **18**(3): p. e143-e152.
84. US Food and Drug Administration, *Clinical Review, September 27, 2011; Drugs@FDA*.
85. Mas-Moruno, C., F. Rechenmacher, and H. Kessler, *Cilengitide: the first anti-angiogenic small molecule drug candidate design, synthesis and clinical evaluation.* Anticancer Agents Med Chem, 2010. **10**(10): p. 753-68.
86. Kummar, S., et al., *Compressing drug development timelines in oncology using phase '0' trials.* Nat Rev Cancer, 2007. **7**(2): p. 131-139.
87. Kummar, S., et al., *Advances in using PARP inhibitors to treat cancer.* BMC Medicine, 2012. **10**(1): p. 25.
88. Kummar, S., et al., *Utilizing targeted cancer therapeutic agents in combination: novel approaches and urgent requirements.* Nat Rev Drug Discov, 2010. **9**(11): p. 843-856.
89. Dudley, J.C., et al., *Microsatellite Instability as a Biomarker for PD-1 Blockade.* Clin Cancer Res, 2016. **22**(4): p. 813-20.

90. Le, D.T., et al., *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency.* N Engl J Med, 2015. **372**(26): p. 2509-20.
91. Chen, P.-L., et al., *Analysis of Immune Signatures in Longitudinal Tumor Samples Yields Insight into Biomarkers of Response and Mechanisms of Resistance to Immune Checkpoint Blockade.* Cancer Discovery, 2016. **6**(8): p. 827-837.
92. Wallin, J.J., et al., *Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma.* Nature Communications, 2016. **7**: p. 12624.
93. Dowlati, A., et al., *Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation.* Clin Cancer Res, 2001. **7**(10): p. 2971-6.
94. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.
95. Bubley, G.J., et al., *Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group.* J Clin Oncol, 1999. **17**(11): p. 3461-7.
96. Rustin, G.J., et al., *Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer).* J Natl Cancer Inst, 2004. **96**(6): p. 487-8.
97. Scher, H.I., et al., *Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.* J Clin Oncol, 2008. **26**(7): p. 1148-59.
98. Vergote, I., et al., *Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup.* J Natl Cancer Inst, 2000. **92**(18): p. 1534-5.
99. Doroshow, J.H., *Commentary: Publishing Cancer Clinical Trial Results: A Scientific and Ethical Imperative.* Oncologist, 2008. **13**(9): p. 930-932.
100. *Investigator's Brochure: Veliparib (ABT-888).* No. 5 ed. 2011: Abbott Laboratories.
101. Yamaguchi, T., et al., *Antitumor activities of JTP-74057 (GSK1120212), a novel MEK1/2 inhibitor, on colorectal cancer cell lines in vitro and in vivo.* Int J Oncol, 2011. **39**(1): p. 23-31.
102. Freymann, J., et al., *Image Data Sharing for Biomedical Research—Meeting HIPAA Requirements for De-identification.* Journal of Digital Imaging, 2012. **25**(1): p. 14-24.

APPENDIX A: Performance Status Criteria

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B: Potential Drug Interactions and Drug Information Handouts

CYP2C19 Inhibitors

Amiodarone	Felbamate	Methoxsalen	Ritonavir
Amitriptyline	Fenofibrate	Methsuximide	Rosiglitazone
Amprenavir	Fluconazole	Miconazole	Saquinavir
Aprepitant	Fluoxetine	Moclobemide	Selegiline
Azelastine	Fluvoxamine	Modafinil	Sertraline
Bortezomib	Fosamprenavir	Nelfinavir	Sildenafil
Buprenorphine	Gefitinib	Nicardipine	Sulconazole
Cholecalciferol/Vitamin D_3	Gemfibrozil	Nilutamide	Telmisartan
Cimetidine	Imipramine	Olanzapine	Ticlopidine
Citalopram	Indinavir	Omeprazole	Tioconazole
Clotrimazole	Indomethacin	Orphenadrine	Topiramate
Clozapine	Isoniazid	Oxcarbazepine	Torsemide
Delavirdine	Ketoconazole	Paroxetine	Tranylcypromine
Diazepam	Lansoprazole	Pentamidine	Valdecoxib
Dimethyl sulfoxide	Letrozole	Pimozide	Valproic acid
Drospirenone	Loratadine	Pioglitazone	Voriconazole
Efavirenz	Losartan	Probenecid	Warfarin
Entacapone	Mephobarbital	Progesterone	Zafirlukast
Ethinyl estradiol	Mestranol	Propofol	
Ethotoin	Methimazole	Rabeprazole	

CYP2C19 Inducers

Aminoglutethimide	Fosphenytoin	Rifampin	St. John's wort
Carbamazepine	Phenytoin		

CYP2C19 Substrates

Carisoprodol	Escitalopram	Methsuximide	Phenobarbital
Cilostazol	Esomeprazole	Moclobemide	Phenytoin
Citalopram	Fosphenytoin	Nelfinavir	Progesterone
Clobazam	Imipramine	Nilutamide	Rabeprazole
Clomipramine	Lansoprazole	Omeprazole	Sertraline
Desogestrel	Mephenytoin	Pantoprazole	Trimipramine
Diazepam	Mephobarbital	Pentamidine	Voriconazole

CYP3A4 Inhibitors

Acetaminophen	Cyclosporine	Glyburide	Modafinil	Ranolazine
Acetazolamide	Danazol	Grapefruit juice	Nefazodone	Risperidone
Amiodarone	Dasatinib	Haloperidol	Nelfinavir	Ritonavir
Amlodipine	Delavirdine	Hydralazine	Nevirapine	Saquinavir
Amprenavir	Desipramine	Ifosfamide	Nicardipine	Selegiline
Anastrozole	Dexmedetomidine	Imatinib	Nifedipine	Sertraline
Aprepitant	Diazepam	Indinavir	Nisoldipine	Sildenafil
Atazanavir	Diclofenac	Irbesartan	Nizatidine	Sirolimus
Atorvastatin	Dihydroergotamine	Isoniazid	Norfloxacin	Sulconazole
Azelastine	Diltiazem	Isradipine	Olanzapine	Tacrolimus
Azithromycin	Disulfiram	Itraconazole	Omeprazole	Tamoxifen
Betamethasone	Docetaxel	Ketoconazole	Orphenadrine	Telithromycin
Bortezomib	Doxorubicin	Lansoprazole	Oxybutynin	Teniposide
Bromocriptine	Doxycycline	Lidocaine	Paroxetine	Testosterone
Caffeine	Drospirenone	Lomustine	Pentamidine	Tetracycline
Cerivastatin	Efavirenz	Losartan	Pergolide	Ticlopidine
Chloramphenicol	Enoxacin	Lovastatin	Phencyclidine	Tranylcypromine
Chlorzoxazone	Entacapone	Mefloquine	Pilocarpine	Trazodone

Cimetidine	Ergotamine	Mestranol	Pimozide	Troleandomycin
Ciprofloxacin	Erythromycin	Methadone	Pravastatin	Valproic acid
Cisapride	Ethinylestradiol	Methimazole	Prednisolone	Venlafaxine
Clarithromycin	Etoposide	Methoxsalen	Primaquine	Verapamil
Clemastine	Felodipine	Methylprednisolone	Progesterone	Vinblastine
Clofazimine	Fentanyl	Metronidazole	Propofol	Vincristine
Clotrimazole	Fluconazole	Miconazole	Propoxyphene	Vinorelbine
Clozapine	Fluoxetine	Midazolam	Quinidine	Voriconazole
Cocaine	Fluvastatin	Mifepristone	Quinine	Zafirlukast
Conivaptan	Fluvoxamine	Mirtazapine	Quinupristin	Ziprasidone
Cyclophosphamide	Fosamprenavir	Mitoxantrone	Rabeprazole	

CYP3A4 Inducers

Aminoglutethimide	Nafcillin	Pentobarbital	Primidone	Rifapentine
Carbamazepine	Nevirapine	Phenobarbital	Rifabutin	St. John's wort
Fosphenytoin	Oxcarbazepine	Phenytoin	Rifampin	

CYP3A4 Substrates

Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate	Repaglinide
Amprenavir	Efavirenz	hydrochloride	Rifabutin
Aprepitant	Eletriptan	Levonorgestrel	Rifampin
Aripiprazole	Enalapril	Lidocaine	Ritonavir
Atazanavir	Eplerenone	Losartan	Saquinavir
Atorvastatin	Ergoloid mesylates	Lovastatin	Sertraline
Benzphetamine	Ergonovine	Medroxyprogesterone	Sibutramine
Bisoprolol	Ergotamine	Mefloquine	Sildenafil
Bortezomib	Erythromycin	Mestranol	Simvastatin
Bosentan	Escitalopram	Methadone	Sirolimus
Bromazepam	Estradiol	Methylergonovine	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Methysergide	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Miconazole	Tamoxifen
Buspirone	Estrogens, conj., esterified	Midazolam	Tamsulosin
Busulfan	Estrone	Miglustat	Telithromycin
Carbamazapine	Estropipate	Mirtazapine	Teniposide
Cerivastatin	Ethinylestradiol	Modafinil	Terbinafine
Chlordiazepoxide	Ethosuximide	Montelukast	Tetracycline
Chloroquine	Etoposide	Moricizine	Theophylline
Chlorpheniramine	Felbamate	Nateglinide	Tiagabine
Cisapride	Felodipine	Nefazodone	Ticlopidine
Citalopram	Fentanyl	Nelfinavir	Tolterodine
Clarithromycin	Flurazepam	Nevirapine	Toremifene
Clobazam	Flutamide	Nicardipine	Trazodone
Clonazepam	Fosamprenavir	Nifedipine	Triazolam
Clorazepate	Fulvestrant	Nimodipine	Trimethoprim
Cocaine	Gefitinib	Nisoldipine	Trimipramine
Colchicine	Halofantrine	Nitrendipine	Troleandomycin
Cyclophosphamide	Haloperidol	Norethindrone	Vardenafil
Cyclosporine	Ifosfamide	Norgestrel	Venlafaxine
Dantrolene	Imatinib	Ondansetron	Verapamil
Dapsone	Indinavir	Paclitaxel	Vinblastine
Delavirdine	Irinotecan	Pergolide	Vincristine
Diazepam	Isosorbide dinitrate	Phencyclidine	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pimozide	Zolpidem

Dihydroergotamine Diltiazem Disopyramide	Isradipine Itraconazole Ketamine	Pioglitazone Primaquine Progesterone	Zonisamide Zopiclone

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference.

PgP substrates, inducers, and inhibitors

Substrates: colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus
Inducers: rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort, talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil

Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated 29-Oct-2012 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Veliparib and Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug **Veliparib**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Veliparib interacts with certain specific enzymes in the liver.

- The enzymes in question are ***CYP1A1, CYP2D6, CYP2C19, and CYP3A4*.** Veliparib is metabolized by these enzymes and may be affected by other drugs that inhibit or induce these enzymes.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Veliparib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Veliparib must be used very carefully with other medicines that need certain **liver enzymes to be effective or to be cleared from your system.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of ***CYP 1A1, CYP2D6, CYP2C19, and CYP3A4*.**"

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
  Your study doctor's name is _____

  and he or she can be contacted at _____.

Study Drug Information Wallet Card

You are enrolled on a clinical trial using the experimental study drug Veliparib. This clinical trial is sponsored by the NCI**. Veliparib may interact with drugs that are processed by your liver**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplements such as St. John's Wort
- Avoid grapefruit, grapefruit juice, Seville oranges, and starfruit while taking this drug

Veliparib interacts with CYP 1A1, 2D6, 2C19, and 3A4, and must be used very carefully with other medicines that interact with these enzymes and proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP 1A1, CYP2D6, CYP2C19, and CYP3A4**"
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is:

  and can be contacted at:

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with AZD1775 and Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug **AZD1775**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

AZD1775 interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzyme in question is ***CYP 3A4.*** AZD1775 is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme. AZD1775 is an inhibitor of CYP 3A4 and may affect the metabolism of other drugs.

- The proteins in question are ***OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP.*** AZD1775 is a substrate of P-gp and BCRP and may be affected by other drugs that inhibit or induce these transporters. AZD1775is an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP and may affect transport of other drugs in and out of cells.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

AZD1775 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

AZD1775 must be used very carefully with other medicines that need certain **liver enzymes or transport proteins to be effective or to be cleared from your system.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors or substrates of **CYP 3A4, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
  Your study doctor's name is _____

  and he or she can be contacted at_____

Study Drug Information Wallet Card

You are enrolled on a clinical trial using the experimental study drug AZD1775. This clinical trial is sponsored by the NCI. **AZD1775 may interact with drugs that are processed by your liver, or use certain transport proteins in your body**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplements such as St. John's Wort
- Avoid grapefruit, grapefruit juice, Seville oranges, and starfruit while taking this drug

AZD1775 interacts with CYP 3A4, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP, and must be used very carefully with other medicines that interact with these enzymes and proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP 3A4, PgP and BCRP, and sensitive substrates of OATP1B1, OATP1B3, MATE1 and MATE2K"**
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is:

  and can be contacted at:

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Everolimus and Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug **Everolimus**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Everolimus interacts with certain specific enzymes in the liver.

- The enzyme in question is ***CYP3A4*.** Everolimus is metabolized by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Everolimus may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Everolimus must be used very carefully with other medicines that need certain **liver enzymes to be effective or to be cleared from your system.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of ***CYP3A4*."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
  Your study doctor's name is _____
  and he or she can be contacted at _____.

Study Drug Information Wallet Card

You are enrolled on a clinical trial using the experimental study drug Everolimus. This clinical trial is sponsored by the NCI. **Everolimus may interact with drugs that are processed by your liver**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplements such as St. John's Wort
- Avoid grapefruit, grapefruit juice, Seville oranges, and starfruit while taking this drug

Everolimus **interacts** with CYP3A4, and must be used very carefully with other medicines that interact with these enzymes and proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP3A4**"
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is:

  and can be contacted at:

APPENDIX C: Medications That May Cause QTc Prolongation

The following table presents a list of drugs that prolong, may prolong, or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: *http://crediblemeds.org/*

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine/Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram/Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine/Anafranil®
Bepridil /Vascor®	Chloral hydrate/Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine/Benadryl®
Chlorpromazine/Thorazine®	Dolasetron /Anzemet®	Diphenhydramine/Nytol®
Cisapride /Propulsid®	Dronedarone/Multaq®	Doxepin /Sinequan®
Clarithromycin/Biaxin®	Felbamate/Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol/Inapsine®	Gatifloxacin /Tequin®	Imipramine/Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron/Kytril®	Ketoconazole /Nizoral®
Halofantrine/Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol/Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl/Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes	Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Methadone/Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone/Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol/Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron/Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol/Betapace®	Paliperidone/Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine/Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin*/Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen/Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil/Levitra®	
	Venlafaxine/Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

References:

Physician's Desk Reference 2002
Facts and Comparisons (update to June 2005)
The Pharmacological Basis of Therapeutics 9th Edition, 1996

APPENDIX D: Patient Study Diaries

Study Name: Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors

CTEP Study ID: 9149

Patient Name: _____

Instructions to the patient:
Please complete this form and return to the research nurse or doctor every cycle (28 days)

You will take:	Veliparib and Temozolomide
Medication dose:	Take Veliparib capsules twice each day (morning and evening) on days 1 to 7 **and** take temozolomide capsules once each day on days 1 to 5 Take temozolomide capsules one at a time with a full glass of water. Temozolomide capsules should not be opened, crushed, or chewed. Temozolomide capsules should be swallowed whole and never chewed. If you vomit the capsules, do not take a second dose. Capsules can be taken with or without food, but please try and take them at the same time every day, and if possible, always with or always without food. Avoid grapefruit, grapefruit juice, Seville oranges, starfruit, and the herbal supplement St. John's Wort while taking this drug. Do not open, crush, or chew Veliparib capsules.

Cycle number: _____
Start date: _____

Patient Signature: _____

DATE	DAY	Time taken Veliparib AM	Time taken Veliparib PM	Time taken Temozolomide	COMMENTS: Side effects/missed dose
	1				
	2				
	3				
	4				
	5				
	6			*No drug taken today*	
	7			*No drug taken today*	
	8	*No drug taken today*		*No drug taken today*	
	9	*No drug taken today*		*No drug taken today*	
	10	*No drug taken today*		*No drug taken today*	
	11	*No drug taken today*		*No drug taken today*	
	12	*No drug taken today*		*No drug taken today*	
	13	*No drug taken today*		*No drug taken today*	
	14	*No drug taken today*		*No drug taken today*	
	15	*No drug taken today*		*No drug taken today*	

	16	*No drug taken today*	*No drug taken today*	
	17	*No drug taken today*	*No drug taken today*	
	18	*No drug taken today*	*No drug taken today*	
	19	*No drug taken today*	*No drug taken today*	
	20	*No drug taken today*	*No drug taken today*	
	21	*No drug taken today*	*No drug taken today*	
	22	*No drug taken today*	*No drug taken today*	
	23	*No drug taken today*	*No drug taken today*	
	24	*No drug taken today*	*No drug taken today*	
	25	*No drug taken today*	*No drug taken today*	
	26	*No drug taken today*	*No drug taken today*	
	27	*No drug taken today*	*No drug taken today*	
	28	*No drug taken today*	*No drug taken today*	

Patient Study Diary

Study Name: Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors

CTEP Study ID: 9149

Patient Name: _____

Instructions to the patient: Please complete this form and return to the research nurse or doctor every cycle (21 days)

You will take: AZD1775 and carboplatin

Medication dose: Take AZD1775 capsules twice each day on days 1 and 2 (morning and evening) and once on day 3 (either in the morning or evening) at least two hours before or two hours after a meal. Do not open, crush, or chew the capsules. Avoid grapefruit, grapefruit juice, Seville oranges, starfruit, and the herbal supplement St. John's Wort while taking this drug.

Carboplatin will be given by intravenous administration at the day hospital **on day 1 only** of each 21-day cycle.

Cycle number: _____
Start date: _____

Patient Signature: _____

DATE	DAY	Time taken AZD1775	COMMENTS: Side effects/missed dose
	1	*AZD1775 and carboplatin will be given in clinic today. Take one dose of AZD1775 in the evening* *Time evening: _____*	
	2	*Take 2 doses of AZD1775 today. Take one dose of AZD1775in the morning and one in the evening.* *Time morning: _____* *Time evening: _____*	
	3	*Take only **one** dose of AZD1775 today* *Time: _____*	
	4	*No drug taken today*	
	5	*No drug taken today*	
	6	*No drug taken today*	
	7	*No drug taken today*	
	8	*No drug taken today*	
	9	*No drug taken today*	
	10	*No drug taken today*	

DATE	DAY	Time taken AZD1775	COMMENTS: Side effects/missed dose
	11	*No drug taken today*	
	12	*No drug taken today*	
	13	*No drug taken today*	
	14	*No drug taken today*	
	15	*No drug taken today*	
	16	*No drug taken today*	
	17	*No drug taken today*	
	18	*No drug taken today*	
	19	*No drug taken today*	
	20	*No drug taken today*	
	21	*No drug taken today*	

Patient Study Diary

Study Name: Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors

CTEP Study ID: 9149

Patient Name: _____

Instructions to the patient: Please complete this form and return to the research nurse or doctor every cycle (28 days)

You will take:	Everolimus
Medication dose:	Take everolimus tablets once a day every day for 28 days. Tablets should not be crushed or chewed, and should be swallowed whole with a glass of water. Tablets can be taken with or without food, but please try and take them at the same time every day, and if possible, always with or always without food. If you vomit the tablet, do not take another tablet that day. Avoid grapefruit, grapefruit juice, Seville oranges, starfruit, and the herbal supplement St. John's Wort while taking this drug. Caregivers should wash their hands with soap and water after touching the tablets.

Cycle number: _____
Start date: _____

Patient Signature: _____

DATE	**DAY**	**Time taken** Everolimus	**COMMENTS:** Side effects/missed dose
	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	13		
	14		

DATE	**DAY**	**Time taken** Everolimus	**COMMENTS:** Side effects/missed dose
	15		
	16		
	17		
	18		
	19		
	20		
	21		
	22		
	23		
	24		
	25		
	26		
	27		
	28		

Patient Study Diary

Study Name: Molecular Profiling-based Assignment of Cancer Therapy for Patients With Advanced Solid Tumors

CTEP Study ID: 9149

Patient Name: _____

Instructions to the patient: Please complete the form on the next page and return it to the research nurse or doctor every cycle (28 days). Store trametinib DMSO tablets in the refrigerator. Keep the tablets in the bottle they come in and do not move to a pill holder. Do not take out the anti-moisture cube or packet.

You will take:	Trametinib DMSO
Medication dose:	Take Trametinib DMSO tablets once a day for 28 days with a full glass of water either 1 hour before or 2 hours after a meal. If you vomit the tablets, do not take an additional dose. If you miss a dose, take it as soon as you remember. If it is less than 12 hours until your next dose, skip the dose.

Cycle number: _____
Start date: _____

Patient Signature: _____

DATE	DAY	Time taken Trametinib DMSO	COMMENTS: Side effects/missed dose
	1		
	2		
	3		
	4		
	5		
	6		
	7		
	8		
	9		
	10		
	11		
	12		
	13		
	14		

DATE	DAY	Time taken Trametinib DMSO	COMMENTS: Side effects/missed dose
	15		
	16		
	17		
	18		
	19		
	20		
	21		
	22		
	23		
	24		
	25		
	26		
	27		
	28		

Study Chart:

Treatment cycles will be repeated as long as you are tolerating the study drug and your cancer is either stable or getting better. Each cycle is numbered in consecutive order. The chart below shows what will happen during Cycle 1 and future cycles. The left-hand column shows the day in the cycle, and the right-hand column tells you what will happen on that day. This schedule shows what will happen to you after you sign the consent and start the study.

Day	What to do and what will happen to you
Before starting study drugs	• Check in at the Outpatient Clinic • Get routine blood tests • EKG • Eye exam (depending on the study treatment) • Pregnancy test • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT scan will be done
Day 1	• Check in at the Outpatient Clinic • Based on analysis of gene variations in your tumor, you may be given one of the following drugs: Trametinib DMSO, **or** everolimus, **or** Veliparib and temozolomide, **or** AZD1775 and carboplatin • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests • During the first week, have a tumor biopsy to confirm your genetic testing report (no biopsy if you already had one for screening on this study)
Day 8	• Continue taking your study drug by mouth each day (if taking everolimus or Trametinib DMSO) according to the instructions in your study medication diary • Get routine blood tests (Cycle 1 only)
Cycle 2 Day 1	• For patients getting AZD1775 plus carboplatin only, check in at the Outpatient Clinic (first day of every cycle only). • Continue taking your study drug by mouth each day • Eye exam (depending on the study treatment)
Cycle 3 onwards	• CT scans to determine how your tumor is responding to the treatment will be done every 2 cycles (less often if you have been on study for more than one year. • Echocardiogram (depending on the study treatment) to check for possible damage to your heart may be done every 3 cycles

On the days that you will be taking the study drug you will be asked to fill in a diary to show when you took the study drug and how many tablets or capsules you took, and report any side effects that you may have had.

APPENDIX E: MPACT (9149) Sample Shipping Instructions and Manifest

This protocol collects formalin-fixed tumor samples (2 cores) from the initial screening biopsy procedure. Please consult with the study PI for more information and discuss the handling requirements for each core sample collected with the interventional radiologist.

Sample collection and shipping items to be purchased by each participating site:
Biopsy collection*:

- Pre-filled 10% neutral-buffered formalin specimen jar, 30 mL (e.g., Leica 3800770), one jar per core sample

Blood collection:

- 2 cell-free DNA BCT tubes, 10 mL (e.g., Streck 218961)

Shipping supplies:

- Specimen bags (zip-lock)
- Absorbent paper for packing
- Controlled room temperature (CRT) gel packs (e.g., STT-521-500 Saf-T-Temp CRT PCM Paks)
- Small thermo-shipper boxes (e.g., Thermo-safe 14100-434)

Notes:
Follow manufacturer's instructions for specimen collection and handling.
Put shipping manifest in a plastic zip-lock bag in case of sample leakage. Include the Clinical Center number, study number (9149), patient ID, site of biopsy, patient diagnosis, biopsy/blood collection date, and fixation time (i.e., initial/date/time placed into 10% NBF) on the manifest. Do not include patient identifiers.

Please do not collect samples on Fridays for overnight delivery as FNLCR cannot accept weekend courier delivery. If Friday collection is unavoidable, ship the samples via overnight delivery but contact **NCI-FrederickMPACTCLIA@mail.nih.gov** and include two CRT gel packs in the shipper boxes. The samples will be stable until Monday delivery.

*Archival FFPE tumor blocks may be acceptable if collected within 6 months of registration and if the patient has not received targeted or investigational therapy since collection; check with study investigator for details

GENETIC SAMPLE SHIPPING MANIFEST			
Protocol 9149	Shipping date:	Carrier:	
SHIP FROM: **Ordering Physician/PI:** **Address:** **Contact Name:** **Telephone:** **Email:**		**SHIP TO:** **Address:** **Telephone:** **Email:**	MoCha Histology Laboratory (K. Benauer) Leidos Biomedical Research Inc. (FNLCR) 1050 Boyles St. Bldg 321, Room #107 Frederick, MD 21702 301-846-6083/301-846-1535 NCI-FrederickMPACTCLIA@mail.nih.gov

Item	Unique GeneMed ID* (Sample ID)	Biopsy Site	Diagnosis	Date Collected	No. Containers/Tubes			Fixation Time
					Biopsy	Blood	FFPE block	Into 10%NBF-Site *(Initial/Date/Time)*
1								
2								
3								
4								
5								
6								
7								
8								
			TOTAL No. ITEMS					

COMMENTS:
*DO NOT include patient identifiers

APPENDIX F: Biopsy Sequencing Results and Analysis Form

Form begins on the next page.

Molecular Characterization Laboratory
Frederick National Laboratory for Cancer Research
(Leidos Biomedical Research, Inc.)
459 Miller Drive, Frederick, MD 21702
301.846.7689

CLIA Laboratory ID 21D2097127

CTEP-9149 TUMOR SPECIMEN REPORT

Patient ID:
Report Date:

Patient ID:				**MoCha ID:**	HIS-		
Principal Investigator:	Alice Chen, MD						
Diagnosis:							
Biopsy Site:		**Date Collected:**		**DNA/cDNA Block Source:**		**Tumor Content (%)[1]:**	

This report identifies only actionable MOIs (aMOIs) relevant to the genes currently validated for clinical application. aMOIs not detected are not otherwise identified.

DNA Repair : None identified *(delete this text if variants are reported)*

aMOIs Detected

Gene	Chr.	Position	REF (hg19)	ALT (Tumor)	Transcript ID	Amino Acid Change	VAF	Variant ID

[1]*Preanalytical preparation was performed by the MoCha Histology Laboratory, 321 Ware Drive, Frederick, MD 21702 [CLIA ID 21D2137521]. Reported assay characteristics cannot be guaranteed for specimens that present a tumor content below 20%.*

KEY: NA=Not Applicable; Chr=Chromosome; REF (HG19)=Reference base, Human Reference Genome hg19); ALT (Tumor)=Variant base

Comments:

SIGNATURE APPROVAL:

The signature below attests that the signee has reviewed the data and results reported and concurs with the stated conclusions.

DISCLAIMER: *This assay is considered a Laboratory Developed Test (LDT). Its performance characteristics have been determined through extensive testing although it has not been cleared by the US Food and Drug Administration and such approval is not required for clinical implementation. Furthermore, any Comments included in this report are strictly interpretive and the opinion of the reviewer. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) for the performance of high-complexity molecular testing for clinical purposes.*

Molecular Characterization Laboratory

Frederick National Laboratory for Cancer Research
(Leidos Biomedical Research, Inc.)
459 Miller Drive, Frederick, MD 21702
301.846.7689

CLIA Laboratory ID 21D2097127

Methodology, Scope, and Application: *The sequencing test utilizes the Thermo Fisher Scientific Oncomine® Comprehensive Assay v3.0 (OCAv3), a next-generation sequencing (NGS) assay that utilizes a multiplex polymerase chain reaction (PCR) with DNA extracted from formalin-fixed tissue for sequencing on the Ion S5XL platform. The OCv3 NGS Assay can reliably identify the presence or absence of known (reported in COSMIC or ClinVar databases) aMOIs in 15 DNA repair genes, with results compared to Human Reference Genome hg19. The table below lists these genes with the aMOIs that can be identified. The remainder of the genes included in the Oncomine panel include no relevant hotspots. Novel deleterious calls and truncating mutations (frameshift indels and/or nonsense mutations) will also be considered actionable. The OCAV3 NGS Assay is a laboratory developed test designed to find gene mutations within tumors (somatic mutations). It was not designed to find hereditary mutations.*

Analytical Sensitivity and Specificity: *The OCAV3 NGS Assay has been determined to be suitably analytically sensitive and specific for the various types of abnormalities within its reportable range, demonstrating 97.18% sensitivity compared with orthogonal assay results and 100% specificity for the mutation types reported. 99.99% or greater reproducibility has been demonstrated. All quality measures for this assay were within defined assay parameters.*

Gene	Pathway	Identifiable aMOIs (defined as Coding Sequence Change)	Functionality
ATM	DNA repair	c.1009C>T, c.1009C>A, c.1010G>C, c.1010G>A, c.5558A>T, c.6490G>C, c.6490G>A, c.7325A>C, c.7325A>G, c.7327C>G, c.7328G>A, c.8083G>T, c.8083G>A, c.8084G>C, c.8494C>T, c.8494C>A, c.8624A>G, c.8624A>C, c.8625T>A, c.8668C>G, c.8669T>G, c.8860T>A, c.8861A>G, c.9022C>A, c.9022C>T, c.9023G>T, c.9023G>A	Loss
NBN	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
RAD51	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
RAD51B	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
RAD51C	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
RAD51D	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
PALB2	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
BRCA1	DNA repair	c.5363G>T, c.5277+1G>A, c.441+2T>G, c.5468-40T>A, c.5467G>A, c.5359T>A, c.5332+1G>A, c.5331_5332+1delinsCAACAT, c.5324T>G, c.5324T>A, c.5297T>G, c.5291T>C, c.5278-2del, c.5212G>A, c.5194-12G>A, c.5153-1G>C, c.5152+3A>C, c.5152+1G>T, c.5143A>C, c.5123C>A, c.5117G>A, c.5095C>T, c.5074+1G>A, c.5074G>A, c.5074G>C, c.5074G>T, c.5054C>T, c.5053A>G, c.4987-1G>A, c.4986+6T>C, c.4986+6T>G, c.4986+4A>G, c.4986+4A>C, c.4986+4A>T, c.4675+3A>T, c.4675+1G>A, c.4675G>A, c.4675G>C, c.4484G>T, c.4357+1G>A, c.4185G>A, c.4097-1G>A, c.547+2T>A, c.302-1G>C, c.302-3C>G, c.213-3C>G, c.213-11T>G, c.213-12A>G, c.212+3A>G, c.212G>A, c.211A>G, c.191G>A, c.181T>G, c.131G>A, c.130T>A, c.122A>G, c.115T>C, c.110C>A, c.65T>C, c.3G>T, c.2T>C, c.2T>G, c.1A>G, c.5513T>A	Loss
BRCA2	DNA repair	c.2T>G, c.3G>T, c.475G>A, c.475+1G>A, c.476-2A>G, c.631G>C, c.631G>A, c.682-2A>G, c.7007G>C c.7007G>T, c.7008-2A>T, c.7617+1G>A, c.7618-1G>A, c.7878G>C, c.7879A>T, c.7976G>C, c.7988A>T, c.8009C>T, c.8165C>G, c.8167G>C, c.8168A>G, c.8243G>A, c.8487+1G>A, c.8953+1G>T, c.8954- 3C>G, c.9154C>T	Loss
CHEK1	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
CHEK2	DNA repair	c.1556G>A, c.1169A>G, c.1141A>G	Loss
FANCA	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
MRE11A	DNA repair	Novel loss of function frameshift or nonsense mutation	Loss
IDH1	DNA repair	c.394C>A, c.395_396GT>AC, c.394_395CG>GT, c.394_395CG>TC, c.395G>A, c.395G>T, c.394C>G, c.394C>T	Altered
IDH2	DNA repair	c.515_516GG>AT, c.516G>C, c.516G>T, c.515G>A, c.515G>C, c.515G>T, c.514A>T, c.514A>G, c.419G>A, c.419G>T, c.418C>G, c.418C>T	Altered
aMOI COSMIC ID may be found at: Catalog of Somatic Mutations in Cancer, https://cancer.sanger.ac.uk/cosmic			

APPENDIX G: Molecular Tumor Board Members

The Molecular Tumor Board is a multidisciplinary group with expertise in molecular and clinical genetics, gene analysis, pharmacogenomics, pharmacodynamics, statistics, and bioinformatics assembled to review and select the genetic variants being assessed on this study. The Board will meet on an ad hoc basis to review and discuss findings and results but will not influence initial treatment assignments.

Name	Affiliation	Specialty
Alice Chen, MD	CTEP/DCTD/NCI	Clinical oncology
James H. Doroshow, MD	DCTD/NCI	Molecular and clinical oncology
Jeff Hildesheim, PhD	CCBB/NCI	Molecular oncology
Robert Kinders, PhD	Leidos Biomed., FNLCR	Molecular oncology and pharmacodynamics
Chris Karlovich, PhD	Leidos Biomed., FNLCR	Molecular oncology and genetic analysis
Paul Meltzer, MD, PhD	GB/CCR/NCI	Molecular oncology and genetic analysis
Eric Polley, PhD	Mayo	Statistics
Yves Pommier, MD, PhD	LMP/CCR/NCI	Molecular oncology
Larry Rubinstein, PhD	DCTD/NCI	Statistics
Jim Tricoli, PhD	Leidos Biomed., FNLCR	Molecular oncology and genetic analysis
Mickey Williams, PhD	Leidos Biomed., FNLCR	Molecular oncology and genetic analysis

APPENDIX H: Example Tumor Variant Patient Report

Variant Annotation Table

Patient ID: 9149101aa01 Sample ID: 9149-MOCK-aa01

aMOI	Gene	Type	Pathway	Drug	Sift Predict	Sift Score	HP	Impact	dbSNP id	HGMD	COSMIC id	Chr	Position	REF (hg19)	ALT (tumor)	Allele Freq	Read Depth	Codon Change	AA Change
Yes	PTEN	Loss	PI3K	Everolimus				STOP_GAINED				10	89717672	C	T	0.60	1250	Cga/Tga	R233*
Yes	BRAF	Gain	RAS	GSK1120212	DAMAGING	0.01		nonsynonymous	rs113488022:T	Yes	476	7	140453136	A	T	0.68	1483	gTg/gAg	V600E

Export to Excel

Legend

Field Name	Description
aMOI	Yes/No: Is the variant one of the actionable mutations for the MPACT trial?
Gene	Gene symbol for location of variant. Links to COSMIC website on that gene
Type	Type: is this gene Gain of function or Loss of function?
Sift Predict	Damaging/Tolerated: SIFT prediction for non-synonymous variants
Sift Score	The score is the normalized probability that the amino acid change is tolerated. The amino acid substitution is predicted damaging is the score is <= 0.05, and tolerated if the score is > 0.05.
HP	Is the variant in a homopolymer region? If so, display the length of the homopolymer region
Impact	Functional impact of variant
dbSNPid	If available, dbSNP ID
HGMD	Is the variant in the HGMD database? If so, link goes to HGMD website
COSMICid	Is the variant in COSMIC, if so, link to the variant in COSMIC
Pathway	RAS, PI3K, or DNA repair
Chr	Chromosome
Position	Position of variant in chromosome based on hg19
REF	Reference base (VCF format, from hg19)
ALT	Variant base (VCF format)
Allele Frequency	Variant allele frequency estimate based on present of reads supporting the variant
Read Depth	Total number of reads at the position
Codon change	Codon change from reference
AA change	Amino Acid change from reference

Patient Clinical Information Report

Patient ID	9149101aa01
Gender	M
Histologic Dx	Melanoma
Date of Diagnosis	02/12/2013
Age at Diagnosis	55

Sequencing Data Summary Report

Sample ID	9149-MOCK-aa01
Date of Sequencing Data Uploaded	01/09/2014 15:28
Lab Review of Variant Report	completed (01/10/2014 08:28)
Date of Mutation Summary Report	01/10/2014 10:28
Actionable Mutation	yes

APPENDIX I: Veliparib plus Temozolomide (Proprietary Information)

Veliparib is an orally available, small molecule inhibitor of PARP. Preclinical and clinical data show that inhibition of PARP potentiates the effects of DNA-damaging chemotherapeutic drugs such as the alkylating agent temozolomide [67]. In this study, Veliparib and temozolomide will be administered to patients with defects in DNA repair pathways.

Nonclinical Studies

One of the most studied alkylating agents in combination with PARP inhibition is temozolomide, which is used in the treatment of CNS tumors and melanoma. In vitro, potentiation of temozolomide-induced cytotoxicity was observed in the MMR-deficient HCT-116 cell line. In nonclinical models of murine melanoma, dose-dependent potentiation of temozolomide was demonstrated with 12.5 mg/kg BID of orally administered Veliparib that was identified as the maximally efficacious dose (AUC, 3 µg•hr/mL) [100]. Preliminary human pharmacokinetic (PK) results indicate that an oral dose of 40 mg Veliparib BID achieves the exposure (AUC) that was maximally effective in murine efficacy models. The predicted efficacious exposures are below Veliparib concentrations that resulted in a NOAEL in repeated-dose toxicity studies in rats and dogs.

The PK profile of Veliparib was evaluated in tumor-bearing rats by measuring drug in plasma as well as in brain and tumor tissues. After multiple doses of Veliparib (50 mg/kg/day), the concentration of the compound 2 hours after dosing (near Cmax) was 1.36 ± 0.16 µg/mL in plasma, 0.72 ± 0.12 µg/g in brain, and 3.00 ± 0.16 µg/g in tumor tissue. Co-administration with temozolomide did not alter the plasma pharmacokinetic profile of Veliparib.

Ataxia, tremors, seizures/convulsions, and other behaviors consistent with CNS effects were observed after repeated oral doses in dogs during multiple studies. In the aggregate of studies in which convulsions were observed in dogs, the lowest plasma concentration of Veliparib measured at time of convulsion was 1.16 µg/mL, and the lowest calculated AUC_{0-24} corresponding to convulsion was 16.7 µg•hr/mL. The lowest observed exposure values correspond to an exposure of approximately 5.5-fold above the predicted clinical maximum plasma concentration (C_{max}) of 0.210 µg /mL, and approximately 6-fold above the predicted clinical AUC_{0-24} of 3 µg•hr/mL. Convulsions were either self-resolving or resolved after treatment with diazepam. There was no evidence of abnormal cortical activity or seizures occurring at a dose of 20 mg/kg BID in an EEG study in the conscious dog. There is no proposed pathophysiologic mechanism for the observed seizures. No seizures have been reported in clinical trials with Veliparib to date.

In a separate study in rats in which Veliparib was combined with temozolomide, observed toxicities were consistent with exacerbation of known temozolomide toxicity. Co-administration of temozolomide at 16 mg/kg/day and Veliparib at doses of 12.5 and 25 mg/kg/day (divided BID) resulted in increased toxicity over that observed with temozolomide administration alone, effecting bone marrow, lymphoid tissues, testes, and ovaries. Most toxicological findings resolved at the end of a 22-day recovery period, with the exception of the testes. In this study, the combination of Veliparib (50 mg/kg/day) in combination with temozolomide significantly reduced tumor volume by 63%, which was more effective than temozolomide alone (44%) [100].

The reversible and nonlethal exacerbation of temozolomide hematologic toxicity in the rat occurred at doses of Veliparib that, in previous studies, resulted in exposures that were similar to or greater than anticipated clinically efficacious exposure (AUC).

Veliparib can produce fetal toxicities, including decreased fetal weights, increased post-implantation loss, fetal malformation and variations (external, visceral, and skeletal), and delayed skeletal ossification. The rat is the most sensitive species for fetal toxicity, with the C_{max} at the NOEL for rat and rabbit of 0.02 and 2.4 µg/mL, respectively. There are no data regarding the effects of Veliparib on pregnancy in humans.

Clinical Studies

Pharmacokinetic results from a Phase I study of Veliparib in combination with temozolomide (Study M06-862) were consistent with those seen in the Phase 0 study [100]. Similar to results from CTEP Study 7675 (A06-161), Veliparib absorption and elimination were relatively rapid after administration of Veliparib alone on Day 7. Across Study M06-862 subjects, the time to the maximum concentration (Tmax) averaged 1.2 hours and the predose concentration averaged 27% of the maximum concentration (C_{max}). The coefficients of variation in dose-normalized Cmax and area under the curve (AUC) over a dosing interval (AUC0-12) on Day 7 were 40% and 50%, respectively. Veliparib 40 mg twice daily (BID) produced an average steady-state AUC0-24 of 4.81 µg•hr/mL, assuming equivalent AUCs following the morning and evening doses. This clinical regimen exposure is comparable to that associated with the maximally effective Veliparib regimens in murine efficacy models (3.0 µg•hr/mL). Across the dose range studied, Veliparib C_{max} and AUC were approximately dose-proportional with minimal accumulation of plasma Veliparib concentrations following BID dosing. Additionally in Study M06-862, the potential pharmacokinetic interaction between Veliparib and temozolomide is being assessed by determination of the pharmacokinetics of temozolomide and Veliparib when administered alone on Days 1 and 7, respectively, and when co-administered on Day 3. At the dose levels studied to date, there is no indication of a significant pharmacokinetic interaction between Veliparib and temozolomide. Preliminary Veliparib pharmacokinetics in another Phase 1 Study M10-128 show trends of approximately dose-proportional pharmacokinetics and absence of a significant food effect.

Preliminary safety and/or efficacy results are available from 5 Phase 1, 1 Phase 1/2, and 4 Phase 2 Abbott-sponsored studies of Veliparib in combination with a DNA-damaging agent [100]. In the Phase 1 Study M06-862, doses in the dose-escalation portion of the study ranged from 10 mg Veliparib BID/150 mg/m^2 temozolomide once daily (QD) to 80 mg Veliparib BID/200 mg/m^2 temozolomide QD. No DLTs were reported for the first 3 dose-escalation cohorts (10, 20, and 40 mg Veliparib BID). In cohorts receiving 60 and 80 mg BID, events of grade 4 neutropenia or thrombocytopenia were reported. The MTD combination dose was defined as 40 mg Veliparib BID/200 mg/m^2 temozolomide QD. In addition to defining the MTD, a second dose, lower than the MTD but also predicted to be biologically active, was defined as 20 mg Veliparib BID/200 mg/m^2 temozolomide QD.

Although no DLTs were reported in Study M06-862 subjects in the 40 mg Veliparib BID 200 mg/m^2 temozolomide QD dose-escalation cohort, 2 subjects enrolled at the same dose in the expanded MTD safety cohort experienced serious adverse events of grade 4 neutropenia and/or thrombocytopenia, and 8 of all 12 subjects receiving 40 mg Veliparib BID 200 mg/m^2 experienced

grade 3 or 4 adverse events of neutropenia and/or thrombocytopenia. In general, subjects with these events recovered after dose reduction of Veliparib and/or temozolomide, and all subjects remained on study.

To minimize these hematologic toxicities, Study M06-862 protocol was modified to treat new subjects with 40 mg Veliparib BID in combination with 150 mg/m^2 temozolomide QD in the first cycle. If a subject did not experience grade 3 or 4 neutropenia or thrombocytopenia or other clinically significant NCI CTCAE greater than grade 3, the temozolomide dose was escalated to 200 mg/m^2 QD. In addition to neutropenia and thrombocytopenia, the other most commonly reported adverse events in Study M06-862 occurring in ≥ 30% of subjects were nausea, fatigue, vomiting, constipation, decreased appetite, and headache. All of the most commonly reported adverse events have previously been reported in subjects receiving temozolomide.

For Study M06-862, preliminary data on tumor assessment was available for 42 subjects. Two of 42 subjects (4.76%) experienced an objective partial response. Of these, one subject, a *BRCA*-deficient ovarian cancer patient, experienced an objective partial response in Cycle 6 and this partial response was confirmed in Cycles 8 and 10. The other, a subject with hepatocellular carcinoma (HCC), experienced a partial response in Cycle 4 that was confirmed in Cycles 6, 8, 10, and the Final Visit.

In the Phase 1/2 Study M10-190, Veliparib was administered in combination with radiation therapy with concurrent and adjuvant temozolomide (75 mg/m^2 for 6 weeks). Preliminary safety data were available for 18 subjects. The most commonly reported adverse events occurring in ≥ 30% of subjects were nausea, fatigue, headache, insomnia, and thrombocytopenia. Study M10-440 is a Phase 2 randomized, double blind, placebo-controlled study of Veliparib (20 or 40 mg BID) in combination with temozolomide (150 mg/m^2/day with possible escalation to 200 mg/m^2). This study is fully enrolled and ongoing. Preliminary blinded safety data are available for 344 subjects. The most common AEs (reported in ≥ 30% of subjects receiving Veliparib plus temozolomide) were nausea, fatigue, constipation, thrombocytopenia, and vomiting.

In the Phase 2 Study M10-757, preliminary safety data are available for 165 subjects. The most common treatment-emergent AEs (reported for ≥ 30% of subjects receiving Veliparib plus temozolomide at any point) reported in subjects with recurrent high-grade serous ovarian cancer treated with Veliparib plus with temozolomide versus PLD alone, were nausea, fatigue, thrombocytopenia, vomiting, constipation, neutropenia, and decreased appetite. Preliminary efficacy data are not yet available. Preliminary safety data are available for 26 subjects. The most common treatment-emergent AEs (≥ 30% of all subjects) reported in Study M11-070, a trial evaluating subjects with metastatic castration-resistant prostate cancer treated with Veliparib plus temozolomide, were fatigue, nausea, and platelet count decreased. Preliminary data on maximum percentage reduction from baseline in PSA values are available for 25 subjects. Confirmed PSA responses have been observed in 2 subjects. The mean (SD) for the largest observed decrease from baseline in PSA values was 11.7% (48.3%). In an extension study of Study M11-846, preliminary safety data available are for 23 subjects. The most common treatment-emergent AEs (≥ 30% of all subjects) reported in Study M12-273, a trial evaluating subjects with solid tumors treated with Veliparib plus temozolomide, were nausea, fatigue, vomiting, abdominal pain, decreased appetite, and thrombocytopenia. No preliminary efficacy data are available.

APPENDIX J: AZD1775 (Proprietary Information)

AZD1775 with Carboplatin (Investigators Brochure)

AZD1775 is a selective, adenosine-triphosphate (ATP) competitive, small molecule inhibitor of Wee1 kinase (IC_{50} = 5.18 nM), that directly inhibits phosphorylation of CDC2 at Tyr15. The antitumor effect of AZD1775 in combination with carboplatin was investigated in the HeLa-luc (human cervical adenocarcinoma) nude rat xenograft model. AZD1775 was administered orally to the animals 24 hr after carboplatin (50 mg/kg: MTD) at doses of 10, 20 and 30 mg/kg; single IV bolus treatments of carboplatin showed significant antitumor efficacy with %T/C = 70%. Tumor growth was not inhibited by AZD1775 monotherapy at a dose of 30 mg/kg, with %T/C = 96%. AZD1775 dose-dependently enhanced the anti-tumor effect of carboplatin in HeLa-luc tumors with %T/C = 85, 39 and 28% at doses of 10, 20 and 30 mg/kg, respectively. AZD1775 did not cause significant enhancement of carboplatin-induced reduction of WBC (38 - 45% control) and platelets (15 - 26% control), and these parameters returned to normal by Day 20 and 10 in the combination arms. AZD1775 alone did not show severe blood cell toxicity. No severe body weight loss (-2 to -5% delta change vs. control), abnormal physical signs or mortality were observed in any treatment group. These results suggest that the combination of AZD1775 with carboplatin has anti-tumor efficacy and is well tolerated.

An additional tolerability study was conducted in non-tumor bearing nude rats dosed with carboplatin alone or in combination with AZD1775 over multiple cycles. Doses of carboplatin (50 mg/kg IV), alone and in combination with AZD1775 (20 mg/kg orally, 24 hrs after carboplatin dosing), were administered once during a 28-day cycle for 3 consecutive cycles. Body weight and blood cell counts were monitored during the study period. There were no significant changes in toxicity parameters between the carboplatin alone and the carboplatin + AZD1775 treatment arms. Thus, AZD1775 did not significantly enhance the toxicity parameters of carboplatin when used in the multi-cycle dosing schedule.

Non-clinical Toxicology

The toxicology profile of AZD1775 in rats involved the lymphoid and hematopoietic organs and gastrointestinal tract, and included decreased food consumption, body weight loss, hematologic and serum chemistry changes, decreased urine volume and soft feces. AZD1775 had no effect on CNS function in mice. The cardiovascular effects of AZD1775 were examined in 5 isoflurane-anesthetized and mechanically vented dogs. At doses of 3 and 10 mg/kg, QTc was marginally prolonged by an average of 5% and 7%, respectively. No QTc changes were observed in the intact dog studies or human studies. Evidence of reversibility of all toxicity changes was generally demonstrated by the end of the 2-week recovery period. In a single dose oral toxicity study, severe irreversible toxicity (mortality) was seen in 1 female out of 10 female rats after a single dose at 300 mg/kg (1800 mg/m^2).

Based on the preliminary safety data available, the most frequent AEs observed were blood and lymphatic disorders (thrombocytopenia, neutropenia, anemia, febrile neutropenia), gastrointestinal disorders (diarrhea, vomiting, nausea, abdominal pain, constipation), and investigation findings (hematology and serum chemistry). The single-dose TD for both the gemcitabine and cisplatin combination therapies was 200 mg of AZD1775. DLTs tended to be hematological in nature in the gemcitabine group and constitutional in the cisplatin group. The single-dose MTD for the

combination with carboplatin was 325 mg of AZD1775. DLTs in this group were related to serum chemistry.

Clinical Studies
AZD1775 has been administered to patients in 12 AstraZeneca-sponsored or Merck-sponsored clinical studies, 6 of which are ongoing.
Completed or terminated early:

- PN001 (NCT00648648): a first-time-in-patients (FTIP), Phase I, dose-escalation study evaluating AZD1775 both as monotherapy and combination therapy with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumours
- PN004 (NCT01357161): a Phase II study evaluating AZD1775 combined with carboplatin and paclitaxel in patients with platinum-sensitive p53-mutant ovarian cancer
- PN005 (NCT01047007): a Phase I, dose-escalation study evaluating AZD1775 as monotherapy (Part 1), combination therapy with 5-FU (Part 2), and combination therapy with 5-FU plus cisplatin (Part 3) in adult Japanese patients with advanced solid tumours was terminated early due to portfolio prioritisation in oncology at Merck after 3 patients had been enrolled in Part 1 and 8 patients had been enrolled in Part 2. Part 3 was not initiated.
- PN008 (NCT01076400): a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients with cervical cancer was terminated early due to portfolio prioritisation in oncology at Merck after 7 patients had been enrolled in the dose-escalation part of the study. The Phase IIa part was not initiated.
- D6011C00001 (NCT02087176; SCRI LUN 262): a lead-in Phase II multicentre, randomised, double-blind study comparing AZD1775 plus docetaxel with placebo plus docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC)
- D6011C00002 (NCT02087241; SCRI LUN 261): a Phase II study of AZD1775 plus pemetrexed and carboplatin followed by a randomised comparison of pemetrexed and carboplatin with or without AZD1775 in patients with previously untreated stage IV non-squamous NSCLC.

Ongoing:

- D6010C00004 (NCT02272790; SCRI GYN 49): multicentre Phase II study of AZD1775 plus either paclitaxel, gemcitabine, carboplatin, or pegylated liposomal doxorubicin in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer
- D6010C00005 (NCT02511795; SCRI REFMAL 384): Phase I study evaluating AZD1775 in combination with olaparib in refractory solid tumours.
- D6011C00003 (NCT02341456): Phase Ib dose-finding study evaluating AZD1775 as monotherapy and in combination with carboplatin and paclitaxel in adult Asian patients with advanced solid tumours
- D6015C00001 (NCT02482311; SCRI REFMAL 383): Phase I, dose escalation, safety and pharmacokinetic study of AZD1775 monotherapy (Schedule 1) in patients with advanced or metastatic solid tumours
- D6015C00002 (NCT02617277; SCRI REFMAL 412): Phase I study assessing the safety, tolerability, and pharmacokinetics of AZD1775 in combination with MEDI4736 in patients with advanced solid tumours
- D6015C00003 (NCT02610075; SCRI REFMAL 398): Phase Ib study to determine the

maximum-tolerated dose (MTD) of AZD1775 monotherapy (Schedule 2) in patients with locally advanced or metastatic solid tumours.

- In addition, Phase I and II studies are being conducted and sponsored by the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program, and by several other institutions as investigator-sponsored studies.

As of 11 November 2016, a total of approximately 551 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. Of these 551 patients, 103 received AZD1775 monotherapy, 407 patients received AZD1775 in combination with cytotoxic chemotherapy agents and the remaining 41 patients received AZD1775 in combination with targeted therapies MEDI4736 or olaparib. In addition, approximately 350 patients have also received AZD1775 as part of externally-sponsored scientific research. These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose in combination with chemotherapy, and 325 mg twice a day (BID) in a multiple-dose regimen in combination with chemotherapy.

The PK data of AZD1775 following a single oral administration showed a moderate rate of absorption with a Tmax occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a t1/2 in the region of 10 hours. Exposure as measured by maximum plasma drug concentration observed (Cmax) and AUC0-∞ increased in a dose-proportional manner over the dose range of 325 to 1300 mg. Following single (100 to 325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg once daily [QD]) with carboplatin, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regime. Preliminary investigation of drug-drug interactions in Study PN001 suggest a 40% to 60% increase in the exposure of AZD1775 in the presence of aprepitant (moderate CYP3A4 inhibitor), but no effect with the concomitant administration of various different corticosteroids (moderate CYP3A4 inducers). Preliminary studies also suggested that the PMF of AZD1775 was similar to that of the FFP formulation.

Based on the safety data from the 3 completed AZD1775 clinical studies and preliminary data from ongoing studies, the most frequent adverse events (AEs) observed were blood and lymphatic disorders (leukopenia, lymphopenia, neutropenia, thrombocytopenia, anaemia, febrile neutropenia, pancytopenia), gastrointestinal disorders (diarrhoea, vomiting, nausea, abdominal pain, constipation), general disorders and administration site conditions (fatigue, fever, chills), and investigation findings (haematology and serum chemistry). Cardiac disorders (tachycardia, palpitations, QTc prolongation) were not observed frequently, but are considered to be important identified risks. Gastrointestinal haemorrhage is considered an important potential risk to be monitored closely as the programme progresses.

Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies adverse drug reactions to AZD1775 monotherapy include: anaemia, neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhoea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite. In addition, the following events are also considered expected during treatment with AZD1775 in combination with cytotoxic chemotherapy: febrile neutropenia, leukopenia, stomatitis, asthenia, fatigue, mucosal inflammation and myalgia.

Based on information emerging during the clinical development programme of AZD1775, potential risks with AZD1775 monotherapy include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation.

In addition, the following events are also considered potential risks for AZD1775 in combination with cytotoxic chemotherapy: tachycardia and pancytopenia. Refer to the IB for AZD1775 for information on the potential benefits and assessment of potential and known risks.

In Study PN001, of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a partial response (PR) (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease (SD) was observed in 94 (53.4%) patients. No complete responses (CRs) or PRs were observed in either of Studies PN005 or PN008 at the time that they were terminated.
In Study PN004, all patients were treated at the 225 mg AZD1775 BID 2.5 day dose level in combination with paclitaxel and carboplatin. Of the 14 evaluable patients by RECIST v1.1 in Part 1, there were 11 PRs (6 confirmed and 5 unconfirmed), and 3 SDs; 7 patients were evaluable by CA-125 with 3 CRs and 4 PRs. Final data for Part 2 was not available as of the cut-off date for this brochure.
In Study D6011C00001, 32 patients with NSCLC were treated with 225 mg AZD1775 BID over 2.5 days in combination with docetaxel (75 mg/m2 IV) administered on Day 1 followed by pegfilgrastim on Day 4 of each 21-day cycle. The 3 patients (9.4%) that achieved PR by RECIST v1.1 had TP53 mutations. Twenty-one patients (65.6%) had SD and 10 (47.6%) of these patients had TP53 mutations. The planned Interim Analysis of 32 patients in the single cohort lead-in (Part A) suggested that toxicities associated with AZD1775 given in combination with docetaxel were greater in frequency and severity than with docetaxel alone. Additionally, the analysis revealed that it was very unlikely the target response rate would be reached in this study and a decision was made to terminate enrolment.

In Study D6011C00002, 14 patients with NSCLC were treated with 225 mg AZD1775 BID over 2.5 days in combination with pemetrexed 500 mg/m2 IV and carboplatin AUC 6 IV, both administered on Day 1 of each 21-day cycle. Enrolment was stopped because of the introduction of new therapies for the treatment of first-line NSCLC, such as immunotherapy, which resulted in challenges in patient recruitment. In addition, the planned Interim Analysis of Study D6011C00001 revealed that it was very unlikely that the target response rate would be reached, and increased gastrointestinal and hematologic toxicities associated with AZD1775 were observed.

Clinical Pharmacokinetics

The major metabolic pathway of AZD1775 in human liver preparations is oxidative metabolism. Oxidative metabolism of AZD1775 is mediated predominantly by cytochrome P450 (CYP) 3A4 and FMO3. AZD1775 is also a weak reversible inhibitor of CYP2C8, CYP2C9, CYP2C19 and CYP3A4. In addition, AZD1775 is a time-dependent inhibitor of CYP3A4 in *in vitro* human liver microsomes.

APPENDIX K: Trametinib DMSO (Proprietary Information)

Trametinib DMSO is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. The safety, pharmacokinetic (PK) and pharmacodynamic (PD) profiles, and activity of trametinib DMSO are currently being evaluated in 13 ongoing monotherapy and combination therapy clinical trials involving subjects with a variety of cancers.

In May 2013, the FDA approved trametinib DMSO for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations. In January 2014, the FDA also granted accelerated approval to the combination of trametinib DMSO and dabrafenib to treat patients with unresectable or metastatic melanoma with BRAF ^{V600E} or ^{V600K} mutations.

Nonclinical Pharmacology
MEK proteins are critical components of the extracellular signal-related kinase (ERK) pathway which is commonly hyperactivated in tumor cells. Oncogenic mutations in both B-RAF and RAS signal through MEK1 and MEK2. Trametinib DMSO is non-competitive towards ATP and inhibits activation of MEK by RAF kinases as well as MEK kinase activity. The specificity of trametinib DMSO to MEK1 and MEK2 was confirmed against a panel of 183 kinases, including MEK5, the closest kinase homolog to MEK1 and MEK2, and no significant inhibitory activity was measured [101]. In vitro, 80% of cell lines carrying activating mutations of B-Raf and 72% of Ras mutant cancer cell lines were sensitive to trametinib DMSO in cell proliferation assays, and a majority (83%) of hematopoietic cancers from acute or chronic myeloid leukemia (AML or CML, respectively) origins were also very sensitive.

Antitumor Activity *in vitro*
Cancer cells expressing high constitutive levels of activated ERK (pERK) tended to be more sensitive to trametinib DMSO than those with lower levels of pERK, suggesting that tumors with B-RAF or RAS mutations and/or high levels of pERK may respond to trametinib DMSO treatment. In all cell lines, pERK was strongly inhibited following treatment with trametinib DMSO and was independent of their proliferative response, suggesting that pERK inhibition is necessary but not sufficient to inhibit cell proliferation. In cell lines that were sensitive to the anti-proliferative activity of the agent, the response was associated with arrest in G1 phase of the cell cycle, accumulation of p27, reduction of cyclin D1 and phospho-retinoblastoma protein. Induction of apoptosis was demonstrated in some cell lines. Inhibition of pERK and inhibition of cancer cell proliferation were fully reversible following compound removal, suggesting that sustained exposure to trametinib DMSO, or potential combination with other drugs, may be required for full activity.

When trametinib DMSO was combined with standard of care drugs against human cancer cell lines in vitro, an additive effect was observed for pancreatic cancer with gemcitabine or erlotinib and for colon cancer with 5-FU or irinotecan. The combination of trametinib DMSO with rapamycin, ara-C, bexarotene or sorafanib produced an additive effect against most AML cell lines tested. In addition, combination of agent with an investigational phosphoinositide 3-kinase (PI3K) inhibitor, as well as with a Centromer Protein-E (CENP-E) inhibitor, was synergistic on inhibition of cell growth in various cancer (pancreas, colon, lung) cells. Additionally, the combination of trametinib DMSO and a CENP-E inhibitor increased caspase activity, indicating enhanced apoptosis in colon cancer cell lines.

While many proliferating human cells are sensitive to trametinib DMSO in vitro, the agent did not affect non-dividing normal cells and did not completely inhibit bone marrow progenitor cells at concentrations demonstrating anti-proliferative activity on very sensitive cancer cell lines.

Antitumor Activity *in vivo*
Trametinib DMSO was orally bioavailable in mice, and doses as low as 1 mg/kg reached blood concentrations that caused sustained reductions of pERK, an accumulation of p27, and a decrease of Ki67 in tumor xenografts; brain exposure levels were ~10% of those in blood, and no significant pERK inhibition was measured in brain tissue. In mice, exposure to trametinib DMSO produced dose- and schedule-dependent anti-tumor responses correlating with blood levels. Typically, B-RAF--mutant xenografts responded with tumor regression while K-RAS-mutant xenografts responded with tumor growth inhibition. In vivo combination studies testing trametinib DMSO together with various other anticancer drugs showed good potential for synergistic effects.

Safety Pharmacology
In a rat neurobehavioral screen, following a single oral dose of trametinib DMSO at 650 mg/m^2 to male rats, diarrhea, prone position, blepharoptosis, piloerection, reduced spontaneous locomotion and mydriasis were observed between 2 and 24 hours post dose. In a respiratory safety pharmacology study in rats, an oral dose of 1 mg/m^2 produced a mild, transient decrease in body temperature (up to 0.8°C) at 1 hour post dose. There were no other effects on ventilatory function, airway resistance or body temperature. Trametinib DMSO inhibited hERG channel repolarization in HEK293 with an IC_{50} of 1.54 μM (950 ng/mL). In a rabbit left ventricular wedge assay, trametinib DMSO had no significant effect on QT interval at concentrations up to 30 μM (18450 ng/mL; limit of solubility). However, significant decreases in isometric contractile force occurred at concentrations of 10 (6150 ng/mL) and 30 μM. Trametinib DMSO also decreased the Tp-e interval at a concentration of 30 μM. A single intravenous infusion of drug in dogs at 20 mg/m^2 over 10 minutes (Cmax of 2.5 μM or 1500 ng/mL) produced no changes in electrocardiogram (ECG) parameters, blood pressure, or heart rate during the 30 minute measurement period. In addition, single oral doses up to 1.5 mg/m^2 in dogs produced no changes in arterial blood pressure, heart rate, body temperature, or ECG intervals, including QTc. While trametinib DMSO affected cardiac electrophysiology in vitro, no effects were observed in vivo at doses that were maximally tolerated in dogs. This difference in responses is likely related to the very low Cmax (~10 ng/mL total drug) at tolerated doses in dogs and the high protein binding (97% in dogs) of agent. The concentrations at which effects were seen in these in vitro studies are significantly higher than the free fraction observed in nonclinical toxicology studies or the clinical dose (2 mg). These results suggest a low risk for cardiovascular effects in the clinic.

Pharmacokinetics and Product Metabolism in Animals
Trametinib DMSO exhibited low plasma clearance among nonclinical species (mouse, rat, dog and monkey) with varied but generally long half-lives. Oral bioavailability ranged between 42% and 100%. Since trametinib DMSO is a low solubility, high permeability molecule, its absorption is likely limited by solubility and dissolution. Plasma protein binding was high in nonclinical species and human (>95%) and blood cell association was low. Consistent with high permeability, trametinib DMSO had moderate to high volume of distribution among the nonclinical species studied and DRM was widely distributed into rat tissues. The low

concentration of DRM observed in the brain up to 8 hours post dose was observed. Although studies showed protracted elimination of DRM (consistent with high volume and long half-life), DRM in tissues was not detectable by 35 days post dose. In rats and dogs after repeat oral dosing up to 13 weeks, systemic exposure increased approximately dose-proportionally at higher doses or when steady state was reached at Week 3. Upon repeat dosing, increases in systemic exposure after Day 1 were observed up to Week 3; however, between Weeks 4 and 13, there was no marked increase in systemic exposure for either pre-clinical species. A tendency for higher exposure in females than in males was observed in some studies in both rats and dogs.

No apparent human-specific metabolite was observed in the in vitro cross-species [14C] trametinib DMSO metabolism study. [^{14}C] trametinib DMSO was also found to metabolize predominantly via a non-cytochrome P450 (CYP) mediated deacetylation with secondary oxidation or glucuronidation biotransformation pathways. CYP3A4 was implicated in the in-vitro formation of M7, a metabolite mediated by both non-CYP and CYP pathways. The relative contribution of CYP3A4 to the total metabolic clearance of trametinib DMSO in human in vivo is not currently understood and, therefore, the possibility of a metabolic drug interaction cannot be eliminated. Elimination of DRM in rat and dog after oral administration occurred predominantly via the feces (>60% of dose), with urinary excretion (<7% of dose) representing a minor route.

Trametinib DMSO is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways (Investigator's Brochure, 2012). Deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Trametinib DMSO has an overall low potential for drug-drug interactions. There was no evidence of time-dependent inhibition with any of the CYP enzymes investigated.

Toxicology

Systemic toxicity of trametinib DMSO has been evaluated following oral dosing in rats and dogs for up to 13 weeks. In the most sensitive nonclinical species, rat, the principal adverse effects seen in oral toxicity studies of up to 13 weeks with daily dosing were skin and stomach erosions, skin ulcerations, which were secondary to reduced proliferation, altered phosphate homeostasis that resulted in soft tissue mineralization, hepatocellular necrosis, bone marrow degeneration/necrosis and ovarian perturbations. The skin and stomach findings and phosphatemia demonstrated reversibility with 4 weeks of recovery. MTD in rats in the definitive 13 week study with daily dosing was 0.25 mg/m^2/day (AUC0-t of 126 ng.h/mL, end of study). Reversible acute effects (diarrhea, decreased body weight gain, prone position, blepharoptosis, piloerection, reduced spontaneous locomotion and mydriasis) were observed following a single high dose of 650 mg/m^2 to rats. In dogs, the principal dose-limiting toxicities seen oral toxicity studies of up to 13 weeks with daily dosing were related to gastrointestinal and hematopoietic perturbations. Inflammatory responses to gastrointestinal erosions were observed in dogs and were reversible following a recovery period. In the definitive 13 week daily oral dosing study in dogs, the NOAEL was 0.45 mg/m^2/day (AUC0-t of 139 ng.h/mL, end of study). Principal adverse effects were consistent with inhibition of cell proliferation and were monitorable and generally reversible. Trametinib DMSO was negative in both in vitro and in vivo genotoxicity assays.

Effects in Humans

The effect of Trametinib DMSO in subjects with a variety of refractory cancers is currently under evaluation in 14 clinical studies. As of 14 April 2011, 657 subjects with cancer have received at least one dose of trametinib DMSO in the ongoing Phase I/II/III clinical studies. There are no completed clinical trials to date. Preliminary trametinib DMSO pharmacokinetics were determined after single- and repeat dose oral administration of tablets in subjects with solid tumors. Trametinib DMSO is absorbed rapidly with median Tmax generally occurring within 1-3 hours after oral administration under fasting conditions. Following repeat-dosing the mean area under the curve (AUC0-τ) and maximum concentrations (Cmax) increased in an approximately dose proportional manner. Trametinib DMSO accumulates with repeat dosing with a mean effective half-life of approximately 5 days. The MTD was established at 3.0 mg once daily (QD), and the recommended Phase II dose was identified as 2.0 mg QD.

Phase	Study #	Treatment Regimen	Study Population
Monotherapy Studies			
I	MEK111054	Single agent (First-time-in-human)	Solid tumors and BRAF-mutant melanoma
I/II	MEK111759	Single Agent	Leukemia
II	MEK113583	Single agent	BRAF-mutant Melanoma
III	MEK114267	Randomized comparison GSK1120212 vs. chemotherapy (dacarbazine, or paclitaxel)	BRAF-mutant melanoma
MEK113708		Phase I ADME study	Solid tumors
MEK113709		Phase I Food-Effect study	
Combination Therapy Studies			
IB/II	MEK112110	Combination with everolimus (mTOR-inhibitor)	Solid tumors
I/IB	MEK112111	Combination with gemcitabine	Solid tumors and pancreatic cancer
I/IB	MEK113486	Multi-arm combination with docetaxel, pemetrexed, pemetrexed/carboplatin, nab-paclitaxel, or erlotinib	Solid tumors
I	MEK114784	Single agent and combination with gemcitabine	Japanese subjects with solid tumors
I/II	BRF113220	Combination with GSK2118436 (BRAF-inhibitor)	BRAF-mutant melanoma
I	TAC113886	Combination with GSK214795 (AKT-inhibitor)	Solid tumors
I	P3K113794	Combination with GSK2126458 (PI3 Kinase-inhibitor)	Advanced solid tumors
II	MEK113487	Randomized combination GSK1120212 with gemcitabine vs. gemcitabine	Pancreatic cancer

Safety/Tolerability Profile
The maximum tolerated dose was established at 3 mg daily. The safety profile at doses greater than 2 mg QD was not as favorable with a larger percent of subjects with Grade 2 rash, rash leading to dose reduction, peripheral edema, and cardiac failure. A dose of 2 mg QD was selected to minimize need for dose reduction and allow subjects to receive the highest dose that is well tolerated.

The most common AEs experienced following 2 mg daily are diarrhea, rash, nausea, fatigue, vomiting, anemia, peripheral edema, abdominal pain, constipation, dermatitis acneiform, decreased appetite, pruritus, dyspnea, pyrexia, pneumonia, febrile neutropenia, AST increased, ALT increased, and dry skin.

Other clinically important adverse reactions observed in ≤10% of patients (n=329) treated with trametinib were: nervous system disorders (dizziness, dysgeusia), ocular disorders (blurred vision, dry eye), infections and infestations (folliculitis, rash pustular, cellulitis), cardiac disorders (bradycardia), gastrointestinal disorders (xerostomia), and musculoskeletal and connective tissue disorders (rhabdomyolysis).

APPENDIX L: NCI Correlative Imaging Studies

Patients at the NCI will be asked to sign a separate consent to allow collection and use of the standard-of-care images (CT or MRI) that qualified the patient for inclusion in this trial, along with the images taken during image-guided biopsy and any follow up imaging studies showing progression, to allow research into correlation of the image phenotypic features with genomic analyses. Research analysis of these images will only be done once the images have been de-identified; no research data generated from any image will be reported back to the patient, and no clinical decisions will be made based on research data generated from any image collected under this protocol.

To accomplish delinking, the NCI's secure GeneMed bioinformatics database will assign an imaging ID that, initially, will be coupled with the MPACT protocol ID in the GeneMed database. When a patient is off-study, GeneMed will provide the limited clinical information from that patient to the Cancer Imaging Archive (TCIA), linked through the imaging ID (not the patient protocol ID). GeneMed will assign a new ID that will trigger permanent recoding of the physical tissue, which will undergo whole exome sequencing. Following recoding, all samples and images will be completely unlinked from the clinical database.

Patient images will be de-identified of PHI at the CCR Molecular Imaging Program before leaving the NIH Clinical Center site and stored in an NIH policy compliant internet-accessible collection, The Cancer Imaging Archive (TCIA), with controlled access.

Images for TCIA are processed at the clinical site through a program developed by the Radiological Society of North America and NCI called the Clinical Trials Processor (CTP) [102]. Images are directly sent to the TCIA where they are sequestered pending, as needed, further QC/QA and appropriate sponsor access approvals.

The individual responsible for this process is Justin Kirby (kirbyju@mail.nih.gov).

The CTP is the primary means for uploading images into TCIA. CTP is a client-server software package with the server installed on a special intake system at TCIA. The CTP client, containing de-identification scripts customized for the trial site and specific trial data collection, will be installed in the Molecular Imaging Program in CCR.

The Digital Imaging and Communications in Medicine (DICOM) image is sequestered in TCIA pending review, QC/QA, and sponsor permission to link to genomic and limited clinical data after it has been delinked from the patient identifiable data.

The de-identification process follows the DICOM WG18 Supplement 142 standard. The following are examples of the changes made:

- Patient Names – Real patient names and initials are removed.
- Patient IDs - Institutionally created patient identifiers that can be traced back to individual patients are replaced with another unique identifier that cannot be traced back to the patient.
- Patient Demographics – Although patient date of birth is removed, patient age and gender are retained.

- Dates related to the examination – For a given collection/site, dates are offset by a fixed number of days, preserving time intervals between exams for each subject.
- Exam Identifiers – Codes assigned to exams and images are altered to prohibit the possibility of tracing an exam back to an institution and individual patient.

As part of the QC/QA process TCIA will also review submitted images for vendor specific DICOM tags. Vendor DICOM Conformance Statements are reviewed to learn which tags might contain PHI. These tags are reviewed and PHI removed if found.

APPENDIX M: Treatment Assignment Flow Chart