SUMMARY OF CHANGES – Protocol

To: CTEP Protocol and Information Office

From: [redacted], MD

Branch: Investigational Drug Branch, CTEP, DCTD, NCI

Date: 09/26/2019

Re: Review of Amendment #05 of Protocol #10147: "A Phase II Randomized Study of Topotecan/Carboplatin with or Without Veliparib in Advanced Myeloproliferative Disorders and Chronic Myelomonocytic Leukemia (CMML)"

I. Recommendations:

#	Section	Comments
1.	4.1	**Please delete the information within this subsection and replace with the following language, in accordance with the new protocol language template.** **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 at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr. RCR utilizes five person registration types. • IVR: MD, DO, or international equivalent, • NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD), • AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,), • Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and • Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
RCR requires the following registration documents:
<table>
<tr><th>Documentation Required</th><th>IVR</th><th>NPIVR</th><th>AP</th><th>A</th><th>AB</th></tr>
<tr><td>FDA Form 1572</td><td>✔</td><td>✔</td><td></td><td></td><td></td></tr>
<tr><td>Financial Disclosure Form</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
<tr><td>NCI Biosketch (education, training, employment, license, and certification)</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
<tr><td>GCP training</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
<tr><td>Agent Shipment Form (if applicable)</td><td>✔</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CV (optional)</td><td>✔</td><td>✔</td><td>✔</td><td></td><td></td></tr>
</table>
An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

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

PI Response: Information deleted and replaced.
</td></tr>
<tr><td>2.</td><td>4.2</td><td>
Please delete the information within this subsection and replace with the following language, in accordance with the new protocol language template.

1. 4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).
</td></tr>
</table>

#	Section	Comments
		IRB Approval Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878). ***For trials that will include sites using their local IRB or REB as well as for a trial with non-U.S.-based NCTN and NCORP sites, include the following paragraph and the three associated bullet points:*** Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes: • Local IRB documentation, • IRB-signed CTSU IRB Certification Form, and/or • Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form. In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record: • Holds an Active CTEP status, • Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster, • If using NCI CIRB, rostered on the NCI CIRB Signatory record, • Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and • Holds the appropriate CTEP registration type for the protocol. **Additional Requirements** Additional requirements to obtain an approved site registration status include: • An active Federalwide Assurance (FWA) number, • An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and • Compliance with all protocol-specific requirements (PSRs).

#	Section	Comments
		PI Response: Information deleted and replaced.

3.	4.2.1	**Please delete the information within this subsection and replace with the following language, in accordance with the new protocol language template.**
		
		Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.
		
		• Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
		• Click on *Protocols* in the upper left of your screen
		  o Enter the protocol number in the search field at the top of the protocol tree, or
		  o Click on the By Lead Organization folder to expand, then select LAO-MD017, and protocol number 10147,
		• Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)
		
		PI Response: Information deleted and replaced.

4.	4.2.2	**Please delete the information within this subsection and replace with the following language, in accordance with the new protocol language template.**
		
		4.2.2 Protocol Specific Requirements For 10147 Site Registration
		
		Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.
		
		• A Site initiation visit (SIV) is required for each participating site prior to activation. The local site PI must participate on the call as well as their research nurse, study coordinator, and pharmacist. To schedule a SIV, please email the Protocol Liaison and crocc@jhmi.edu and reference the protocol in the subject line of the email.
		• Specimen Tracking System Training Requirement:
		  o All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
		  o Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
		  o The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN

#	Section	Comments
		study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training. o This training will need to be completed before the first patient enrollment at a given site. o [redacted] and [redacted] are the main points of contact at Theradex for the training [redacted] and [redacted] Theradex phone: 609-799-7580). **PI Response: Information deleted and replaced.**
5.	4.2.3	**Please delete the information within this subsection and replace with the following language, in accordance with the new protocol language template.** 4.2.3 Submitting Regulatory Documents Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website. To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission. Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. **PI Response: Information deleted and replaced.**
6.	4.2.4	**Please delete the information within this subsection and replace with the following language, in accordance with the new protocol language template.** 4.2.4 Checking Site Registration Status You can verify your site's registration status on the members' side of the CTSU website. • Log on to the CTSU members' website • Click on *Regulatory* at the top of your screen • Click on *Site Registration* • Enter your 5-character CTEP Institution Code and click on Go Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol

#	Section	Comments
		requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks. **PI Response: Information deleted and replaced.**
7.	4.3.2, 4.3.3	**Please delete the information within these subsections and replace with the following language, in accordance with the new protocol language template.** 4.3.2 OPEN / IWRS The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave. Requirements for OPEN access: • A valid CTEP-IAM account. • To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. • If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site. • Have an approved site registration for a protocol prior to patient enrollment. To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL. Prior to accessing OPEN, site staff should verify the following: • Patient has met all eligibility criteria within the protocol stated timeframes, and • All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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		Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records. Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com. **PI Response: Information deleted and replaced.**
8.	4	**As 10147 has been identified as a specimen tracking study, please create the following subsection.** **Special Instructions for Patient Enrollment** This Study will use the ETCTN Specimen Tracking System (STS). • All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted. • The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository. • Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab. • **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS. **PI Response: Subsection added (4.3.5).**
9.	7	**As this study has a CTEP-held IND, CTEP-AERS integration will be used. Please insert the following subsection into section 7.** **Rave-CTEP-AERS Integration** The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

#	Section	Comments
		All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade. Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave: • The reporting period (course/cycle) is correct, and • AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success). The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation. Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave. Additional information about the CTEP-AERS integration is available on the CTSU website: • Study specific documents: Protocols > Documents > Education and Promotion, and

#	Section	Comments
		• Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides. NCI requirements for SAE reporting are available on the CTEP website: • NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf. **PI Response: Subsection added.**

10.	12.2	**Please delete the information within the "Data Reporting" subsection and replace with the following language, in accordance with the new protocol language template.**
		
		Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:
		
		• Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
		• Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
		  ○ To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
		  ○ To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
		  ○ To hold Rave Read Only role, site staff must hold an Associates (A) registration type.
		
		Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC*

#	Section	Comments
		link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name. Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com. **PI Response: Information deleted and replaced.**
11.	12.2.1	**Verify if 10147 will be using Central Monitoring, and add the following language if applicable.** Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (*i.e.*, source data verification). Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted. Additional information on the SDP is available on the CTSU members' website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com). **PI Response: Study is reviewed by CTMS (Clinical Trials Monitoring System).**

#	Section	Comments
12.	12	**Please add the following subsection to section 12.** **2. Data Quality Portal** The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP. To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules. Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality. **PI Response: Subsection added.**

II. Additional Changes

#	Section	Comments
1.	Title Page	Protocol version date updated to reflect current changes.
2.	Title Page	[redacted] added as Co-Investigator.
3.	Title Page	Principal Investigator information updated.
4.	N/A	Formatting and editorial changes were made throughout the protocol (e.g., page numbers)

(Please retain the section break below, so that the Title Page is page "1" of the document.)

NCI Protocol #: **10147**

Local Protocol #: ETCTN10147

ClinicalTrials.gov Identifier: NCT03289910

TITLE: NCI 10147: A Phase II randomized study of topotecan/carboplatin with or without veliparib in advanced myeloproliferative disorders and chronic myelomonocytic leukemia (CMML).

Corresponding Organization: **LAO-MD017** / JHU Sidney Kimmel Comprehensive Cancer Center LAO

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Participating Organizations

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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
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NCI-Supplied Agent(s): *Veliparib, NSC#737664*
Other Agent(s): Topotecan, NSC#609699, commercial; Carboplatin, NSC#241240, commercial

IND #: [redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:
Revision / Version #8.4 / 06/11/2018
Amendment / Version #9.0/ 08/03/2018
Amendment / Version #10.0 / 03/29/2019
Amendment / Version #11.0 / 04/22/2019
Amendment / Version #12.0 / 09/20/2019
Amendment / Version #13.0 / 10/24/2019

SCHEMA

We recently conducted a phase I study of Topotecan + Carboplatin administered by 5-day continuous IV infusion along with the PARP inhibitor veliparib in patients with acute leukemias, aggressive myeloproliferative neoplasms (MPNs) and chronic myelomonocytic leukemia (CMML). The response rate was 33% overall but was 64% for patients with antecedent or associated aggressive MPNs or CMML. Based on these results, we now propose a phase II study evaluating the efficacy of the addition of veliparib to topotecan and carboplatin in accelerated phase CMML and MPNs as well as both newly diagnosed and relapsed/refractory CMML- or MPN-related AML. Eligible patients would be randomized between ARM A (Topotecan 1.2 $mg/m^2/d$ + Carboplatin 150 $mg/m^2/d$ continuous IV infusion on days 3-7 plus veliparib 80 mg PO BID Day 1-21) vs ARM B (Topotecan 1.6 $mg/m^2/d$ + Carboplatin 150 $mg/m^2/d$ continuous IV infusion on days 1-5). In conjunction with the clinical trial, we aim to evaluate and validate biomarkers of response defined in our initial Phase I trial that may predict for response to the V/T/C combination.

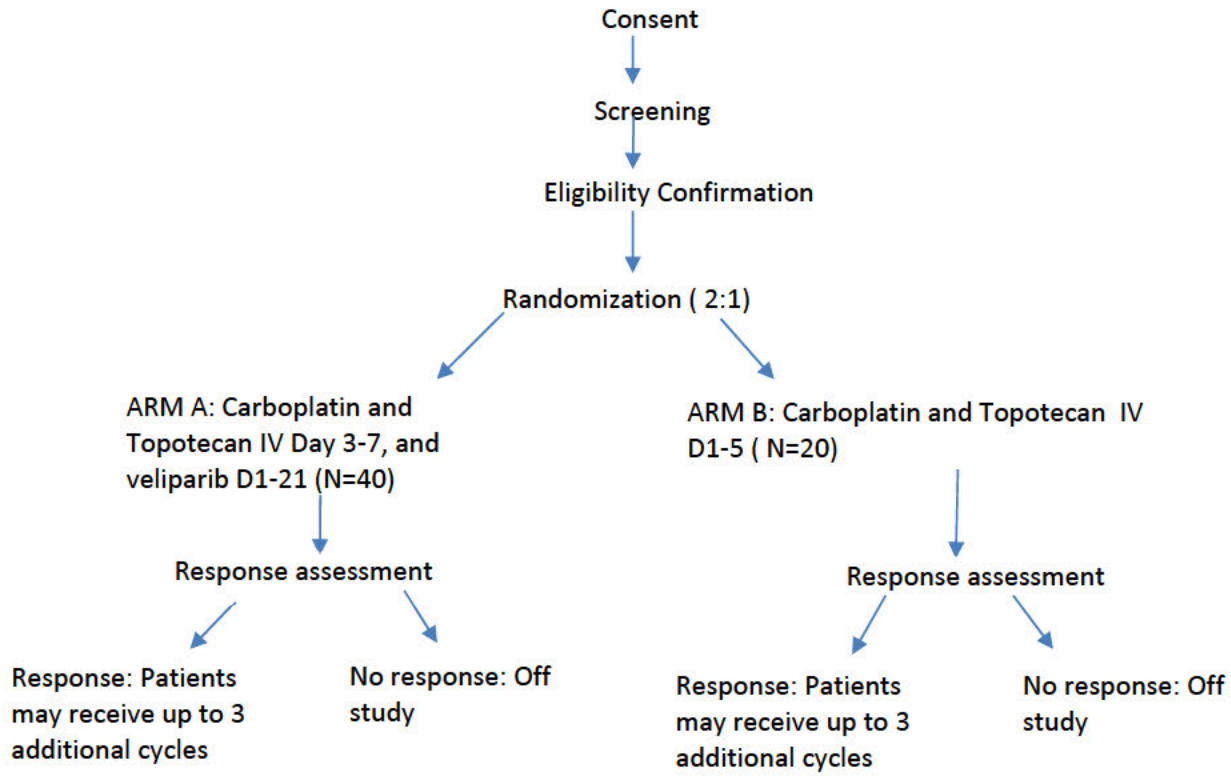

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

To estimate and compare the Complete Response/Complete Response with incomplete recovery (CR/CRi) rate of induction therapy with Topotecan/Carboplatin (T/C) with or without Veliparib (V) in myeloproliferative disorder associated leukemias and CMML.

1.2 Secondary Objectives

1. To evaluate and compare the toxicities of T/C/V vs. T/C
2. To compare the 2-year disease-free survival (DFS) and overall survival (OS) in response to T/C/V vs. T/C
3. To detect and compare the presence of minimal residual disease (MRD) remaining after T/C/V vs. T/C
4. Evaluate predictive biomarkers of response via assessment of pretreatment impaired homologous recombination via assessment of:
   a. NGS panel for genes mutated in myeloid malignancies done as standard of care per institution. The Johns Hopkins assay assesses mutations in ABL1, ASXL1, ATM, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CDKN2A, CEBPA, CSF3R, DNMT31, EP300, ERBB2, ETV6, EZH2, FLT3, GATA1, GATA2, GNAS, IDH1, IDH2, IKZF1, JAK2, KDM2B, KDM6A, KIT, KRAS, KMT2D, KMT2C, MPL, NF1, NLRP1, NOTCH1, NOTCH2, NPM1, NRAS, NSD1, NUP98, PDGFRA, PIK3CA, PHF6, PIGA, PTEN, PTPN11, RAD50, RECQL4, RUNX1, SETBP1, SF3BA, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1 and ZRSR2 genes.
   b. Functional impairment of DNA damage response via assessment of pretreatment samples for radiation-induced RAD51 foci.
   c. Topotecan-induced stabilization of topoisomerase I-DNA covalent complexes, which has recently been observed to be a critical predictor of response to combination of a topoisomerase I poison and PARP inhibitor in xenografts
5. To evaluate veliparib exposure and contribution to response (efficacy and toxicity)

2. BACKGROUND

2.1 *Myeloproliferative neoplasms and CMML*

Myeloproliferative neoplasms (MPNs) represent a heterogeneous group of clonal diseases with a common propensity to progress to acute leukemia.[1-4] Essential Thrombocythemia (ET), Polycythemia Vera (PV), and Primary Myelofibrosis (MF), as well as mixed myelodysplastic/myeloproliferative neoplasms such as Chronic Myelomonocytic Leukemia (CMML) are all clonal neoplasms derived from aberrant early hematopoietic precursors but have varied clinical manifestations. Upon progression, they are uniformly refractory to standard acute leukemia therapies, with median survival less than six months.

One common mutation in MPNs, an activating V617F point mutation in the tyrosine kinase JAK2, is found in greater than 80% of cases of PV,[5] 40% of cases of ET, and 30% of cases of MF,[6] *JAK2* mutation and overexpression have been associated with increased homologous recombination (HR) and genomic instability.[7-9] Other alterations conferring an MPN-like phenotype, such as *BCR/ABL* translocations in CML, *FIP1L1-PDGFR* rearrangements in eosinophilic leukemias, and *FLT3* mutations in acute myeloid leukemia, have also been associated with changes in the DNA repair pathways leading to increased genomic instability and drug resistance.[9,10] For example, even though early studies indicated that RAD51, a critical component of the homologous recombination (HR) pathway, is upregulated in *BCR/ABL*-positive CML cells,[11] subsequent studies demonstrated that repair in these cells is error-prone and leads to mutations and large deletions or insertions.[12] Further analysis traced this genomic instability to several changes, including (i) enhanced tyrosine phosphorylation of RAD51, leading to its aberrant function;[13] (ii) downregulation of BRCA1;[14] (iii) stimulation of single-strand annealing, an error-prone DNA repair pathway;[15] and (iv) other changes in the Fanconi anemia/BRCA pathway that can be reverted by ectopic BRCA1 expression.[16]

2.2 Veliparib (ABT-888)

Poly(ADP-ribose) polymerase (PARP) inhibitors are a class of antineoplastic agents being widely tested in solid tumors.[17-22] These agents target PARP1, PARP2, and PARP3, three enzymes that contribute to various aspects of DNA repair.[18,20,21,23-25] PARP inhibition not only diminishes base excision repair, but also impairs alternative end-joining[26] and accelerates nonhomologous end-joining.[27] In cells with diminished HR, these changes lead to error-prone DNA repair and cell death.[18,20,28] In addition, PARP inhibition leads to trapping of PARP1 on DNA, preventing access of downstream repair proteins to sites of DNA damage[29-31] and providing a potential mechanism for PARP inhibitor-induced killing in HR proficient cells that contain high levels of PARP1 protein. Importantly, chromosome 1q (including the *PARP1* locus at 1q42) is amplified in a subset of chronic phase MPNs and even more commonly in transformed MPNs,[32,33] providing a potential opportunity for PARP1 trapping even in MPNs without HR defects.

Veliparib (ABT-888) is an orally available, small molecule PARP inhibitor that enhances the cytotoxicity of diverse classes of DNA damaging agents, including ionizing radiation,

alkylating agents, platinating agents and topoisomerase I (topo I) poisons.[34-36] Studies in AML cell lines and clinical samples demonstrated that veliparib enhanced the antiproliferative and proapoptotic effects of topotecan *in vitro,* whereas no synergy was found with cytarabine or etoposide.[37] Further analysis indicated that the synergy resulted from trapping of PARP1 on the damaged DNA, thereby inhibiting repair downstream of topo I-DNA covalent complex stabilization.[37,38]

We previously compared the sensitivity of clinical isolates from several BCR/ABL-negative chronic myeloid neoplasms, including CMML, ET, PV and PMF, to normal controls using two different PARP inhibitors in colony forming assays *ex vivo*.[39] Results of this analysis demonstrated that myeloid progenitors from many patients with *JAK2* wildtype MPNs and CMML exhibit enhanced PARP inhibitor sensitivity, which is greatest in those with defective formation of RAD51 foci after DNA damage. These observations support the further study of PARP inhibitors, alone or in combination with other therapies, in certain MPNs and CMML.

2.3 Topotecan & Carboplatin

Topotecan and carboplatin induce synergistic cytotoxicity in acute leukemia cell lines and primary AML cells *in vitro*.[40] This observation was the basis for a phase I study of topotecan + carboplatin by five-day intravenous continuous infusion (IV CI) in adults with relapsed or refractory acute leukemia.[40] Oral and gastrointestinal (GI) mucositis were the dose limiting toxicities (DLTs) of this combination. Complete remissions (CRs) were observed at multiple dose levels, including 3 of 6 patients at the maximum tolerated dose (MTD) of topotecan 1.6 mg/m^2/day and carboplatin 150 mg/m^2/day simultaneously for 5 days.[40] A subsequent ECOG Phase II trial of topotecan/carboplatin at this MTD resulted in CRs in 5 of 35 (14%) patients with relapsed and refractory AML, a response rate similar to a mitoxantrone/etoposide/cytarabine- (MEC-) based arm in the same trial.[41] This Phase II trial of topotecan and carboplatin only studied the doses of 1.6 mg/m^2/day topotecan with 150 mg/m^2/day of carboplatin combination. In the phase I study of the combination, there were 21 evaluable patients in the doses below the 1.2 mg/m^2/150 mg/m^2 combination and responses in 3 of these patients (14%). In the dose levels above 1.2/150, there were 14 patients treated with 6 responses (43%). These data should be interpreted with caution, however, as these patients included a mixture of acute myeloid leukemia, acute lymphoid leukemia, myelodysplastic syndrome, and blast crisis CML. Of the 46 patients on this phase I study, only three had antecedent myeloproliferative disorders, which is the study population we are targeting with the present study. In the control ARM B we will use the recommended phase II dose of topotecan (1.6mg/m^2/day) in combination with carboplatin to maximize chemotherapeutic exposure in absence of veliparib.

2.4 Rationale

Building on recent demonstrations that veliparib enhances the antineoplastic effects of topotecan and carboplatin, we conducted a study evaluating veliparib incorporation into leukemia induction therapy using a backbone associated with significant DNA damage.[42] Using a standard 3+3 trial design, we dose-escalated veliparib in combination with topotecan + carboplatin in relapsed and refractory acute leukemias, aggressive myeloproliferative neoplasms (MPNs) and CMML. A total of 99 patients were treated with veliparib 10-100 mg orally twice daily on Days 1-8, 1-14 or 1-21 along with continuous infusion topotecan 1.0-1.2 mg/m^2/d +

carboplatin 120-150 mg/m^2/d on Days 3-7. The maximum tolerated dose was veliparib 80 mg twice daily with topotecan 1.2 mg/m^2/d + carboplatin 150 mg/m^2/d. Mucositis was dose limiting and correlated with higher veliparib exposure. The duration of veliparib administration was 8 days during the dose escalation. Veliparib dosing was extended in two MPN/CMML cohorts to 14 and 21 day durations after completion of the topotecan/carboplatin infusion to take advantage of the PARP inhibitor sensitivity and defective DNA repair inherent in some CMML and MPN cells. Veliparib systemic exposure in plasma positively correlated with bone marrow supernatant but not blasts.[43] Overall response rate was 33% (33/99), with 14 CR, 11 CRi, and 8 PR. Patients with antecedent or associated MPNs or CMML had an overall response rate of 64% (14/22). The median survival for patients with antecedent or associated MPN or CMML was 13.3 months vs 5.1 months for those without antecedent myeloid neoplasms. The one-year relapse free survival for MPN and CMML patients was 41% vs 12 % for those without prior MPNs or CMML. Leukemias with baseline DNA repair defects, as evidenced by impaired DNA damage-induced FANCD2 monoubiquitination, had modestly better survival. A single 80 mg dose of veliparib, as well as veliparib in combination with topotecan + carboplatin, induced DNA damage as manifested by histone H2AX phosphorylation in CD34$^+$ leukemia cells, with greater damage being detected in cells from responders. Utilizing the data from the Phase I trial, an exposure-response analysis was performed. [43] Despite shallow exposure-efficacy relationship, doses lower than 80 mg do not exceed veliparib single agent preclinical IC50. Shallow exposure-mucositis relationship also supports the 80 mg dose. Based on benefit/risk assessment, veliparib at a dose of 80 mg BID for at least 14 days in combination with topotecan plus carboplatin is recommended to be studied in patients with advanced MPNs or CMML.

We now propose a phase II study evaluating the efficacy of the addition of veliparib to topotecan and carboplatin in accelerated phase CMML and MPNs[44] as well as both newly diagnosed and relapsed/refractory CMML- or MPN-related AML. Eligible patients would be randomized between ARM A (Topotecan 1.2 mg/m^2/d + Carboplatin 150 mg/m^2/d IV on days 3-7 plus veliparib 80 mg PO BID Day 1-21) vs ARM B (Topotecan 1.6 mg/m^2/d + Carboplatin 150 mg/m^2/d IV on days 1-5). In conjunction with the clinical trial, we aim to evaluate and validate potential biomarkers of response defined in our initial Phase I trial or subsequently identified that may predict for response to the T/C/V combination. The dosing of topotecan in ARM B (1.6 mg/m^2/day) chosen for study is the recommended phase II dose of topotecan when given in combination with carboplatin for acute leukemia.

2.5 Correlative Studies Background

2.5.1. Leukemia Mutation Panel

Molecular analysis of AMLs, MPNs and CMML has revealed a broad array of mutations contained in the malignant clone. Characterization of specific mutations associated with MPN- and CMML-associated acute leukemia in the context of response to therapy has the potential to allow for patient specific therapies with improved efficacy. We intend to use a standard leukemia mutation panel (MDL JHH) to examine the molecular features of the leukemias treated on this study and examine for response predictors in the post-trial analysis.

2.5.2. RAD51 Focus forming assay

An impaired DNA damage response, as evidenced by lack of development of RAD51 foci in response to ionizing radiation, was observed in ~40% of MPN samples assayed (**Figure 1**).[39] This observation suggests that the HR pathway is impaired in those samples. These results are consistent with prior observations of extensive chromosomal and subchromosomal copy number changes in MPN,[33,45] which are another hallmark of HR deficiency.[46] Because formation of RAD51 foci only provides an assessment of HR pathway integrity upstream of RAD51 and is unaffected by changes downstream, e.g., loss of RAD51C,[47] it is important to emphasize that the results in Figure 1 might underestimate the true frequency of HR repair defects in MPNs.

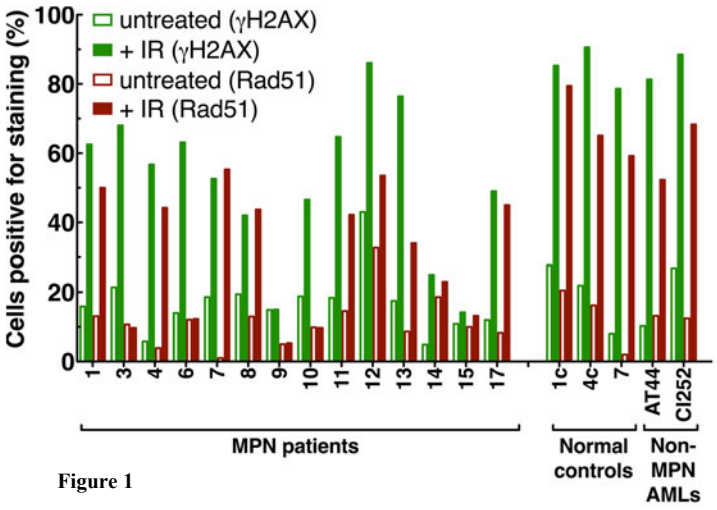

Figure 1

The causes of this HR pathway dysfunction in MPNs are incompletely understood at present. Some of the samples with impaired RAD51 foci formation also exhibited diminished formation of H2AX foci (**Fig. 1**). Because H2AX phosphorylation after double strand breaks typically reflects activation of ATM and phosphorylation of its substrate MDC1,[48] diminished formation of both phospho-H2AX and RAD51 foci might reflect a defect in ATM or its activation as described in other neoplasms. Other samples formed phospho-H2AX foci but nonetheless failed to form RAD51 foci, suggesting one or more defects between these two events in the DNA damage response. Consistent with this heterogeneity, we have previously examined 144 cases of MPN via SNP arrays and found that 26% have heterozygous deletions in genes encoding one or more DNA repair pathway proteins such as *BRCA2*, *ATM*, *FANCC* or *FANCL*.[49] Because the other copy remains intact, however, it is unclear whether these heterozyogous deletions cause sufficient changes in protein expression to impact the HR pathway. Accordingly, we have examined a subset of MPN samples for methylation changes in FANC proteins, *ATM*, and *BRCA2* but did not observe frequent changes in methylation that would confer increased genomic instability.[39] *BRCA1* promoter methylation was found in a 6 of 27 samples analyzed but also was not associated with increased sensitivity to PARP inhibition *ex vivo*.[39] Given the apparent relationship between impaired formation of radiation-induced RAD51 foci and PARP inhibitor sensitivity in MPNs and CMML *ex vivo*, we propose to examine this assay as a potential predictor of sensitivity to the T/C/V and T/C arms.

2.5.3. Stabilization of topoisomerase (topo) I-DNA covalent complexes

The first step in the action of topo I poisons is stabilization of topo I-DNA covalent complexes. We have recently raised a monoclonal antibody that specifically detects these covalent topo I-DNA complexes.[50] This reagent has confirmed that topo I-DNA covalent complexes are stabilized by platinum agents as well as topotecan. Subsequent studies have demonstrated that staining with this antibody, which can detect covalent topo I-DNA complexes in tumor cells[50]

and normal tissues[51] *in situ*, discriminates between BRCA wildtype patient-derived xenografts that are sensitive vs. resistant to a topo I poison/PARP inhibitor combination ([redacted] ms. in preparation). These observations provide the impetus for assessing Topotecan-stabilized topo I-DNA covalent complexes in the context of the present trial.

2.5.4 Whole Exome sequencing

Examination of genomic aberrations outside known leukemia mutations may identify somatic genetic mutations conferring sensitivity to PARP targeted therapy. In order to examine both somatic and germline samples, pre-treatment tumor samples along with peripheral blood for t-cell specific germline DNA will be collected and analyzed as part of the ETCTN-DNA-RNA tissue procurement protocol.

3. PATIENT SELECTION

3.1 Pre-Registration Eligibility Criteria

3.1.1 Patient has or suspected to have one of the following:
-Newly diagnosed Acute Myeloid Leukemia (AML) associated with antecedent myeloproliferative disorder (Polycythermia Vera, Essential Thrombocythemia, Myelofibrosis, atypical Chronic Myeloid Leukemia, Chronic Myelomonocytic Leukemia and related undifferentiated myeloproliferative/myelodysplastic disorders)

-Relapsed/refractory AML associated with antecedent myeloproliferative disorder (Polycythermia Vera, Essential Thrombocythemia, Myelofibrosis, atypical Chronic Myeloid Leukemia , Chronic Myelomonocytic Leukemia and related undifferentiated myeloproliferative/myelodysplastic disorders) who have received two or fewer prior induction chemotherapy courses

-Accelerated phase myeloproliferative disorders per Zeider et al[44] with two or fewer prior therapies.

- For aggressive phase MPD (P. Vera, essential thrombocythemia, Ph-negative chronic myelogenous leukemia), one or more of the following criteria must be met: marrow blasts >5%, peripheral blood blasts plus progranulocytes > 10%, new onset or increasing myelofibrosis, new onset or > 25% increase in hepatomegaly or splenomegaly, new onset constitutional symptoms (fever, weight loss, spleni pain, bone pain). Zeider et al44
- For Chronic Myelomonocytic Leukemia (CMML), the following criteria must be met: 5-19% bone marrow blasts (aggressive) or $\geq$ 20% marrow blasts (transformation).

3.1.2 Bone marrow and/or peripheral blood specimens will be submitted for correlative studies as outlined in Section 9. Patients with a dry tap will still be eligible.

3.2 Randomization Eligibility Criteria

3.2.1 Bone marrow aspirate and/or peripheral blood specimens were submitted to the central lab and site has confirmation by the local institution that the patient meets one of the criteria specified in 3.1.1 above.

3.2.2 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of veliparib in combination with topotecan and carboplatin in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.2.3 ECOG performance status ≤2 or Karnofsky ≥60% (see Appendix A).

3.2.4 Patients must have normal organ function as defined below:

– Total bilirubin	less than 2.0 mg/dL unless due to Gilbert's Syndrome, then less than 5.0 mg/dL
– AST(SGOT)/ALT(SGPT)	less than 5 × institutional upper limit of normal
– Creatinine Clearance	GFR greater than 30 ml/min per modified Cockcroft-Gault formula

3.2.5 Interval of greater than 4 weeks since allogeneic blood or marrow transplantation (BMT) if performed; and absence of active GVHD

3.2.6 The effects of veliparib on the developing human fetus are unknown. For this reason and because PARP inhibiting agents as well as topoisomerase inhibitors and platinating agents are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months following the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of veliparib administration.

3.2.7 Ability to understand and the willingness to sign a written informed consent document.

3.3 Exclusion Criteria

3.3.1 Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study with the exception of hydroxyurea for cytoreduction. Therapy with tyrosine kinase inhibitors (TKIs) directed against JAK2, BCR-ABL or FLT3 will be allowed to be continued until 24 hours prior to start of therapy on trial.

3.3.2 Patients with active uncontrolled infection. Antibiotic therapy for fevers, and continuation of treatment of prior infection are allowed.

3.3.3 Patients who have active CNS disease are excluded. Patients with known active CNS leukemia should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.3.4 Patients who are receiving any other investigational agents. Patients who have completed therapy with an investigational agent should be off this therapy for at least 5 half-lives or two weeks, whichever is shorter.

3.3.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to veliparib, topotecan or carboplatin.

3.3.6 Uncontrolled intercurrent illness including, but not limited to, active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3.7 Pregnant women are excluded from this study because veliparib is PARP inhibiting agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with veliparib, breastfeeding should be discontinued if the mother is treated with veliparib. These potential risks may also apply to topotecan and carboplatin used in this study.

3.3.8 HIV-Patients positive patients are not excluded if they have CD4+ cells $\geq$ 250/mm3 and negligible viral load and are on a stable combination antiretroviral therapy.

3.2.9 History of uncontrolled seizure disorder, including focal or generalized seizure within the past year

3.4 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

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 at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

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

4.2 Site Registration

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

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

For trials that will include sites using their local IRB or REB as well as for a trial with non-U.S.-based NCTN and NCORP sites, include the following paragraph and the three associated bullet points:

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation,
- IRB-signed CTSU IRB Certification Form, and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol PI (*i.e*., the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-MD017, and protocol number 10147,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Requirements For NCI protocol #10147 Site Registration:

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

- A Site initiation visit (SIV) is required for each participating site prior to activation. The local site PI must participate on the call as well as their research nurse, study coordinator,

and pharmacist. To schedule a SIV, please email the Protocol Liaison and crocc@jhmi.edu and reference the protocol in the subject line of the email.

- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
  - This training will need to be completed before the first patient enrollment at a given site.
  - [redacted] and [redacted] are the main points of contact at Theradex for the training [redacted] and [redacted], Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

4.2.4 Checking **Site** Registration Status

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

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. 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.

4.3 Patient Registration

4.3.1 Pre-Registration Procedures

In order to submit the baseline bone marrow aspirate and biopsy and peripheral blood samples, the patient must be pre-registered and assigned a subject ID. The following should be confirmed by the site prior to pre-registering the patient:

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Correlative Studies:** bone marrow and/or peripheral blood will be submitted for correlative studies for all patients pre-registered to this study. Note: If the procedure is a dry tap, the patient is still eligible. The peripheral blood must be submitted.

4.3.2 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

4.3.3 OPEN/IWRS User Requirements

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

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

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.4 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: 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 at 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.3.5 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *3* days.* 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.
*[*Note: For leukemia protocols, treatment should be started as rapidly as possible.]*

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an inpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Patient's adherence to oral therapy will be documented through hospital charting.

Arm A : Veliparib 80 mg by mouth twice daily days 1-21. Topotecan 1.2 mg/m^2/d and Carboplatin 150 mg/m^2/day continuous intravenous infusion (CIV) over 5 days for a total of 120 continuous hours on days 3-7.

Arm B : Topotecan 1.6 mg/m^2/d and Carboplatin 150 mg/m^2/day continuous intravenous infusion (CIV) over 5 days for a total of 120 continuous hours on days 1-5.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Topotecan	Premedicate with minimum of ondansetron 8 mg IV twice daily	ARM A: 1.2 mg/m^2/day in 250 mL D5W ARM B: 1.6 mg/m^2/day in 250 mL D5W	IV as **continuous infusion** over 24 hours for 5 days	Days 3-7***(ARM A) or Days 1-5***(ARM B)	28 days: if responding, second cycle can be administered as early as day 28 but no later than day 63. Responding patients may receive up to 3 more cycles (4 total) (see **Section 6.1**)
Carboplatin		150 mg/m^2/day in 250 cc D5W	IV as **continuous infusion** over 24 hours for 5 days	Days 3-7*** (ARM A) or Days 1-5***(ARM B)	
Veliparib**		80 mg	PO twice daily	Days 1-21 (ARM A)	
Randomized administration. ****Begins at the start of Day 3 or 1 and runs for 5 days continuously, i.e., through the end of Day 7 or 5*					

5.1.1 **Veliparib**

Because there is a potential for interaction of Veliparib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Veliparib is not known to be a potent inhibitor of the major human CYPs *in vitro*, indicating a low risk for drug-drug interactions at the proposed dosing concentrations.

5.1.2 **Topotecan and Carboplatin**

Carboplatin and Topotecan each have 24 hour stability information described in literature(carboplatin)[52] or package insert (Topotecan). Additionally, Topotecan and Carboplatin were tested in a Simulated Y-site administration using glass vials for a study period of 4 hours. The volume past the Y site is about 5 mL and at the current rate (500 mL over 24 hrs = 21 mL/hr), the drugs will only be in the line together for ~ 15 minutes. This is much less than the 4 hour study period and the agents should be stable through this period.[53] No special premedications are required for these agents except for anti-emetics described in section 5.1 & 5.1.2. Topotecan is a mild irritant, and subjects will be monitored closely for extravasation during administration.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Antiemetics

Antiemetics will be used according to standard practices with a minimum of ondansetron 8 mg IV (or equivalent) twice daily starting prior to topotecan/carboplatin through completion of topotecan and carboplatin.

5.2.2 Hyperuricemia prophylaxis

To prevent the occurrence and complications of tumor lysis-induced hyperuricemia, all patients without known allergy will receive Allopurinol 300 mg daily orally 24 hours prior to beginning veliparib and continuing through the period of maximal tumor lysis (at least through Day 8).

5.2.3 Hyperphosphatemia prophylaxis

For individuals at risk for tumor lysis-induced hyperphosphatemia, sevelamer carbonate 800 mg with each meal (or institutional standard) orally day 1-8 can be instituted on admission and continued as tolerated until maximum tumor lysis has abated.

5.2.4 Menstrual suppression

To achieve menstrual suppression please follow institutional standard practices.

As noted in Section 3.2, women who are pregnant or lactating will not be eligible for this trial, as

the antiproliferative activities of the experimental combination therapy may be harmful to the developing fetus or the nursing infant.

5.2.5 Antibiotic Prophylaxis

Patients will receive prophylaxis directed against gram-negative gastrointestinal infections (GI), candidiasis, and/or herpes simplex virus (HSV), according to individual institutional practices. With regard to GI prophylaxis to prevent local and disseminated aerobic gram-negative infections, the use of moxifloxacin 400 mg by mouth daily (or other quinolone) will begin Day 1 of therapy and continue for the entire duration of profound neutropenia (unless parenteral quinolones are administered). Due to the high risk of typhlitis, prophylaxis with metronidazole 500 mg PO TID should begin day 1, and continue through day 14. In the event of patient allergy or hypersensitivity, institutional standards for antibacterial prophylaxis should be followed. HSV prophylaxis with Acyclovir or Valacyclovir will begin on Day 1 and will continue until absolute neutrophil count exceeds 100/mm^3. Prophylaxis against candidal infections (e.g. posaconazole 300 mg po daily) may be instituted according to institutional practices.

5.2.6 Prevention of perianal mucositis

All patients will receive daily bulk laxatives (e.g., psyllium) and a stool softener (e.g., docusate sodium) unless diarrhea is present, in order to prevent straining at stool and the possibility of perirectal tears.

5.2.7 Need to capture all concurrent medications on case report forms

Because there is a potential for interaction of Veliparib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

5.2.8 Seizure risk.

Seizures with veliparib were seen in some animal toxicology studies, although at doses much higher than those anticipated for this study. Seizures in animals were successfully treated with lorazepam.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 4 cycles (total) or until one of the following criteria applies:

- Failure to meet response criteria of CR, CRi, PR or MR as defined by protocol
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.4 Duration of Follow Up

Patients will be followed for ***minimum*** *of 30 days, or longer* after removal from protocol treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dosing Delays

Once a cycle is started, prescribed therapy will not be delayed. Patients unable to take veliparib due to toxicity will have those doses skipped.

For patients achieving CR, CRi, PR, or MR following cycle 1, a repeat cycle of the same regimen may be administered beginning no sooner than Day 28 of the preceding cycle and no later than Day 63 from the initiation of the previous cycle (**see Section 5.1)**. Delays beyond day 63 should be reviewed with the principal investigator and may be approved if patient is deemed be achieving clinical benefit.

6.2 Veliparib Dose Reductions

Veliparib dose will not be adjusted due to end organ dysfunction.

6.3 Topotecan and Carboplatin Dose Reductions

Topotecan should dose-reduced for decreases in creatinine clearance (CrCl) using modified Cockgroft-Gault formula as follows:

CrCl >40 ml/min: no reduction
CrCl 20-39 ml/min: 50% reduction
CrCl <20 ml/min: topotecan will not be given

Carboplatin should be dose-reduced for decreases in CrCl as follows:

CrCl 40-59 ml/min: 30% reduction (give 70% original dose)
CrCl 16-39 ml/min: 45% reduction (give 55% original dose)
CrCl $\leq$ 15 ml/min: carboplatin will not be given.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

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.
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.

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for Veliparib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
ABT-888 (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.

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)***
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: ABT-888 (Veliparib) 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.

7.1.2 Adverse Event List(s) for **Topotecan and Carboplatin**

Please refer to appropriate package inserts for the comprehensive list of adverse events for each agent.

Topotecan: Myelosuppression, fatigue, nausea, vomiting, oral/colonic/perianal mucositis, abdominal pain, anorexia, constipation or diarrhea, alopecia, fever.

Carboplatin: Myelosuppression, nausea, vomiting, rash, transaminitis, nephrotoxicity (mainly when given with other potential nephrotoxins), electrolyte wasting, peripheral neuropathy (rare).

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 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **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 Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if

applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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.
A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

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:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via 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:

- "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.
- "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

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Anemia	Anemia	Any	No
Leukopenia	White blood cell decreased	Any	No
Neutropenia	Neutrophil count decreased	Any	No
Neutropenic fever	Febrile neutropenia with or without hospitalization	Any	No
Infection	Infection with Grade 3 or 4 neutrophils with or without hospitalization	Any	No
Thrombocytopenia	Platelet count decreased	Any	No
Mucositis	Mucositis oral/esophagitis	Any	No

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

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 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 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 expeditiously via CTEP-AERS. Options are available to describe the event:

- Treatment-related secondary malignancy

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

Reports of secondary malignancy will be reported within 30 days in RAVE and will include a pathology report and staging information if available.

7.7 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 AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Veliparib NSC 737664, ABT-888, IND #TBD)

Chemical Name: 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide

Other Names: A-861695.0, ABT-888

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

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

Approximate Solubility: ABT-888 (veliparib) is freely soluble at pH < 6.9, soluble at pH 6.9 to 7.1, and slightly soluble at pH > 7.1.

Description: light orange opaque capsule with two black bands

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, cisplatin, carboplatin, cyclophosphamide, irinotecan, topotecan or radiation therapy.

Storage: Store intact bottles between 15^0 and 25^0 C (59^0 to 77^0 F).

Stability: Shelf-life stability studies for veliparib capsules are on-going.

Route(s) **of Administration:** Oral. Veliparib capsules may be administered without regard to meals.

Drug Interactions: Nonclinical studies suggest ABT-888 (veliparib) is a substrate of P-gp, OCT2, and MATE1/MATE2K transporters. Co-administration of ABT-888 (veliparib) with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K drugs may result in a decrease of ABT-888 (veliparib) renal clearance and an increase in ABT-888 (veliparib) plasma concentration. Therefore, use caution when administering ABT-888 (veliparib) with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K drugs. At high dose (e.g., 400 mg BID), ABT-888 (veliparib) may inhibit OCT1 in the liver and MATE1/MATE2K in the kidney.

ABT-888 (veliparib) is not a potent inhibitor of the major human CYPs and does not significantly induce activities of major human CYP isoforms, suggesting a negligible potential for CYP-mediated drug-drug interactions as a perpetrator at the anticipated therapeutic concentrations.

In human, ABT-888 (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. Drug-associated with kidney toxicities or kidney diseases could change ABT-888 (veliparib) pharmacokinetics. Use cautions when concomitantly administer oxalipaltin, carboplatin, cisplatin, and topotecan in patients with pre-existing renal impairment.

Pharmacokinetics
Absorption: The absorption of veliparib after oral dosing was relatively rapid, with average time to maximum observed plasma concentration (Tmax) ranging from 1 to 2 hours across dose levels. The maximum observed plasma concentration (Cmax) and the area under the plasma concentration curve from time zero to infinity (AUC∞) of veliparib were approximately dose-proportional across the dose range studied, with minimal accumulation following BID dosing. Available data, while not definitive, shows an absence of significant food effect.

Distribution: The apparent volume of distribution (V/D) of veliparib was large, and oral clearance was rapid.

Metabolism: Results from in vitro analysis reveal that this agent is metabolized by multiple isoenzymes – CYP1A1, 2D6, 2C19 and 3A4. Veliparib has one major metabolite in plasma, M8, a lactam derivative of the parent drug. The cellular PARP-inhibitory activity of M8 is 18-fold lower than veliparib.

Excretion: The average terminal half-life (t½) of veliparib ranged from 4 to 5 hours across dose levels. Recovery of the dose as parent drug in the urine over 24 hours after dosing averaged 78% (N = 6). Following multiple oral doses given twice daily, total recovery of the dose in the urine (as both parent drug and M8 metabolite) over 12 hours averaged 86% (N = 34). Veliparib is primarily cleared in the urine as intact parent drug along with metabolites, suggesting that renal function plays an important role in the clearance of veliparib 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.

How Supplied: Veliparib (NSC 737664) will be provided free of charge by AbbVie Inc. and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Veliparib 40 mg will be supplied as immediate release capsules in bottles containing 16 capsules or 64 capsules. The veliparib capsule contains veliparib, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5.

ABT-888 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).

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact the PMB via e-mail at PMBAfterHours@mail.nih.gov.

8.1.2 Agent Orders

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.

8.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents 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 and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 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/index.jsp
- CTEP Associate Registration and 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)

8.2 *Commercial agent:* Topotecan hydrochloride (Hycamptin)

Product Description: Topotecan hydrochloride is commercially available in vials containing 4 mg sterile lyophilized powder (pH adjusted to 3), 60 mg mannitol and 25 mg tartaric acid for reconstitution in sterile water, and is stable at room temperature.

Solution Preparation: Lyophilized Topotecan powder is reconstituted in 5% Dextrose Injection USP. Since the powder does not contain any preservatives, reconstituted drug should be used immediately and should be discarded 24 hours after reconstitution. Please refer to the commercial package insert for complete prescribing and safety information.

Administration: Carboplatin and Topotecan have 24 hour stability information described in literature(carboplatin)[52] or package insert (Topotecan) after dilution into PVC bags. Additionally, Topotecan and Carboplatin were tested in a Simulated Y-site administration using glass vials for a study period of 4 hours. The volume past the Y site is about 5 mL and at the current rate (500 mL over 24 hrs = 21 mL/hr), the drugs will only be in the line together for ~ 15 minutes. This is much less than the 4 hour study period and the agents should be stable together. [53] Topotecan and carboplatin will not be mixed together, but the IV solutions can be administered via a Y-site IV line.

Agent Ordering: Topotecan hydrochloride is commercially available and will not be provided by the study.

8.3 *Commercial agent:* Carboplatin

Product Description: Carboplatin (CBDCZ, Paraplatin) is a second generation tetravalent organic platinum compound that is commercially available in vials of 50, 150 and 450 mg. Intact vials are stored at room temperature protected from light.

Solution Preparation: Carboplatin is reconstituted in sterile water or 5% dextrose to yield a concentration of 10 mg/ml. Reconstituted solution is stable for at least 24 hrs. Please refer to the commercial package insert for complete prescribing and safety information.

Administration: Carboplatin and Topotecan each have 24 hour stability information described in literature(carboplatin)[52] or package insert (Topotecan) after dilution into PVC bags. Additionally, Topotecan and Carboplatin were tested in a Simulated Y-site administration using glass vials for a study period of 4 hours. The volume past the Y site is about 5 mL and at the current rate (500 mL over 24 hrs = 21 mL/hr), the drugs will only be in the line together for ~ 15 minutes. This is much less than the 4 hour study period and the agents should be stable together.[53] Topotecan and carboplatin will not be mixed together, but the IV solutions can be administered via a Y-site IV line.

Agent Ordering: Carboplatin is commercially available and will not be provided by the study.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies –

The present study contains the following laboratory correlative studies:

- Limited pharmacokinetic sampling for veliparib exposure (Section 9.2) – integrated biomarker
- Leukemia mutation panel to provide molecular diagnostic information (Section 9.3.1) – exploratory biomarker
- Rad51 focus formation assay in pretreatment marrow samples to assess homologous recombination pathway integrity (Section 9.3.2) – exploratory biomarker
- Assay for topotecan-induced topoisomerase I-DNA covalent complexes (Section 9.3.3) – exploratory biomarker
- Whole exome sequencing (Section 9.3.4) – exploratory biomarker

#	Correlative Assay	Timepoint	Sample information
Integrated 1	Pharmacokinetic assessments (Blood)	Pre-treatment: Day 1, Day 8, Day 15, Day 22 (~24 hrs post last dose) (ARM A only)	6 mL peripheral blood in a 6 mL green top heparin tube
Integrated 2	Pharmacokinetic assessments (Bone marrow)	Pre-Registration (All Pts) and Pre-treatment Day 14 (Arm A only)	7 mL bone marrow aspirate in a 10 mL green top heparin tube
Exploratory 1	Leukemia Mutation Panel	Pre-treatment bone marrow aspirate	3 mL bone marrow aspirate in lavender EDTA vial
Exploratory 2	Rad 51 Focus Formation Assay	Pre-treatment bone marrow aspirate	6-8 mL total bone marrow aspirate in two 4 ml green top heparin tube
Exploratory 3	Assay for Topotecan-induced Topo I-DNA complexes	i) Pre-treatment peripheral blood, ii) peripheral blood immediate-ly before start of topotecan/ carboplatin infusion; and iii) peripheral blood 72 ± 24 into topotecan/carboplatin infusion	5 mL peripheral blood in a 6 mL lavender top EDTA tube
Exploratory 4	Whole exome sequencing	Pre-treatment peripheral blood	3 mL peripheral blood in a 3 mL lavender EDTA vial
Exploratory 5	Analysis of 5-mC and 5-h-mC	Pre-treatment peripheral blood	5 mL peripheral blood in a 6 mL lavender

			EDTA tube
Exploratory 6	Sample of ChIPseq	Pre-treatment peripheral blood	7 mL peripheral blood in a 10 mL lavender EDTA tube

9.2 Integrated Correlative Studies

9.2.1.1 **Veliparib exposure– – Integrated Laboratory Correlative Study #1** (ARM A only)

Collection of Specimen(s): ARM A patients will have ~6 ml samples of blood collected in tubes containing heparin as an anticoagulant (green top; i.e., Becton Dickinson Catalog # 367878 or 367866, Franklin Lakes, NJ) at the time points specified below:

Plasma
C1D1: Pre-treatment
C1D8: Pre-treatment
C1D15: Pre-treatment
C1D22: ~24 hours after the last dose

- Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.
- Fill-up the tubes as much as possible until blood flow stops.
- GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis.
- Place samples immediately **on ice** after collection; samples must be processed **within 30 minutes**.

9.2.1.2 Handling of Specimens(s)

Processing instructions

1. Invert sample 8-10 times and immediately place on ice.
2. Within 30 minutes of collection, invert sample 8 times and centrifuge at 3000 rpm for 10 minutes at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
3. Carefully remove tube from centrifuge.
4. Using a pipette, transfer equal aliquots of plasma into 2-3 labeled 2 mL cryovials, not exceeding 1.5 mL per cryovial.
5. Label samples as Veliparib Plasma PK, including protocol number (NCI-10147), unique patient ID assigned at registration, initials, date of collection, draw time, time point, and protocol time point.
6. Store plasma samples at -70ºC or below until shipment or transfer to Johns Hopkins.

9.2.1.3 Shipping of Specimen(s)

Specimens should be stored through the end of Cycle 1 of T/C/V and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has >1 participant on-study). A participant's samples should be shipped to the APC lab within 6 months of the last sample's collection date. (i.e., if C1D18 sample is collected on 1/1/2018, all of that participant's samples should be at the APC lab by 7/1/2018). The APC lab may contact the study team to request shipment off-schedule.

Please ship 1-2 aliquots to the APC laboratory. Once receipt is confirmed, the back-up aliquot may be shipped. The back-up can be shipped later. For Johns Hopkins samples, the normal SOPs should be followed for specimen transfer.

Preparing the shipment
*Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH).
*Please organize the samples by Patient and Time point in the box.
*Do not store in plastic bags (they break on dry-ice and labels will detach).
*A copy of each of the pharmacokinetic sample collection forms, available on the CTSU website, for the respective patients is to be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet.
*Note the study number, PI, and the drugs used/to be measured.
*A name, phone number and email address should be included with samples so that receipt can be acknowledged.
*Please notify the lab by telephone (410-502-7192 or 410-955-1129) or fax (410-502-0895) at least 24 hours prior to shipment.

Shipping
*Samples collected at Johns Hopkins University can be transferred utilizing the current SOPs.
*All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state.
*Overnight shipments should occur on Monday through Wednesday (Tuesday is the preferred day) except when the following day is a holiday.

Analytical Pharmacology Core Laboratory*
Attn: NCI10147 Veliparib/T/C Study Samples
1650 Orleans St. CRB1 Rm 184
Baltimore, MD 21231-1000**
Phone: 410-502-7192 or 410-955-1129
Fax: 410-502-0895

**This zip code is for FedEx shipments. If UPS will be utilized, please ship to the following zip code: 21287

Site(s) Performing Correlative Study Sidney Kimmel Cancer Center at Johns Hopkins, Analytical Pharmacology Core

9.2.2.1 **Veliparib exposure–** – Integrated Laboratory Correlative Study #2 (ARM A only) Collection of Specimen(s): ARM A patients will have 7 ml samples of bone marrow (or peripheral blood in an inaspirable bone marrow patient) collected in tubes containing heparin as an anticoagulant (green top) at the time points specified below:

Bone marrow
C1 Pretreatment: Pre-treatment (SOC)
C1D14: Pre-treatment

- Obtain Bone marrow samples at time of day 14 bone marrow assessment.
- Place samples immediately **on ice** after collection; samples must be processed **within 30 minutes**.

9.2.2.2 Handling of Specimens(s)

Processing instructions

1. Invert sample 8-10 times and immediately place on ice.
2. Within 30 minutes of collection, centrifuge at 1000xg for 10 minutes at 4ºC in a refrigerated centrifuge.
3. Without disturbing the buffy cell layer, make three 1mL aliquots of plasma using 2mL cryovials labeled as VELIPARIB PK BMA - PLASMA. **IF PERIPHERAL BLOOD WAS PROCESSED - label cryovials as VELIPARIB PK DRY TAP (PB)-PLASMA**
4. Transfer the entire remaining content (cell layers) from the NaHep tube into a new 50mL conical tube and dilute with 10mL RPMI 1640.
5. Prepare a 50mL conical tube with 15mL Ficoll. Overlay Ficoll with the diluted cells from step 3.
6. Centrifuge at 600xg for 5 minutes at 4 degrees C, NO BREAK (if proper separation has not occured, centrifuge again for 15 minutes at 600xg at 4 degrees C, NO BREAK).
7. Transfer the buffy coat to a new 15mL conical tube and bring volume up to 14mL with PBS.
8. (WASH 1) Centrifuge at 400xg for 10 minutes at 4 degrees C.
9. Without disturbing the cell pellet, aspirate and discard the supernatent.
10. Resuspend cell pellet with 10mL PBS and perform cell count per BR/SAC standard protocol.
11. Record the TOTAL VIABLE cell count.
12. (WASH 2) Centrifuge at 400xg for 10 minutes at 4 degrees C.
13. Resuspend cell pellet with 1mL PBS and transfer to one 2mL cryovial.
14. Centrifuge at 400xg for 10 minutes at 4 degrees C.
15. Without disturbing the cell pellet, aspirate and discard the supernatent.
16. Label cryovial as VELIPARIB PK BMA - CELL PELLET and record TOTAL

VIABLE cell count on label. (The cell pellet will NOT be suspended in any freezing media). **IF PERIPHERAL BLOOD WAS PROCESSED - label cryovial as VELIPARIB PK DRY TAP (PB)-CELL PELLET and record TOTAL VIABLE cell count on label.**

17. Store three plasma aliquots and one cell pellet at -70 degrees C.

9.2.2.3 Shipping of Specimen(s)

Please see Section 9.2.1.3 for shipping instructions. The plasma and bone marrow samples can be shipped in the same box at the same time.

9.3 Exploratory/Ancillary Correlative Studies

9.3.1 **Leukemia Mutation Panel** – Exploratory/Ancillary Laboratory Correlative Study #1

9.3.1.1 Collection of Specimen(s): 3 mL of bone marrow aspirate (or peripheral blood in the event of an inaspirable marrow) collected in a lavender top EDTA tube at the time of screening prior to therapy.

9.3.1.2 Handling of Specimens(s): No processing needed. Refrigerate specimens at 4 degrees C until shipped. Do not freeze.

9.3.1.3 Shipping of Specimens(s): Ship one lavender top tube (3 ml bone marrow) harvested prior to therapy and Shipping Manifest form, available on the CTUS website, by Federal Express priority overnight with cold pack to (no receipt on Saturday, Sunday or holidays):

Molecular Diagnostics Lab
Johns Hopkins Genomics
1812 Ashland Avenue, Room 245
Baltimore, MD 21205

Notify the Molecular Diagnostics Lab of the upcoming shipment, preferably 24 hours prior to sending the specimens: molecularpathresults@jhmi.edu.

Specimens collected on a Friday or day before a Holiday will be refrigerated at 4 degrees C until and shipped the next business day to arrive Monday through Friday.

9.3.1.4 Site(s) Performing Correlative Study: Johns Hopkins MDL.

9.3.2 **RAD51 focus formation assay** – Exploratory/Ancillary Laboratory Correlative Study #2

9.3.2.1 Collection of Specimen(s): Patients will have 3-4 ml samples of bone marrow (or peripheral blood in an inaspirable bone marrow patient) collected in 2 tubes containing heparin as an anticoagulant (green top) for a total of 6-8 ml of bone marrow at the time point specified below:

PRE-TREATMENT/SCREENING BONE MARROW:

9.3.2.2 Handling of Specimens(s): No processing needed. Ship the 2 green top tubes or peripheral blasts to Mayo Clinic Kaufman laboratory on the same day of collection for RAD51 focus formation assay.

9.3.2.3 Shipping of Specimen(s): Ship bone marrow and/or peripheral blasts to Dr. [redacted] Mayo Clinic, priority overnight by Federal Express:

[redacted], M.D., Ph.D.
Division of Oncology Research
Gonda 19-205B
Mayo Clinic
200 First St., S.W.
Rochester, MN 55905

During the spring, summer and autumn these samples should be packed in styrofoam containers containing cold packs (but shielded from freezing). During the winter ice packs should be omitted but styrofoam shipping containers should still be used to prevent the freezing of samples en route.

These samples should be shipped Monday-Thursday. At the time samples are shipped, please e-mail Dr. [redacted] and copy [redacted] with the FedEx tracking number to facilitate sample accessioning and analysis.

9.3.2.4 Site(s) Performing Correlative Study: [redacted] laboratory, Mayo Clinic

9.3.3 **Assay for Topo I-DNA covalent complexes** – Exploratory/Ancillary Laboratory Correlative Study #3

9.3.3.1 Collection of Specimen(s): Patients will have at least 5 ml samples of peripheral blood collected in a 6 ml tube containing EDTA as an anticoagulant (lavender top) at the time points specified below.

1: PRE-TREATMENT/SCREENING (preferably at the same time as on-study marrow)
2: Immediately before start of topotecan/carboplatin infusion
3: 48-96 hours into the 5-day topotecan/carboplatin infusion

9.3.3.2 Handling of Specimens(s): No processing needed. Samples will be shipped to Kaufman laboratory at Mayo Clinic for assay of topo I-DNA covalent complexes.

9.3.3.3 Shipping of Specimen(s): Peripheral blood specimens will be shipped on the day they are drawn to Dr. [redacted], Mayo Clinic, overnight by Federal Express. Ship purple top tubes (5 cc peripheral blood) harvested prior to therapy, prior to initiation of topotecan/carboplatin infusion and once 48-96 hours into the topotecan/carboplatin infusion to

[redacted], M.D., Ph.D.
Division of Oncology Research
Gonda 19-205B
Mayo Clinic
200 First St., S.W.
Rochester, MN 55905

During the spring, summer and autumn these samples should be packed in styrofoam containers containing cold packs (but shielded from freezing). During the winter ice packs should be omitted but styrofoam shipping containers should still be used to prevent the freezing of samples en route.

These samples should be shipped Monday-Thursday. At the time samples are shipped, please e-mail Dr. [redacted] and copy [redacted] with the FedEx tracking number to facilitate sample accessioning and analysis.

9.3.3.4 Site(s) Performing Correlative Study: [redacted] laboratory, Mayo Clinic

9.3.4 **Whole Exome Sequencing –** Exploratory/Ancillary Laboratory Correlative Study #4.

9.3.4.1 Collection and Handling of Specimen(s): Gene mutation analysis via whole exome sequencing will be performed at the NCI per attached substudy methods and techniques. Whole exome sequencing will be performed on pre-treatment samples containing 100 ng of DNA previously collected and stored as allowed by protocol. Germline DNA will be obtained thru isolation of T-cells from pre-treatment peripheral blood sampling sent to JHH MDL prior to therapy.

Patients will have 3 ml of peripheral blood collected in a 3 ml lavender EDTA tube. No processing needed. Refrigerate and ship overnight via Federal Express with cold pack. Do not freeze.

9.3.4.2 Shipping of Specimen(s): Ship one lavender top tube (3ml peripheral blood) harvested prior to therapy and the Shipping Manifest form, available on the CTSU website, by Federal Express overnight with cold pack to (no receipt on Saturday, Sunday or holidays):

Molecular Diagnostics Lab
Johns Hopkins Genomics
1812 Ashland Avenue, Room 245
Baltimore, MD 21205

Notify the Molecular Diagnostics Lab of the upcoming shipment, preferably 24 hours prior to sending the specimens: molecularpathresults@jhmi.edu.

Specimens with an expected delivery day of Saturday, Sunday or holiday may be held refrigerated at 4 degrees C until shipped.

Harvested DNA specimens will be shipped from SKCCC MDL to the MoCha lab.

9.3.4.3 Site(s) Performing Correlative Study: DNA libraries for WES will be generated at the central sequencing laboratories by standard procedures. Sequencing will be carried out on an Illumina HiSeq 2500 sequencer and these results will have variant calling through the procedures associated with the Genomic Data Commons. Analysis of sequencing results will be performed at Johns Hopkins. Mutation status will be correlated with clinical outcomes for the patients on study.

9.3.5 **Analysis of 5-mC and 5-h-mC –** Exploratory/Ancillary Laboratory Correlative Study #5**.**

9.3.5.1 Collection and Handling of Specimen(s): Analysis of 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-h-mC) will be performed in the laboratory of [redacted] at Mayo Clinic. 5-mc will be analyzed RRBS and a 850 kb array; and 5-h-mc will be analyzed by DIP-seq, TAB-RRBS, and 5-H-MC pull down. These analyses will be performed on pre-treatment samples containing 500 ng of DNA previously collected and stored as allowed by protocol. Patients will have 5 ml of peripheral blood collected in a lavender EDTA tube.

Patients will have at least 5 ml of peripheral blood collected in a 6 ml lavender EDTA tube.

9.3.5.2 Shipping of Specimen(s): Peripheral blood specimens will be shipped on the day they are drawn to Dr. [redacted], Mayo Clinic, overnight by Federal Express. Ship purple top tube (5 cc peripheral blood) harvested prior to therapy to:

[redacted], M.D., Ph.D.
Division of Oncology Research
Gonda 19-205B
Mayo Clinic
200 First St., S.W.

Rochester, MN 55905

During the spring, summer and autumn these samples should be packed in styrofoam containers containing cold packs (but shielded from freezing). During the winter ice packs should be omitted but styrofoam shipping containers should still be used to prevent the freezing of samples en route.

These samples should be shipped Monday-Thursday. At the time samples are shipped, please e-mail Dr. [redacted] and copy [redacted] with the FedEx tracking number to facilitate sample accessioning and analysis.

9.3.5.3 Site(s) Performing Correlative Study: [redacted] laboratory, Mayo Clinic

9.3.6 **Samples of viably frozen cells for ChIPseq –** Exploratory/Ancillary Laboratory Correlative Study #6**.**

9.3.6.1 Collection and Handling of Specimen(s): Analysis of selected chromatin modifications by ChIPseq (chromatin immunoprecipitation followed by sequencing). These analyses will be performed on viably frozen cells after thawing.

Patients will have 7 ml of peripheral blood collected in a 10 ml lavender EDTA tube.

9.3.6.2 Shipping of Specimen(s): Peripheral blood specimens will be shipped on the day they are drawn to Dr. [redacted], Mayo Clinic, overnight by Federal Express. Ship purple top tube (7 cc peripheral blood) harvested prior to therapy to

[redacted], M.D., Ph.D.
Division of Oncology Research
Gonda 19-205B
Mayo Clinic
200 First St., S.W.
Rochester, MN 55905
During the spring, summer and autumn these samples should be packed in styrofoam containers containing cold packs (but shielded from freezing). During the winter ice packs should be omitted but styrofoam shipping containers should still be used to prevent the freezing of samples en route.

These samples should be shipped Monday-Thursday. At the time samples are shipped, please e-mail Dr. [redacted] and copy [redacted] with the FedEx tracking number to facilitate sample accessioning and analysis.

9.3.6.2 Site(s) Performing Correlative Study: [redacted] laboratory, Mayo Clinic

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Baseline labs must be repeated if done greater than 7 days prior to C1D1. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Reg	Pre-Rand	Day1-7							Day 8-13	Day 14 (± 2d)	Day 15-22 (+/- 2d)	Recovery assessment (day 28-42)
Veliparib ARM A			A	A	A	A	A	A	A	A	A	A	
Topotecan/Carboplatin ARM A					A	A	A	A	A				
Topotecan/Carboplatin ARM B			B	B	B	B	B						
Informed consent	X												
Demographics		X											
Medical history		X											
Concurrent meds		X			X----------							----------X	
Physical exam		X	X			X					X		
Vital signs		X	X			X					X		
Height		X											
Weight		X	X	X	X	X	X	X	X	X	X		
Performance status		X	X										X
CBC w/diff, plts		X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[a]		X	X	X	X	X	X	X	X	X	X	X	
ECG (as indicated)		X											
Tumor Lysis Labs[d]		X	X	X	X	X	X				X	X (day 22)	
Adverse event evaluation					X----------							----------X	X
B-HCG		X[b]											
Bone marrow Aspirate/Biopsy[c]	X										X[e]		X
Peripheral blood sample[g]		X[g]			X[g]		X[g]						
Leukemia mutation panel /Whole exome sequencing sample		X											
RAD51 Assay		X											
Pharmacokinetic blood[f]		X								X	X	X	
WES peripheral blood for T cells		X											

			A: *Veliparib 80mg PO BID day1-21* a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. b: Serum pregnancy test (women of childbearing potential). c: Cytogenetics, immunophenotype, histochemistries; bone marrow aspirate and/or biopsy as medically indicated and to document remission. Bone marrow PK(screening) d: Phosphorous, Uric Acid, LDH, PT, APPT, Fibrinogen, e: Day 14 bone marrow assays: Aspirate differential, Bone marrow core, bone marrow PK. f: ARM A only See Section 9. Day 15 PK +/- 2d, Day 22 PK, only day 20 or 21 pre-treatment is allowed alternative g: For patients with greater than 5000 circulating blasts/mcm^3, one peripheral blood sample harvested at the time of on-study marrow, one right before initiation of topotecan/carboplatin infusion, and third after 48-72 hours of topotecan/carboplatin administration will be assayed for detectable topo I-DNA covalent complexes.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Hematologic Tumors

11.1.1 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.

11.1.2 Progression-Free Survival

PFS is defined as the duration of time of randomization to time of progression or death, whichever occurs first.

11.1.3 Response Review

Response will be graded by the principle investigator, and will be according to the response criteria below.

Aggressive Myeloproliferative Disorders

Complete remission (CR): The patient must be free of all symptoms or signs related to MPD and have a white blood cell count (WBC) between 1 and 10 x 10^9/L with no peripheral blood blasts, promyelocytes or myelocytes and normalization of bone marrow (<5% blasts in normocellular or hypercellular marrow) for at least 4 weeks; resolution of pretreatment cytopenias including Hgb $\geq$ 12.0 gm/dl ($\geq$ 11.0 gm/dl for females) without erythropoietin or transfusion support; ANC $\geq$ 1.0 x 10^9/L and platelet count >100x10^9/L without support; and resolution of pretreatment hyperleukocytosis and/or thrombocytosis (>450 x 10^9/L).

Partial remission (PR): improvement in two or more of the following: 1) ANC increase of 100% up to >10^9/L for neutropenia and WBC count between 1 and 10 x 10^9/L with persistence of immature cells (blasts, progranulocytes, myelocytes); 2) increase in Hgb of 2 gm/dl if baseline value was <10 gm/dl and a decrease in transfusion requirements by at least 50% (frequency and/or volume); 3) persistent thrombocytosis >450 x 10^9/L but <50% of pretreatment values; 4) reduction in bone marrow blasts to $\leq$ 5% if blasts were >10% in normocellular or hypercellular marrow; and 5) reduction in splenomegaly and/or hepatomegaly by 50% of pretreatment dimensions.

These definitions are consistent with those published by Giles et al. (48).

MPDs Transformed to Acute Leukemias

Complete remission (CR): The patient must be free of all symptoms related to leukemia and have a neutrophil count >$1x10^9$/L and platelet count >$100x10^9$/L, and normal marrow differential (<5% blasts). Must have clearance of extramedullary disease (including splenomegaly).

Partial remission (PR): meets the above criteria with the exception that leukemic blasts in the bone marrow may range from 6-25%, or ≥ 50% decrease in bone marrow blasts. May have persistent splenomegaly.

Hematologic Improvement: As per PR but ANC < $1x10^9$/L and platelet count <$100x10^9$/L. May have persistent splenomegaly and/or hepatomegaly.

These definitions are consistent with Giles et al (48) and Cheson, et al (49).

Chronic Myelomonocytic Leukemia (CMML)

The definitions below are consistent with those detailed by Cheson, et al (50).

Complete response is defined by bone marrow showing <5% myeloblasts with normal trilineage maturation without dysplasia. When erythroid precursors constitute <50% of marrow cells, the blast percentage is based on total nucleated cells; otherwise, the blast percentage is based on non-erythroid compartment. Peripheral blood criteria consist of Hemoglobin ≥11 gm/dl, ANC ≥ 1 x 10^9/L, Platelets ≥ 100 x 10^9/L, absence of peripheral blood blasts, all in the absence of transfusions and growth factors.

Partial response is defined by all of the above criteria with the exception of bone marrow blasts decreasing by >50% from pretreatment levels and/or achievement of a less advanced MDS FAB classification.

Stable Disease is defined by failure to achieve PR but without progression for at least 2 months.

Progression is defined according to initial blast percentages:

For patients with <5% blasts: ≥50% increase in blasts to >5%
For patients with 5-10% blasts: ≥50% increase in blasts to >10%
For patients with >10-20% blasts: ≥50% increase in blasts to >20%
For patients with >20-30% blasts: ≥50% increase in blasts to >30%

In addition, there must be ≥1 of the following criteria: ≥50% decrease from maximum response levels in granulocytes or platelets, a decrease in hemoglobin concentration by at least 2 gm/dl, or becoming transfusion dependent.

Acute myeloid leukemia

The following definitions are consistent with those published by Cheson/Dohner et al for acute leukemia (47).

Complete Remission (CR): Bone marrow showing less than 5% leukemic blasts with normal maturation of all cell lines, an ANC of at least 1000/μL and a platelet count of 100,000/μL, absence of blast in peripheral blood, absence of identifiable leukemic cells in the bone marrow, clearance of disease-associated cytogenetic abnormalities, and clearance of any previously existing extramedullary disease. Repeat marrow confirmation 4-6 weeks following the marrow documenting CR is not required due to the need for continued treatment in CR.

Complete Remission with Incomplete Recovery (CRi): All CR criteria except for residual neutropenia (ANC < 1000/μL) or thrombocytopenia (platelets < 100,000/μL).

Partial remission (PR): The presence of trilineage hematopoiesis in the bone marrow with recovery of ANC and platelets to the above stated levels, but with 5 to 25% bone marrow blasts, AND at least 50% decrease in bone marrow blast percentage from baseline.

Clinical improvement/Minor Response (MR): Non-progressive disease with at least a 20% decrease in marrow blasts and/or a decrease in leukemia-related symptoms (e.g., fever, bone pain, splenic pain, transfusion requirements) and signs (decrease in extramedullary site of leukemia).

Treatment Failure (TF):

- **Resistant Disease (RD).** Failure to achieve CR or CRi; only includes patients who survive ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.
- **Death in Aplasia (DA).** Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic without evidence of persistent leukemia.
- **Death from Indeterminate Cause (DIC).** Death occurring before completion of therapy or < 7 days following its completion, or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood but without bone marrow available.

Relapse: Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease.

11.2 Other Response Parameters

Response criteria typically applied to MPN patients with acute leukemic transformation fails to capture meaningful clinical responses per the Cheson criteria(see below). A recent publication by the post-Myeloproliferative Neoplasm Acute Myeloid Leukemia Consortium describes revised response criteria per Table 1 below.[56] As these response criteria have yet to be validated in a clinical trial, we intend to report responses both as criteria used in our phase I study(above) and as assessed by the proposed criteria by the MPN-AML consortium. These criteria are not to be

applied for CMML patients. A separate working group has developed revised response criteria for MDS/MPN including CMML which we will use as a secondary assessment for CMML patients per Table 2 below. [57]

Table 1.
Myeloproliferative neoplasm in blast phase (MPN-BP) response categories.

Complete molecular response (CMR)	
Description	Complete remission of both leukemia and MPN without detectable molecular markers associated with either leukemia or MPN
Hematologic profile	ANC > 1000
	Hemoglobin > 10 g/dL
	Platelets > 100 × 10^9/L
	Absence of leukoerythroblastosis[a]
Spleen	Non-palpable
Bone marrow	Cellularity appropriate for age
	Resolution of abnormal morphology
	Blasts ≤ 5%[b]
	≤Grade 1 marrow fibrosis
Cytogenetics	Normal karyotype[c]
Molecular markers	Loss of any previously documented markers associated with either the leukemic or MPN clone[d]
Complete cytogenetic response (CCR)	
Description	Complete remission of both leukemia and MPN with detectable molecular markers associated with either leukemia or MPN
Hematologic profile	ANC > 1000
	Hemoglobin > 10 g/dL
	Platelets > 100 × 10^9/L
	Absence of leukoerythroblastosis[a]
Spleen	Non-palpable
Bone marrow	Cellularity appropriate for age
	Resolution of abnormal morphology
	Blasts ≤ 5%[b]
	≤Grade 1 marrow fibrosis
Cytogenetics	Normal karyotype[c]
Molecular markers	Residual expression of MPN/leukemia associated gene mutations (e.g. JAK2V617F, MPL515L/K)[d]
Acute leukemia response-complete (ALR-C)	
Description	Complete remission of leukemia with residual MPN features
Hematologic profile	Absence of blasts[a]
Spleen	<25% increase in spleen size by palpation or imaging if baseline spleen <10 cm or <50% if baseline spleen ≥10 cm

Bone marrow	Blasts ≤ 5%[b]
Cytogenetics	Loss of cytogenetic abnormality associated with leukemic clone, may have persistent abnormality associated with MPN
Molecular markers	Loss of any previously identified markers in leukemic clone, may have persistent molecular markers associated with MPN[d]
Acute leukemia response-partial (ALR-P)	
Description	Decrease in leukemic burden but without resolution of peripheral blood or bone marrow blasts and residual MPN features
Hematologic profile	>50% reduction in blasts
Spleen	<25% increase in spleen size by palpation or imaging if baseline spleen <10 cm or <50% if baseline spleen ≥10 cm
Bone marrow	>50% reduction in blasts
Cytogenetics	No new abnormalities
Molecular markers	No new abnormalities
Stable disease (SD)	
Description	Failure to achieve at least LR-P, but no evidence of progression for at least 8 weeks.
Progressive disease (PD)	
Description	Progression of leukemia and/or background MPN
Hematologic profile	For patients with 10-20% blasts: ≥50% increase to >20% blasts
	For patients with >20% blasts: ≥50% increase to >30% blasts
Spleen	>25% increase in spleen size by palpation or imaging if baseline spleen <10 cm and >50% if baseline spleen ≥10 cm
Bone marrow	For patients with 5–10% blasts: ≥50% increase to >10% blasts
	For patients with 10–20% blasts: ≥50% increase to >20% blasts
	For patients with >20% blasts: ≥50% increase to >30% blasts
Cytogenetics	Does not apply
Molecular markers	Does not apply

a
Absence of peripheral blood blasts by morphologic review of the peripheral smear on two occasions separated by at least 2 weeks.

b
Blast percentage can be assessed by morphologic review of aspirate and in cases of inaspirate marrows, immunohistochemical staining of the marrow for $CD34^+$, $CD117^+$ is acceptable.

c
Normal karyotype by conventional cytogenetics in peripheral blood or bone marrow aspirate, if a cytogenetic abnormality is detected prior to treatment it must not be identified at time of assessment; if an abnormality is detected at baseline by FISH it must be absent by FISH at time of assessment.

d
Absence or loss of evidence of mRNA transcript by quantitative PCR assay performed in a validated laboratory, this will also include any exploratory biomarkers determined to be positive prior to therapy.

Table 2
Proposed criteria for measurement of treatment response in adult MDS/MPN

CR (presence of all of the following improvements)*
Bone marrow: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis)†
Peripheral blood‡
WBC ≤10 × 10^9 cells/L
Hgb ≥11 g/dL
Platelets ≥100 × 10^9/L; ≤450 × 10^9/L
Neutrophils ≥1.0 × 10^9/L
Blasts 0%
Neutrophil precursors reduced to ≤ 2%
Monocytes ≤1 × 10^9/L
Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Provisional category of CR with resolution of symptoms:‡ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*
Complete cytogenetic remission
Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH§
Partial remission
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast

equivalents) reduced by 50%, but remaining >5% of cellularity *except* in cases of MDS/MPN with ≤5% bone marrow blasts at baseline
Marrow response
Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.
Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, *or* reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart
Clinical benefit
Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥8 wk) to be considered a clinical benefit
Erythroid response
Hgb increase by ≥2.0 g/dL
TI for ≥ 8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk
Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation‖
Platelet response
Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk
Pretreatment ≤20 × 10^9/L: increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L: absolute increase of ≥30 × 10^9/L‖
Neutrophil response
Pretreatment ≤0.5 × 10^9/L at least 100% increase and an absolute increase ≥0.5 × 10^9/L
Pretreatment, >0.5 × 10^9/L and ≤1.0 × 10^9/L At least 50% increase and an absolute increase ≥0.5 × 10^9/L‖
Spleen response

Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
Symptom response
Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit.¶

- ↵* Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.
- ↵† If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.67
- ↵‡ Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.
- ↵§ Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.
- ↵‖ Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 wk. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 10^9/L) and resolution of leukocytosis to WBC ≤10 × 10^9 cells/L but ≥1.5 × 10^9/L. Hgb should be maintained >11 g/dL and platelets ≥100 × 10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤2-3%) and/or 1 × 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.
- ↵¶ MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

12.1 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.

In addition, the Protocol Principal Investigator will have at least monthly conference calls with the site Study Investigators and study teams to review accrual, progress, adverse events, and unanticipated problems.

12.2 Data Reporting

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

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

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

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance).

Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 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) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 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 the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is 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) the recommended phase 2 dose (RP2D) 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).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

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

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

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

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

restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

Genomic data obtained as part of this study will be shared according to the data sharing plan of the NCI. Please refer to the NCI Genomic Data Sharing Policy at http://www.cancer.gov/grants-training/grants-management/nci-policies/genomic-data for considerations regarding the sharing of data, protection of patient confidential information, and the provision of adequate information in the patient informed consent.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This phase II study will randomize patients 2:1 to Arm A (T/C/V) or to the standard Arm B (T/C), respectively. The primary end point is Overall Response (CR/CRi). We expect that these MPN patients will fall into two risk categories based on the percent blasts at baseline: < 20% blasts versus 20% or higher. The expected CR/CRi rate with traditional regimens in this group of patients ranges from 14% for patients with worse disease to 29% for patients with blasts 20% or higher.

For each group, the level of response that would confer interest in pursuing the therapy is a CR/CRi rate of 58%. This CR/CRi response rate was the response rate seen in our phase I trial[42] in the subset of MPN patients with a lower response rate (those with less than 20% blasts), where we observed responses in 7 out of 12 cases (58.3%). The proportion of patients in each subgroup are assumed to be 33% in the low blast count group and 67% in the higher blast count group, respectively. These proportions are considered in the sample size calculation. The final analysis will be by an exact Cochrane-Mantel-Haenszel test, which tests for an overall treatment difference while adjusting for subgroup. The primary analysis will conclude a significant benefit for Arm A over Arm B if the one-sided p value < 0.10.

The study design includes interim monitoring for futility (i.e., stopping early if there is high probability that the study will not show a significant benefit for Arm A over Arm B). [58] Futility is based on the predictive probability of a statistically significant treatment difference at the end of the study if the study enters, treats, and follows the total number of patients planned for the study. If we determine at any interim analysis that there is a < 10% chance of ultimately finding a statistically significant difference between Arm A and Arm B, we will pause for a safety review by the PI, study team, and CTEP if one of the stopping boundaries is hit. We determined the predictive probability of a significant trial result through simulations using a beta-binomial model to predict future observations conditional on data available at the time of the test. In the simulations, the predicted test was an exact Cochran-Mantel-Haenszel test, and a predicted test was significant if the one-sided p value of the test was < 0.10, as stated in the primary analysis.

13.2 Sample Size/Accrual Rate

We expect to enroll 1-2 patients per month at JHU alone. With 7-8 other centers participating in this study, we expect their accrual to average 3 patients per month, for a study-wide total of 3 patients per month. We fully expect that we will be able to complete accrual in 12-16 months, allowing for some patients who may drop out before randomization, and accrual holds for interim analysis.

The futility analysis will begin when 24 patients (16 in Arm A, 8 in Arm B) have entered the study and received treatment. If the study does not stop after the first interim analysis, a second interim analysis will be done when another 18 (12 in Arm A, 6 in Arm B) patients have entered the study and received treatment (42 patients total). Each interim analysis will project the remaining patients yet to be enrolled and compute the predicted significance level of the primary analysis, conditional on the data available at the time of analysis (i.e., predictive power).[58]

The prior distribution for the interim futility analyses is a non-informative beta(1,1) prior. Provided the study does not stop for futility, the final sample size will be 60 patients, with 40 in Arm A and 20 in Arm B.

The operating characteristics of the design are shown in the table below. We performed 1,000 simulations with varying values of the underlying probability of a response for each treatment and disease subgroup. The table shows that this study will have approximately 91% power to detect an increase (given in the first paragraph of this section) in the subgroup-specific probabilities of a complete response for Arm A compared to Arm B.

Sample Size (A/ B)	Probability of a CR in < 20% blasts group (A / B)	Probability of a CR in 20% or higher blasts group (A / B)	Estimated Power	Probability of stopping early at each interim analysis (1st / 2nd)	Cumulative probability of stopping early	Probability of failing to reject at the end of the study
40 / 20	0.58/ 0.29 0.40/0.29 0.29/ 0.29	0.58/ 0.14 0.40/ 0.14 0.14/ 0.14	0.91 0.475 0.036	0.042 / 0.014 0.182 / 0.125 0.638 / 0.214	0.056 0.307 0.852	0.034 0.218 0.112

13.3 Stratification Factors

At the time of randomization, we will stratify according to 1) marrow blast percentage (<20% vs. ≥ 20%).

13.4 Early Stopping Guidelines

ln addition to monitoring for futility, we will stop the trial if there is evidence of excess toxicity. We plan to monitor each treatment arm separately for the occurrence of any of following adverse events:

1) Grade 4 or higher generalized infection or
2) Grade 4 or higher radiologically diagnosed lower GI mucositis or
3) Grade 3 or higher hand and foot syndrome or
4) Grade 3 or higher cardiac arrhythmias or
5) Treatment-related mortality or
6) Duration of neutropenia exceeding 60 days

Toxicity will be monitored after every 5 patients. If the risk of any of the above adverse events convincingly exceeds 30% in Arm A or 20% in Arm B, the study PI will contact CTEP for a safety consultation. The stopping rule for toxicity will hold enrollment if the posterior probability of risk being larger than 30% (Arm A) or 20% (Arm B) exceeds 0.75. The prior for this toxicity monitoring rule for Arm A is a beta (2,4) distribution and for Arm B is a beta (1,4). This means that our prior guesses at the proportion of severe toxicities is 33% for Arm A and 20% for Arm B. There is a 90% probability that these proportions are between 7.6% and 65.7%, and 1.2% and 52.7%, respectively. The operating characteristics of the stopping rule are shown below and

based on 5000 simulations.

Toxicity Stopping Rules

Arm B			Arm A		
N toxicities	N patients	Probability of too much toxicity *	N toxicities	N patients	Probability of too much toxicity *
3	5	0.914	3	5	0.850
4	10	0.870	5	10	0.869
5	15	0.837	6	15	0.772
6	20	0.811	8	20	0.811
			10	25	0.841
			11	30	0.773
			13	35	0.807
			15	40	0.836

* The probability of too much toxicity is the posterior probability of toxicity being larger than 20% for Arm A and 30% for Arm B

Operating Characteristics of stopping rule, based on 5000 simulations:

Arm B			Arm A		
True Toxicity Rate	Probability of declaring treatment too toxic	Average sample size	True Toxicity Rate	Probability of declaring treatment too toxic	Average sample size
10%	0.030	19.7	20%	0.113	36.8
15%	0.101	19.2	25%	0.253	33.2
20%	0.263	18.1	30%	0.468	28.1
25%	0.457	16.4	35%	0.660	23.1
30%	0.643	14.7	40%	0.842	17.6
35%	0.805	12.7	45%	0.943	13.5

To ensure balanced randomization between the 2 arms with respect to disease classification, we will stratify up-front according to the two disease categories described above.

13.5 Analysis of Endpoints

For descriptive purposes, the CR/CRi rate will be reported at the end of the study separately for Arm A and Arm B as intent to treat analysis with exact binomial 95% confidence intervals. The final analysis will be by an exact Cochrane-Mantel-Haenszel test, which tests for an overall treatment difference while adjusting for subgroup. The primary analysis will conclude a significant benefit for Arm A over Arm B if the one-sided p value < 0.10. The odds ratio for the probability of CR/CRi for Arm A versus Arm B will also be estimated using a logistic regression model that adjusts for baseline blast count group, to account for the randomization stratification factor. The estimate will be provided with a 95% confidence interval. The secondary analysis of results will include reporting preliminary estimates of the odds ratio (comparing Arm A over Arm B) for the two blast (risk) groups separately. The differences in the odds ratios (i.e., differential treatment effect) will be described using an interaction analysis from a logistic regression model.

An overall toxicity rate and a rate for each specific toxicity listed above in the early stopping guidelines will be reported for Arm A and Arm B separately and together with exact binomial 95% confidence intervals.

The distribution of mutations in DNA repair defects via assessment in Leukemia mutation panel will be summarized using descriptive statistics. The frequency of patients with functional impairment of DNA damage response via assessment with RAD51 assay will be reported with exact binomial 95% confidence intervals. The association between these biomarkers and response will be described with appropriate tests for continuously measured biomarkers (t tests, Wilcoxon rank sum tests) and categorical biomarkers (Fisher's exact test). These descriptive analyses for addressing secondary objectives will be performed for the whole cohort and also separately for Arms A and B. Differential treatment outcomes for patient subgroups defined by these biomarkers may be explored using appropriate tests for interactions.

Veliparib Exposure

Pharmacokinetic (PK) sampling studies are proposed for all participating patients on the study V/T/C arm. Plasma trough levels will be obtained weekly through the first cycle to provide a steady-state assessment. Bone marrow or peripheral blood supernatant and blasts will be obtained pre-treatment and at C1D15. Samples will be measured using a validated liquid chromatography/tandem mass spectrometric (LC/MS/MS) method in the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins. [42] Steady-state plasma concentrations will be calculated for each patient. Exploratory correlative studies between veliparib exposure (plasma and bone marrow) with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	3	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	6	9	0	0	**15**
White	12	16	3	4	**35**
More Than One Race	1	1	1	2	**5**
Total	**21**	**29**	**4**	**6**	**60**

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13.6 Analysis of Secondary Endpoints

The distribution of mutations in DNA repair defects via assessment in Leukemia mutation panel will be summarized using descriptive statistics. The frequency of patients with functional impairment of DNA damage response via assessment with RAD51 assay will be reported with exact binomial 95% confidence intervals. The association between these biomarkers and response will be described with appropriate tests for continuously measured biomarkers (t tests, Wilcoxon rank sum tests) and categorical biomarkers (Fisher's exact test). These descriptive analyses for addressing secondary objectives will be performed for the whole cohort and also separately for Arms A and B. Differential treatment outcomes for patient subgroups defined by these biomarkers may be explored using appropriate tests for interactions.

Veliparib Exposure

Pharmacokinetic (PK) sampling studies are proposed for all participating patients on the study V/T/C arm. Plasma trough levels will be obtained weekly through the first cycle to provide a steady-state assessment. Bone marrow or peripheral blood supernatant and blasts will be obtained pre-treatment and at C1D15. Only samples obtained on the V/T/C arm will be measured for veliparib using a validated liquid chromatography/tandem mass spectrometric (LC/MS/MS) method in the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins.[42] Attempts to obtain dosing diary information and

PK sample times will be consistent across all patients. Steady-state plasma concentrations will be calculated for each patient. Exploratory correlative studies between veliparib exposure (plasma and bone marrow) with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Veliparib.

13.7.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	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.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with 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 transporter proteins that help move drugs in and out of cells.

- The proteins in question are ***OCT2, MATE1, MATE2K, and P-gp*.** Veliparib is a substrate of P-gp, OCT2, and MATE1/2K and may be affected by other drugs that inhibit these protein transporters. Veliparib is an inhibitor of OATP1B1, OATP1B3, MATE1/2K, OAT1/3and OCT1 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.

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:

Use caution when administering veliparib with other medicines that need certain **transport protein 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 ***P-gp, OCT2, and MATE1/2K.***

- 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 _____.

February 2016

STUDY DRUG INFORMATION WALLET CARD	**Use caution as veliparib may interact** with medicines that stop transport proteins **MATE1/2K, OCT2, and P-gp** to process further in the body**.**
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 need 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 supplement.	➢ 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 P-gp, MATE1/2K, and OCT2.**" ➢ 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 BIOASSAY TEMPLATES

Leukemia Mutation Panel (JHH)

Method

This assay uses next-generation sequencing to analyze exons of the following genes: ABL1, ASXL1, ATM, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CDKN2A, CEBPA, CSF3R, DNMT3A, EP300, ERBB2, ETV6, EZH2, FLT3, GATA1, GATA2, GNAS, IDH1, IDH2, IKZF1, JAK2, KDM2B, KDM6A, KIT, KMT2A, KMT2D, KRAS, MPL, NF1, NLRP1, NOTCH1, NOTCH2, NPM1, NRAS, NSD1, NUP98, PDGFRA, PHF6, PIGA, PTEN, PTPN11, RAD50, RECQL4, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1, ZRSR2. DNA is extracted from blood or bone marrow specimens, captured with Agilent SureSelectXT reagents, and sequenced using Illumina paired end technology. 97% of all exons within the 60 genes of the Heme Panel are covered by this assay. The Heme Panel does not cover mutations occurring in the first exon of the following genes: ASXL1, ATRX, BRAF, CALR, CBL, DNMT3A, (NM_153759), ERBB2, FLT3, IDH2, KMT2A, MPL, NF1, NOTCH1, PIGA, PTPN11, RECQLR, and WT1. Designated exons from the following genes are also not covered by the Heme Panel: CALR (9), CSF3R (7), DNMT3A (2), ERBB2 (2,3,4,25), MPL (9), NLRP1 (10(9)), NOTCH1 (3,9,11,17,19,24), NPM1 (7), and RECQL4 (2,3,12). The remaining exons cover 99% of the variants reported in Cosmic for these genes. *For individual specimens, additional target regions that result in coverage depths of <100x will be noted in the "Genes with Low Coverage (<100 reads)" section above. Mutations present in a low percentage of cells or present in genes with low coverage may not be detected. Analysis was performed using the following human reference sequence genome assembly: hg19 (NCBI build GRCh37). In a context of lower neoplastic cell percentage, variants with mutation allele frequencies of approximately 50% or near 100% may represent germline variations.

Sensitivity	Base Substitutions at >5% Mutant Allele Frequency	98%
	Insertions/Deletions (1-40 base pairs) at >5% Mutant Allele Frequency	>95%
	Copy Number Alterations	Not tested
	Translocations	Not tested
Specificity	Positive Predictive Value (PPV)	>99%
Reproducibility	Concordance between replicates inter-batch	99%
	Concordance between replicates intra-batch	99%

RAD51 assay

RAD51 focus formation assay methods

Ten million Ficoll/Hypaque-purified mononuclear cells (MNCs) from normal controls and MPN patients were exposed to 10 Gy ionizing radiation (IR) from a Rad Source RS200 X-ray irradiator (Brentwood, TN), then allowed to recover for 6 h in a humidified 37 °C tissue culture incubator equilibrated at 5% (vol/vol) CO_2. Leukocytes were pelleted by centrifugation at 200×*g*

for 10 min and fixed in 2% (wt/vol) paraformaldehyde in Dulbecco's calcium- and magnesium-free phosphate-buffered saline (PBS) for 10 min at 20-22 C. Leukocytes were re-pelleted as above, washed with PBS, and stored in PBS at 4 °C. For analysis, 2.5 x 10^4 leukocytes were deposited onto glass coverslips by cytocentrifugation and processed as previously described [37]. Briefly, coverslips were washed 3 times with PBS, permeabilized in PBS + 0.25 % (vol/vol) Triton X-100 for 10 min, washed an additional 3 times with PBS, then incubated for 1 h in blocking buffer [PBS, 1 % (vol/vol) glycerol, 0.1% (wt/vol) gelatin from cold-water fish, 0.1% (wt/vol) bovine serum albumin, 5% (vol/vol) goat serum and 0.4 % (wt/vol) sodium azide] for 1 h at room temperature. Coverslips were incubated with RAD51 rabbit polyclonal (Active Motif; Carlsbad, CA) and phospho-Ser^{139}-H2AX mouse monoclonal (Millipore; Billerica, MA) antibodies diluted 1:500 in blocking buffer overnight at 4 °C. Coverslips were then washed 3 times with PBS, followed by incubation for 1 h in secondary Alexa Fluor 488-conjugated goat anti-mouse IgG and Alexa Fluor 568-tagged goat anti-rabbit IgG (Invitrogen; Carlsbad, CA) diluted 1:1000 in blocking buffer. Coverslips were further washed 3 times with PBS, counterstained with 1 g/ml Hoechst 33258 in PBS, and mounted using UltraLong antifade reagent (Invitrogen, Carlsbad, CA). PEO1 and PEO4, cell lines with a truncating *BRCA2* mutation and a reversion mutation, respectively, were utilized as negative and positive controls for radiation-induced RAD51 foci. Confocal images were captured on a Zeiss LSM 710 scanning confocal microscope with a 100×/1.4 N.A. oil immersion objective. For quantitation, 100 cells per sample from greater than 5 fields were manually scored for RAD51 and phoshopho-H2AX foci by an investigator blinded to clongenic assay results. Cells with >5 foci were graded as positive. Quantitation and image processing were performed with the Zeiss Zen software package and Adobe Photoshop CS3.

Bioanalytical method for determining Veliparib in plasma, bone marrow supernatant and blasts

1. Name of marker: Veliparib drug concentration
2. Role of Integrated Biomarker: This is for an integrated assay aimed at assessing drug exposure in patients on the clinical trial.
3. Laboratory who will be considered for conducting the assay for the trial: The Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (SKCCC) will be considered to conduct the assay. Michelle A. Rudek, PhD., Pharm D. is an Associate Professor of Oncology and the director of the SKCCC Analytical Pharmacology Core. She has over extensive experience in clinical pharmacology and the early development of anticancer agents. Dr. Rudek has expertise in bioanalysis, drug metabolism, and pharmacokinetic and pharmacodynamic analysis. She has the authority to commit equipment, space, and professional and technical effort in the SKCCC Analytical Pharmacology Core to this project. The SKCCC Analytical Pharmacology Core is a shared resource that was established in 1985 and provides expertise in pharmacological trial design, analytical method development, quantitative assay implementation, isolation and identification of drug metabolites, metabolic profiling, protein binding studies, pharmacokinetic and pharmacodynamic modeling, and data interpretation in a centralized and experienced facility. The SKCCC Analytical Pharmacology Core is one of the few academic labs in the United States which operates according to Good Laboratory Practices (GLP), a standard necessary to ensure FDA-quality data. The GLP

guidelines are applied toward the development, validation and implementation of analytical assays for quantification of drug concentrations. We do not expect technical issues with the conduct of the pharmacokinetic and MIC-1 studies as Dr. Rudek's laboratory has much experience with these bioanalyses.

5. Describe the assay: An abbreviated assessment of systemic and site of action veliparib exposure will be performed. Veliparib blood levels will be measured by LC-MS/MS in the blood: on C1D1, C1D8, C1D15, and C1D22 pre-treatment. Bone marrow or peripheral blood supernatant and blasts will be obtained pre-treatment and at C1D15. The analytical assay for determining veliparib in human plasma, bone marrow supernatant and blasts by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).has been developed and validated by the SKCCC Analytical Pharmacology Core. Briefly, p Sample preparation involved a single protein precipitation step by the addition of the sample with acetonitrile. Separation of veliparib and the internal standard, A620223.69, was achieved on a Atlantis dC(18) column (100mmx2.1mm, 3microm) column using a mobile phase consisting of acetonitrile-ammonium acetate (2mM) containing formic acid (0.1%, v/v) using isocratic flow at 0.2mL/min for 3min. The analyte and internal standard were monitored by tandem mass spectrometry with electrospray positive ionization. Linear calibration curves were generated over the range of 5-1000nM. The analytical assay for determining decitabine has been developed and validated by the SKCCC Analytical Pharmacology Core on the ABI3000 triple quadrupole instrument in 2009 and will need to be partially validated (precision/accuracy) on a newer instrument. The analytical method was validated as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 [59]. The LLOQ of veliparib was 5 nM. No major interferences observed at the same retention time as veliparib and the internal standard, A620223.69. The average signal to noise ratio of the veliparib LLOQ was 34.4 ± 14.8 for plasma, and 78.2 ± 29.7 for bone marrow supernatant and 93.1 ± 23.1 for bone marrow cells. The values for both within day and between day precision and accuracy were well within the generally accepted criteria for analytical methods.

7. Provide data on the clinical utility of the integrated assay as it will be used in the trial: This assay will be utilized to determine veliparib concentrations and ultimately the drug exposure. This data will be utilized to: 1) correlate systemic pharmacokinetics to veliparib at the site of action (supernatant and cells); 2)) correlate exposure-response relationships with the reported pharmacodynamics output and veliparib exposure.