CTEP # P9771
Clinical Center # 16-C-0087

TITLE: **Phase I Study of Veliparib (ABT-888), an Oral PARP Inhibitor, and M6620 (VX-970), an ATR Inhibitor, in Combination with Cisplatin in Patients with Refractory Solid Tumors**

Abbreviated Title: Ph I Veliparib + M6620 (VX-970) + cisplatin

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Study Sponsor:	CTEP
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Roles: [A]obtains information by intervening or interacting with living individuals for research purposes; [B]obtains identifiable private information about living individuals; [C]obtains the voluntary informed consent of individuals to be subjects; [D]makes decisions about subject eligibility; [E]studies, interprets, or analyzes identifiable private information or data/specimens for research purposes

PRÉCIS

Background:

- Ataxia-telangiectasia-related (ATR) protein kinase is central to the DNA damage response and homologous recombination, activating a series of phosphorylation cascades, culminating in cell cycle arrest to allow time for DNA repair. ATR additionally facilitates homologous recombination repair through modulation of the p53-replication protein A (p53-RPA) complex bound to ssDNA during the DNA repair process.
- Poly (ADP-ribose) polymerase-1 (PARP-1) plays a pivotal role in base-excision repair of single strand breaks formed either due to direct genotoxic stress or during the processing of double strand breaks. PARP also plays a role in alternative end joining, which may contribute to combination activity. PARP-1 binding to sites of DNA damage results in activation of its catalytic activity and generation of chains of poly (ADP-ribosyl)ated polymers, which serve as docking sites for recruitment of DNA repair proteins.
- Veliparib (ABT-888) is a potent PARP 1/2 inhibitor with clinical evidence of potentiation of antitumor activity in combination with cisplatin in BRCA mutation carriers and patients with sporadic triple-negative breast cancer.
- M6620 (VX-970) is a potent ATR inhibitor, with IC_{50} of 20 nM and antitumor activity across a broad range of cell lines in combination with DNA damaging agents. Preclinical studies show M6620 (VX-970) synergizes with cisplatin to induce DNA damage and antitumor activity. The addition of PARP inhibitor veliparib with ATR inhibitor M6620 (VX-970) allows for impairment of DNA repair, the induction of a "BRCA null" phenotype, and potentiation of the antitumor activity of cisplatin.

Primary Objective:

- To establish the safety, tolerability, and the maximum tolerated dose (MTD) of the combination of M6620 (VX-970) and veliparib in combination with cisplatin in patients with advanced refractory solid tumors

Secondary Objectives:

- To assess the effect of the combination of M6620 (VX-970), veliparib, and cisplatin on markers of DNA damage and apoptosis
- To assess antitumor activity of the combination

Exploratory Objective:

- To investigate tumor genomic alterations potentially associated with acquired resistance to the combination of M6620 (VX-970), veliparib, and cisplatin

Eligibility:

- Patients must have histologically confirmed solid tumors for which standard therapy known to prolong survival has failed in the metastatic setting, or for which standard therapies do not exist
- Patients must have had no major surgery, radiation, or chemotherapy within 3 weeks prior to entering the study
- Patients must have adequate organ function

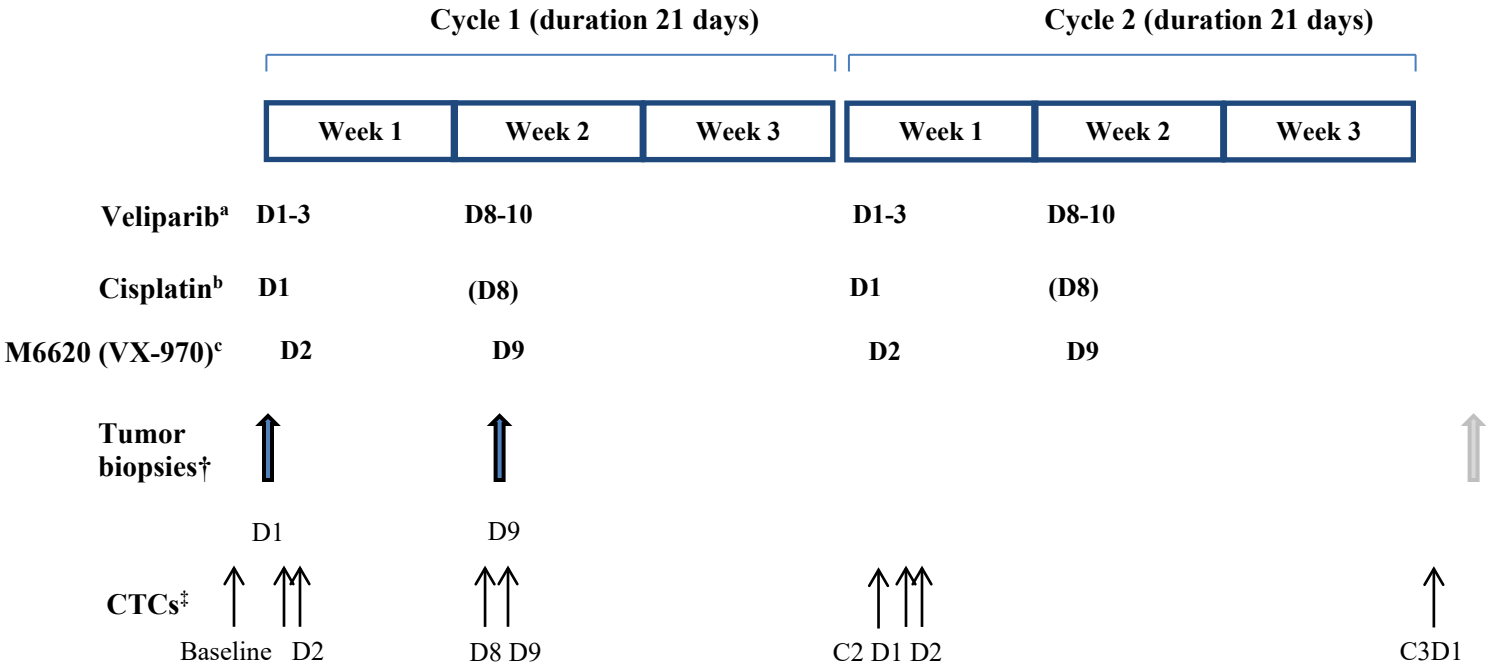
Study Design:

- Initially, M6620 (VX-970) will be administered intravenously on Days 2 and 9 of each 21-day

cycle. Veliparib will be administered orally twice a day (q12 hours ± 1 hour) for Days 1-3 and 8-10 of each 21-day cycle. Cisplatin will be administered at 40 mg/m^2 intravenously on Day 1 (and Day 8 from DL3 onwards) of each 21-day cycle.

- As of ***Amendment I*** (12/7/2017), patients who have been on study for at least 6 cycles may have cisplatin administration held or discontinued at the discretion of the PI, Dr. [redacted] in recognition of the cumulative neurotoxicity seen with cisplatin treatment. If cisplatin is not administered during a cycle, M6620 (VX-970) will be administered on Days 1 and 8 of that cycle.
- The escalation portion of the trial will follow a standard 3+3 design, whereby patients will be dose escalated in cohorts of 3 until dose-limiting toxicity is observed
- Once the MTD is established, up to 15 additional patients will be enrolled to an expansion phase at the MTD. Mandatory tumor biopsies will be obtained in the expansion phase to assess PD endpoints

SCHEMA



[a] Veliparib po q12 hours ± 1 hour on days 1-3, 8-10 of each cycle. Veliparib should be administered before cisplatin and M6620 (VX-970).

[b] Cisplatin IV day 1 only each cycle for dose levels up to DL 3; days 1 and 8 for dose level 3 and higher; as of ***Amendment I*** (12/7/2017), patients who have been on study for at least 6 cycles may have cisplatin administration held or discontinued at the discretion of the PI, Dr. [redacted]

[c] M6620 (VX-970) IV days 2 and 9 of each cycle (or days 1 and 8 if cisplatin administration has been held or discontinued)

† Tumor biopsies to evaluate pharmacodynamic markers of DNA damage (optional during the escalation phase and mandatory during the expansion phase) after administration of cisplatin on C1D1 and on C1D9, 2-5 hours after the day 9 dose of M6620 (VX-970). One optional biopsy may also be performed, either at "restaging follow-up" on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed (according to RECIST criteria) for patients on study 4 or more cycles, or at the time of disease progression. (For example, a restaging follow-up biopsy would be performed on cycle 6 day 1 for a 10-19% tumor volume increase detected at the restaging following cycle 4).

‡ Circulating tumor cells (optional) will be collected at baseline (prior to administration of study agents), prior to administration of M6620 (VX-970) on cycle 1 day 2, 8 hours (± 30 minutes) after the start of M6620 (VX-970) administration on cycle 1 day 2, on cycle 1 day 8 prior to veliparib/cisplatin administration, on cycle 1 day 9 prior to M6620 (VX-970) administration, on cycle 2 day 1 prior to veliparib/cisplatin administration, on cycle 2 day 2 prior to M6620 (VX-970) administration and again 10 hours (± 2 hours) after the start of M6620 (VX-970) administration (or, at NCI only, at 7:00pm ± 30 minutes; the time elapsed between M6620 (VX-970) administration and blood collection on cycle 2 day 2 will be recorded), and on the first day of every subsequent cycle prior to veliparib/cisplatin administration.

Dosing Schema:

Dose Level	Veliparib (PO q12 hours ± 1 hour)	M6620 (VX-970) (IV Days 1/2 and 8/9)	Cisplatin (IV Day 1 or Days 1 and 8)
-2	20 mg days 1-3, 8-10	40 mg/m^2	40 mg/m^2 day 1
-1	40 mg days 1-3, 8-10	60 mg/m^2	40 mg/m^2 day 1
1	100 mg days 1-3, 8-10	90 mg/m^2	40 mg/m^2 day 1
2	100 mg days 1-3, 8-10	140 mg/m^2	40 mg/m^2 day 1
3	100 mg days 1-3, 8-10	120 mg/m^2	40 mg/m^2 days 1, 8
4	100 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
5	150 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
6	200 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
7	300 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
8	400 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8

As of Amendment L (dated 4/22/2019), the MTD for this combination has been established as DL6.

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1 OBJECTIVES

Primary Objective:

- To establish the safety, tolerability, and the maximum tolerated dose (MTD) of the combination of M6620 (VX-970), an ATR inhibitor and veliparib, an oral PARP 1/2 inhibitor, in combination with cisplatin in patients with advanced refractory solid tumors.

Secondary Objectives:

- To assess the effect of the combination of M6620 (VX-970), veliparib, and cisplatin on markers of DNA damage and apoptosis
- To assess the antitumor activity of the combination

Exploratory Objective:

- To investigate tumor genomic alterations potentially associated with acquired resistance to the combination of M6620 (VX-970), veliparib, and cisplatin

2 BACKGROUND

2.1 Rationale for combining cisplatin with ATR and PARP inhibitors

Platinum compounds act through the formation of covalent bonds with DNA purine bases, forming intrastrand and interstrand cross-links with DNA, stalling replication forks and halting transcription [1]. Poly (ADP-ribose) polymerase-1 (PARP-1) plays a pivotal role in base-excision repair (BER) and the DNA damage response [2]. Once DNA damage is detected, surveillance protein complexes such as Mre11-Rad50-Nbs1 and Rad9/Rad1/Hus1 recruit repair proteins and halt cell cycle progression, allowing time for DNA repair. Ataxia-telangiectasia mutated (ATM) protein kinase and ataxia-telangiectasia-related (ATR) protein kinase, two members of the phosphatidyl inositol 3-kinase-like kinase (PIKK) family, are central to the DNA damage repair process. Depending on the type of genotoxic stress, either ATM or ATR is preferentially activated [3]. ATM is primarily activated in response to double-stranded DNA breaks (DSBs), while ATR is activated by a broader spectrum of genotoxic stimuli and primarily activated in response to single-strand DNA breaks (SSBs) arising through the processing of DSBs or the stalling of DNA replication forks after treatment with platinum compounds. Both kinases initiate a cascade of phosphorylation events, culminating in cell cycle arrest to allow time for repair of DNA. ATR additionally facilitates homologous recombination (HR) repair through modulation of the p53-replication protein A (p53-RPA) complex bound to ssDNA during the process of DNA repair [4]. SSBs are additionally repaired by PARP-1 through BER. Binding of PARP-1 to sites of DNA damage results in activation of its catalytic activity and generation of chains of poly (ADP-ribosyl)ated polymers, which serve as docking sites for recruitment of DNA repair proteins [5, 6]. The accumulation of lethal DSBs during replication as a result of platinum compounds, in the setting of inhibition of both PARP and ATR, allows for chemopotentiation and a means to overcome treatment resistance.

Early preclinical studies of ATR depletion with siRNA demonstrate sensitization of ovarian cancer cells to chemotherapy and PARP inhibition, independent of BRCA status (Figure 1) [7]. Strong preclinical evidence exists for the enhancement of synthetic lethality of tumor cells through simultaneous inhibition of multiple DNA repair pathways. Impairment of homologous recombination through inhibition of ATR effectively creates a "BRCA-null" phenotype in tumor cells, increasing sensitivity to PARP inhibition. We hypothesize that dual inhibition of HR and BER through co-administration of M6620 (VX-970), a potent inhibitor of ATR, and veliparib, a potent inhibitor of PARP 1/2, results in accumulation of lethal DSBs induced by cisplatin, chemopotentiation, and enhancement of antitumor activity.

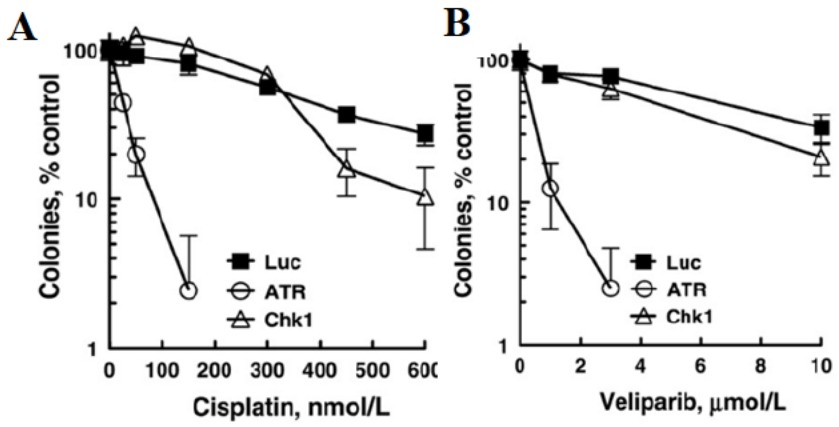


Figure 1. ATR depletion sensitizes OVCAR-8 cells to multiple chemotherapy agents, including cisplatin (panel A), and veliparib (panel B) [7]. OVCAR-8 cells were transfected with control (Luc) or ATR siRNA. After transfection, cells were plated, allowed to adhere for 4-6 hrs, and treated with cisplatin (A), and veliparib (B) for 8 days.

More recent preclinical studies show synergism of the combination based on Bliss analysis of MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(-4-sulfophenyl)-2H-tetrazolium) cell viability assays (Figure 2).

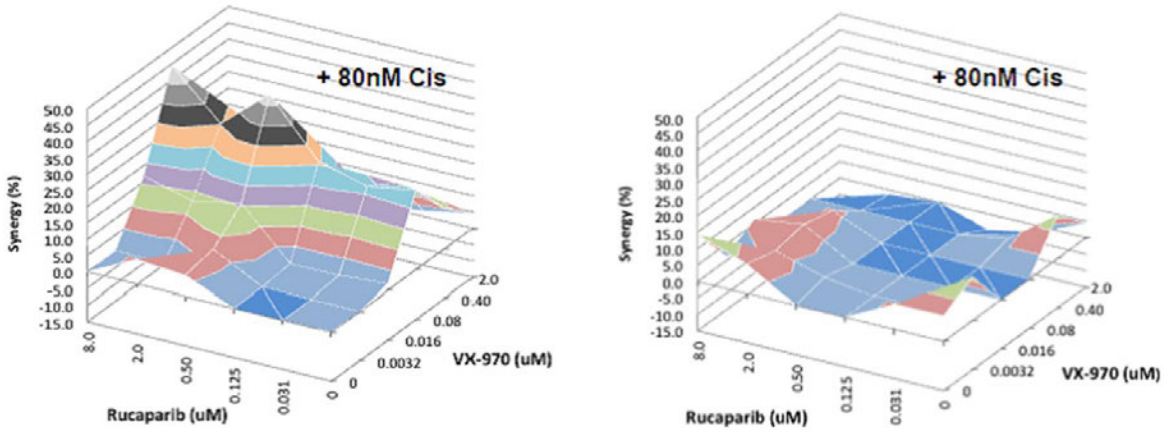


Figure 2. Synergy of PARP inhibition + M6620 (VX-970) + cisplatin in H23 lung carcinoma (left panel) vs. HFL1 human fetal lung non-cancerous (right panel) cell lines. Data from MTS cell viability assays of the combination of PARP inhibition with rucaparib + M6620 (VX-970) + 80 nM of cisplatin subjected to statistical Bliss analysis in order to quantitate synergy or antagonism demonstrates synergy in cancer cell lines, with minimal effect in non-cancerous cell lines [Confidential communication with Vertex, unpublished data].

Data from nonclinical studies conducted by Vertex showed that the combination of cisplatin, Veliparib, and M6620 (VX-970) at clinically relevant doses and schedule was well tolerated in MF1 nude mice (Figure 3); body weight changes did not exceed ± 5% and were similar to vehicle.

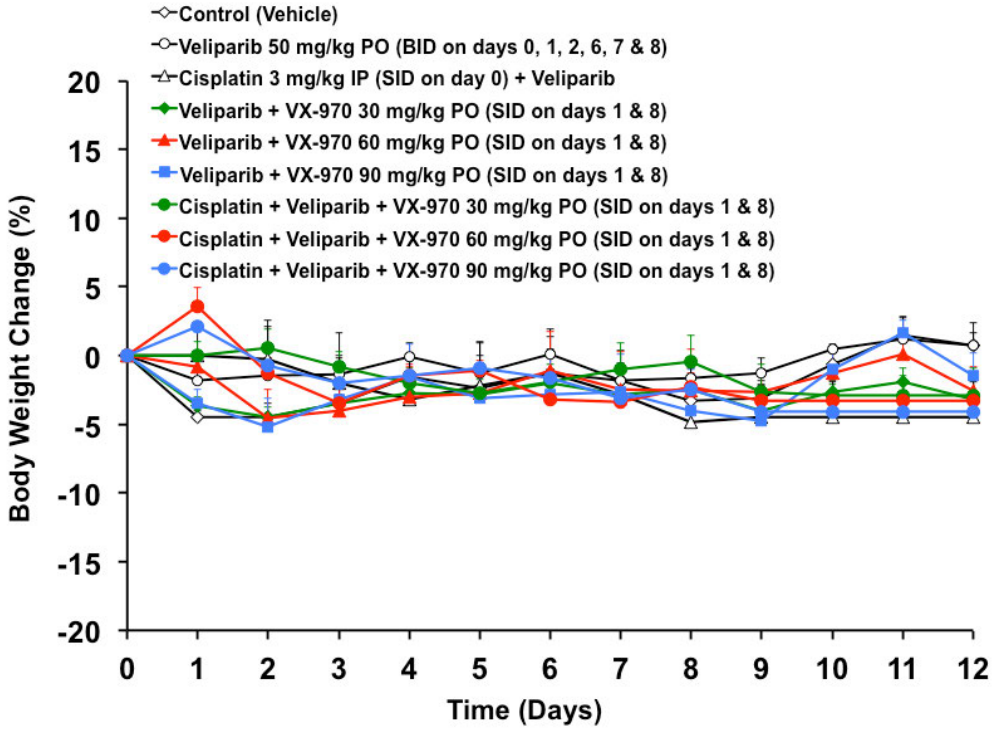


Figure 3. Tolerability of cisplatin, Veliparib, and M6620 (VX-970) combination in MF1 nude mice administered on days 1 and 8 and assessed for 2 cycles. Doses/routes of administration:

cisplatin 3 mg/kg IP; Veliparib 50 mg/kg PO; M6620 (VX-970) 30, 60, and 90 mg/kg PO. Drugs were administered on days 1 and 8 [Confidential communication with Vertex, unpublished data].

2.2 M6620 (VX-970)

ATR plays a central role in the DNA damage response; therefore, inhibition of ATR is expected to enhance the effects of DNA damage, either as a result of exposure to genotoxic chemotherapy agents or secondary to inherent errors in replication. In vitro studies show that M6620 (VX-970) sensitized a panel of human cancer cell lines and primary human tumor cells to the cytotoxic effects of various DNA-damaging agents whereas normal cells (lung and skin fibroblasts and mammary epithelial cells) treated with the same DNA-damaging agents tolerated ATR inhibition with a reversible increase in growth [8].

Mechanism of Action

M6620 (VX-970) is a potent, ATP-competitive, inhibitor of ATR (Ki < 300 pM; measured Ki values over the range of 0.1 to 0.3 nM). It showed > 100-fold selectivity against closely-related DNA damage repair proteins, ATM, and DNA-dependent protein kinase. Minimal inhibitory activity was observed against a large panel of unrelated protein kinases, with > 500-fold selectivity for ATR.

Preclinical Studies
In vitro studies of M6620 (VX-970) in HCT116 colorectal carcinoma cells, show synergism of M6620 (VX-970) with various DNA-damaging agents, with the most dramatic response in combination with cisplatin, where a 20-fold reduction in the IC_{50} for cisplatin was observed. Cell viability assays were assessed by MTS assay at 96 hours (Figure 3 left panel) [Investigator's Brochure]. The effects of M6620 (VX-970) in combination with a range of DNA-damaging agents were also tested against a panel of lung, pancreatic, and 9 primary lung tumors in combination with cisplatin, using CellTiter-Glo™ assays, demonstrating enhanced synergy, with concurrent dose-dependent decreases in pCHK1 confirming downstream target effect, and dose-dependent increases in pH2AX demonstrating downstream DNA-damage effect (data not shown).

M6620 (VX-970) and cisplatin were also assessed in a panel of primary human non-small cell lung cancer (NSCLC) xenografts in SCID mice with enhancement of antitumor activity in 7 of 9 xenografts (Figure 4 right panel).

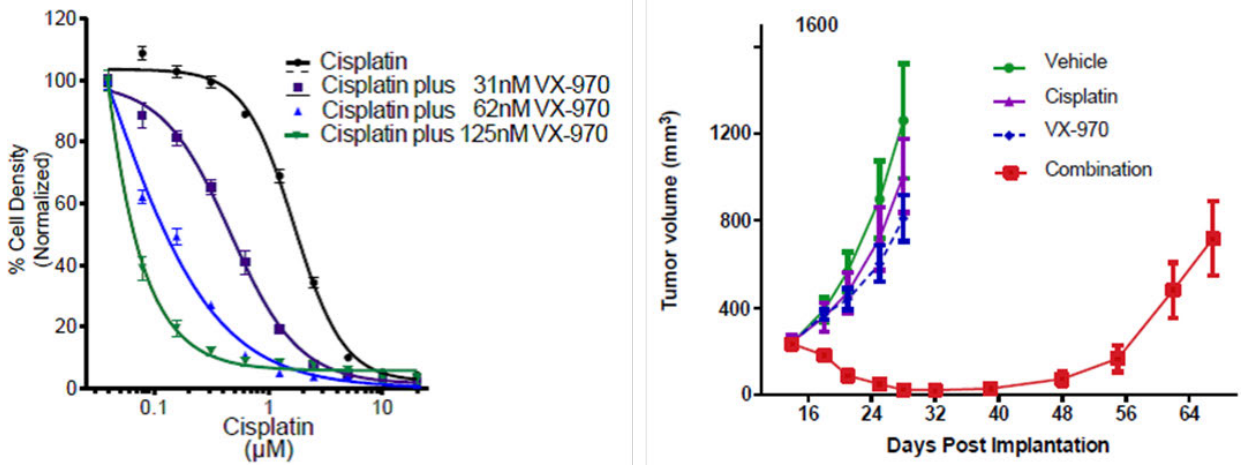


Figure 4. In vitro (left panel) and in vivo (right panel) synergy of cisplatin and M6620 (VX-970). Left panel shows MTS cell viability assays of cisplatin + M6620 (VX-970), with dose-dependent increased potency with the addition of ATR inhibition with M6620 (VX-970). Right panel shows M6620 (VX-970) improves tumor responses to cisplatin in a PDX NSCLC model in SCID mice, as reflected in reduction in tumor volumes. M6620 (VX-970) was dosed at 60 mg/kg PO daily x 4, cisplatin was dosed at 1 mg/kg IP q weekly [14].

Nonclinical Pharmacokinetics

M6620 (VX-970) partitions between blood and plasma, and varies with dose and species. Therefore, whole blood is recommended for the determination of drug exposure. The volume of distribution in rats, mice, dogs, and monkeys (21, 20, 10, and 6 L/kg, respectively) for M6620 (VX-970) was high and exceeded the volume of total body water. Tissue exposure, including tumor, was high with maximum concentrations reached after 3 hours for all tissues except for kidney and thymus, which peaked at 6 hours. In rats, no accumulation or retention was observed in tissues and the elimination half-lives were similar across all tissues and whole blood. Whole blood half-lives in rats and dogs were 11.6 and 9.8 hours, respectively. M6620 (VX-970) had high plasma protein binding and the free fraction in human was 2.1%. A low potential for drug-drug interactions was predicted, based on minimal inhibition or induction of (CYP) 450 isozymes by M6620 (VX-970), however strong inducers or inhibitors or CYP3A4 may alter M6620 (VX-970) kinetics and blood levels. M6620 (VX-970) was primarily eliminated by oxidative metabolism, in the urine and bile. All metabolites observed in human hepatocyte incubations were also observed in either rat or dog hepatocyte incubations and in the blood, bile, or urine from rats or dogs. The systemic clearance values of M6620 (VX-970) following IV administration were determined to be 26 and 13 mL/min/kg in the rat and dog, respectively. The impact of drug-efflux pumps on the cellular activity of M6620 (VX-970) activity was tested in MDR-1 and MRP-1 expressing cancer cells and matched drug sensitive cells, with no decrease in M6620 (VX-970) activity in cancer cells expressing drug efflux pumps [Investigator Brochure].

Preclinical Safety Pharmacology Studies and Toxicology Studies

In vitro and in vivo safety pharmacology studies designed to evaluate effects of M6620 (VX-970) against multiple protein targets and the cardiovascular system did not demonstrate any toxicologically significant effects at exposures or concentrations that significantly exceed the

targeted maximum circulating concentration of M6620 (VX-970) in humans. M6620 (VX-970) was administered by both oral and IV routes to rats and dogs for up to 28 days. The rat severely toxic dose in 10% of rats (STD_{10}) was considered to be an IV dose of 30 mg/kg/day, and the dog highest non-severely toxic dose was considered to be an IV dose of 20 mg/kg/day. Target organs of toxicity in the rat included the testes and peripheral blood cell populations (red cell mass, eosinophils, and platelets), and M6620 (VX-970) produced mild irritation at the infusion site. Target organs in the dog included the liver, testes, and peripheral blood cell populations (red cell mass and eosinophils). M6620 (VX-970) had no cardiovascular toxicities, was not genotoxic in a non-GLP 2-strain mutagenicity assay, had no hemolytic potential in human blood or compatibility issues in human plasma, and was well-tolerated in an acute rabbit parenteral injection study. M6620 (VX-970) does absorb in the ultraviolet-visible spectrum and has tissue distribution in rats [Investigator's Brochure].

Clinical Pharmacokinetic Studies

Preliminary clinical PK data available from the Phase I first-in-human study of M6620 (VX-970) [Study 001] show mean M6620 (VX-970) plasma concentration versus time profiles were similar in shape to those of the corresponding whole blood profiles. Variability in the plasma matrix was generally reduced, however, and similar PK trends were detected between both matrices. PK exposures tended to increase proportionally with increasing dose based upon C_{max} (ranged from 72.0 ng/mL in the 18 mg/m^2 dose group to 817 ng/mL in the 140 mg/m^2 dose group) and area under the concentration versus time curve extrapolated to infinity ($AUC_{0-\infty}$) (ranged from 351 h*ng/mL in the 18 mg/m^2 dose group to 6148 h*ng/mL in the 210 mg/m^2 dose group). The mean volume of distribution at steady-state (Vss) ranged from 1148 L to 1602 L and mean clearance ranged from 60.6 L/h to 98.2 L/h in the 140 mg/m^2 and 18 mg/m^2 dose groups, respectively, showing no apparent trends. Similar to the whole blood matrix, the terminal elimination half-life was approximately 16 hours across all dose groups. The administration of gemcitabine 24 hours prior to M6620 (VX-970) administration did not appear to affect the pharmacokinetics of M6620 (VX-970) [Investigator's Brochure].

Clinical Experience

As of February 2015 (data reporting cut-off date), preliminary safety and efficacy data are available for 38 subjects from Study 001 parts A and B (A: 7-14-day lead in with M6620 (VX-970) then M6620 (VX-970) in combination with gemcitabine; B: 21-day lead in with M6620 (VX-970) and then M6620 (VX-970) in combination with cisplatin) and for 11 subjects from Study 002A (single agent M6620 (VX-970)) [9]. Preliminary PK data are also available from study 002B (M6620 (VX-970) in combination with carboplatin) [Investigator's Brochure].

In Study 001A (M6620 (VX-970) from 18 to 140 mg/m^2 IV, gemcitabine from 500 to 875 mg/m^2 IV), 5 of 6 subjects with NSCLC, 7 of 13 subjects with other types of cancers, and 4 of 9 subjects with colorectal cancer had stable disease as best overall response, and one subject with EBV+ nasopharyngeal cancer exhibited a partial response. Several subjects had an overall response of stable disease for at least 4 cycles. In Study 001B, 4 of 7 subjects had stable disease as best overall response; one subject with endometrial cancer had stable disease for 6 cycles (ongoing at time of report). In Study 002A, 3 of 10 subjects with other types of cancers had stable disease as best overall response; one subject with colorectal cancer exhibited a partial response (80% reduction of tumor lesion diameter) and continues on treatment after 11 cycles.

During the lead-in phase of Study 001A (single dose M6620 (VX-970) ranging from 18 to 210 mg/m^2 IV), 2 subjects had SAEs of palpitations, pyrexia, and dyspnea; during the combination phase, 9 of 31 subjects had SAEs classified as related to study drug, 3 had SAEs of Grade 1 pyrexia classified as possibly related or related to study drug, and 2 had SAEs of Grade 4 thrombocytopenia classified as related to study drugs. The most common AEs, regardless of causality, were nausea (20 subjects), vomiting (17 subjects), and fatigue (15 subjects).

During Study 001B, one subject had an SAE of metastases to the central nervous system that led to study drug discontinuation; during the combination phase (M6620 (VX-970) at 90 or 140 mg/m^2 IV in combination with cisplatin 40 mg/m^2 IV), 1 of 6 subjects had an SAE of metastases to central nervous system and one had dyspnea, which were not related to study drugs. The most common AEs, regardless of causality, were nausea (4 subjects) and fatigue (4 subjects).

In Study 002, 11 subjects received M6620 (VX-970) at doses ranging from 60 to 480 mg/m^2 IV. Two subjects had SAEs of Grade 3 ascites, which were classified as not related to study drug, and Grade 3 fatigue, which was classified as possibly related to study drug. Serious acute hypersensitivity has been identified as an adverse drug reaction for M6620 (VX-970). As of 17 April 2015, a serious acute hypersensitivity reaction occurred in 2 of 66 subjects and a third reaction occurred after the SAE data cut-off date of 17 April 2015, raising the estimated incidence of this ADR to between 4% and 5%.

Preliminary clinical pharmacokinetic data are available from Studies 001 and 002. PK exposures tended to increase proportionally with increasing dose based upon Cmax (ranged from 72.0 ng/mL in the 18 mg/m^2 dose group to 817 ng/mL in the 140 mg/m^2 dose group) and AUC0-∞ (ranged from 351 h*ng/mL in the 18 mg/m^2 dose group to 6148 h*ng/mL in the 210 mg/m^2 dose group). The mean volume of distribution at steady-state (Vss) ranged from 1148 L to 1602 L and mean clearance (CL) ranged from 60.6 L/h to 98.2 L/h in the 140 mg/m^2 and 18 mg/m^2 dose groups, respectively, showing no apparent trends. The terminal elimination half-life was approximately 16 hours across all dose groups. Overall, the Cmax were 1.36-fold greater and the AUC0-∞ was 1.43-fold greater in whole blood than plasma matrix, suggesting that plasma is an appropriate matrix to characterize the pharmacokinetics of M6620 (VX-970). M6620 (VX-970) PK exposure parameters were similar when dosed alone versus after gemcitabine or carboplatin administration and indicated no apparent interactions between M6620 (VX-970) and these agents.

Dose escalation for M6620 (VX-970) on this current study P9771 was informed by results from ongoing Study 002B, which has reached 480 mg/m^2; no DLTs have been observed (Vertex communication).

At the time of Amendment L, dated 4/22/2019, 36 patients have been enrolled onto this study and the MTD established as DL6 (200 mg veliparib q12 hours on days 1-3 and 8-10, 210 mg/m^2 M6620 on days 2 and 9, and 40 mg/m^2 cisplatin on days 1 and 8 of 21-day cycles). The DLTs on DL7 were a grade 4 thrombocytopenia and an infusion reaction to M6620 (VX970) that kept the patient from completing the cycle.

Potential Drug Interactions

Because the drug interaction profile of M6620 (VX-970) has not been fully characterized, caution should be used when co-administering medications with M6620 (VX-970). As M6620 (VX-970) is primarily metabolized by CYP3A4, concomitant administration with potent inhibitors or inducers of CYP3A4 should be avoided [Investigator's Brochure].

2.3 Veliparib (ABT-888)

Poly (ADP-ribose) polymerases (PARPs) are a family of nuclear protein enzymes involved in the post-translational modification of proteins and synthesis of poly (ADP-ribose) required for recognition of DNA damage and repair. PARP-1 and PARP-2 are the best characterized members of the PARP family, and play a key role in the DNA damage response and repair of SSBs through BER. PARP inhibition has been shown to result in catalytic inhibition, trapping of PARP-1 on DNA repair intermediates at SSBs, and stalling of replication forks that require BRCA-dependent HR for resolution [10].

Mechanism of Action

Veliparib is an orally available, potent small molecule inhibitor of PARP1/2 that has shown activity through sensitization of a broad range of tumor cells and xenografts to various DNA-damaging agents [11]. Expression of PARP is higher in tumor cells compared to normal cells and increased PARP activity is one of the mechanisms by which tumor cells avoid apoptosis caused by DNA damaging agents [12]. PARP inhibition impairs the cell's ability to repair DNA damage through exposure to chemotoxic agents, such as cisplatin, and further defects in compensatory DNA repair mechanisms further impairs the ability to withstand genotoxic stress and allows for potentiation of antitumor activity.

Nonclinical Toxicology Studies

In a variety of nonclinical models, veliparib increased the sensitivity of tumor cells to DNA-damaging agents, including temozolomide, irinotecan, cyclophosphamide, cisplatin, carboplatin, and radiation at therapeutic doses that do not increase the toxicity of chemotherapeutic agents.

[redacted]

Pharmacokinetic Studies

A Phase 0 study of veliparib administered as a single dose, ranging from 10 to 50 mg, to 13 subjects, showed that veliparib was rapidly absorbed, with peak plasma levels occurring between 0.5 and 1.5 hours post-dosing [13]. At a dose of 25 mg, the mean plasma concentration of veliparib (0.15 μg/mL) was higher than the plasma concentration associated with maximal efficacy in nonclinical models (0.070 μg/mL) for an average of 4.1 hours. These results were consistent with the projected human pharmacokinetic profile based on nonclinical data.

In Phase 1 studies, the exposure of veliparib was approximately dose-proportional over the 10 through 500 mg twice daily (BID) dosing range, with peak plasma concentrations at approximately 1 to 2 hours after dosing across dose levels. The terminal half-life ($t_{1/2}$) of veliparib was about 6 hours, with minimal accumulation following multiple BID dosing. Food did not have a significant effect on veliparib bioavailability. The administration of a high-fat meal had no significant effect on AUC and only caused a slight decrease in veliparib C_{max} (17%) and a delay of approximately 1 hour in T_{max}. In clinical studies, the mean urinary recovery of unchanged veliparib was 72% and the total urinary recovery of veliparib (as parent compound and M8 metabolite) was 86% [Investigator's Brochure].

Drug Interactions

Veliparib is not a reversible or time-dependent inhibitor of the human cytochrome P450 (CYP) enzymes CYP1A2, 2C8, 2C9, 2D6, or 3A4/5 (half maximal inhibitory concentration, $IC_{50} > 30$ μM). It is not a reversible CYP3B6 inhibitor ($IC_{50} > 30$ μM), and causes minimal time-dependent inhibition of CYP2B6 at 50 μM. Veliparib does not significantly induce activities of major CYPs CYP1A2, 2B6, 2C9, and 3A4. 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 at anticipated therapeutic concentrations.

Veliparib is a substrate of P-gp and kidney transporters OCT2, MATE1, and MATE2K. Consequently, co-administration of veliparib with potent inhibitors of OCT2, MATE1, and MATE2K and/or P-gp may decrease veliparib renal clearance and increase its plasma exposure. Veliparib does not inhibit P-gp or BCRP at concentrations up to 1000 μM. At therapeutic doses in combination, veliparib has a low potential for clinical pharmacokinetic drug-drug interactions with transporters: P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K). Veliparib may inhibit OCT1 in the liver and MATE1 and MATE2K in the kidney at higher doses (e.g., 400 mg BID) [Investigator's Brochure].

Summary of Clinical Studies

As of March 24, 2014, approximately 1255 patients have been treated with veliparib in AbbVie-sponsored clinical trials, with veliparib administered as either monotherapy or in combination therapy in patients with various solid tumors. As of March 31, 2014, approximately 1687 adult patients and 44 pediatric patients have been treated with veliparib in CTEP-sponsored studies. Veliparib has been generally administered in doses up to 500 mg BID as monotherapy, and up to 400 mg BID in combination with cytotoxic chemotherapies or radiation therapy [Investigator's Brochure]. Recent published results of Phase I studies of veliparib in combination with cisplatin and vinorelbine in patients with advanced triple-negative breast cancer and/or BRCA mutation-associated breast cancer show tolerability of veliparib at a dose of 300 mg BID when combined with cisplatin at 75 mg/m^2 on day 1 and vinorelbine at 25 mg/m^2 on days 1 and 8 of a 21-day cycle. Responses were seen in 73% of patients who carried a BRCA mutation (6/11 partial responses, 2/11 complete responses) compared with 53% of patients without a known BRCA mutation (11/21 partial responses) and 33% of patients with unknown BRCA status (2/6 partial responses). The majority of toxicities were hematologic [14].

Veliparib, when used in combination with cytotoxic chemotherapy, is expected to have unique toxicities reflected in amplification of the toxicities of the backbone regimen, and have included hematologic, gastrointestinal, and CNS toxicities, and possibly thromboembolic events in combination with temozolomide. Secondary malignancies are a potential risk of veliparib based on its mechanism of action [Investigator's Brochure].

2.4 Cisplatin

Cisplatin injection is currently FDA-approved in combination with other chemotherapeutic agents in patients with transitional cell bladder cancer no longer amenable to local treatments, metastatic ovarian tumors after surgery and/or radiotherapeutic procedures or as second-line in the refractory setting, and for metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures.

Mechanism of Action:
Cisplatin is a divalent inorganic, water-soluble, platinum-containing complex. Following administration, cisplatin undergoes mono- and di-hydroxyl substitution of its cis-oriented chloride, allowing for interaction with negatively charged DNA bases, and the formation of interstrand and intrastrand crosslinks. DNA adducts formed by cisplatin interfere with DNA replication and transcription, leading to DNA breaks.

Pharmacokinetics:
Cisplatin plasma concentrations decay mono-exponentially with a half-life of ~20-30 minutes following bolus administrations of 50 or 100 mg/m^2, and after 2 hour or 7 hour infusions of cisplatin 100 mg/m^2. The total body clearance and volume of distribution at steady-state after 7 hour infusion of cisplatin at 100 mg/m^2 are ~ 15-16 L/h/m^2 and 11-12 L/m^2, respectively.

Cisplatin does not undergo the instantaneous and reversible binding to plasma proteins that is characteristic of normal drug-protein binding. However, the platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins, including albumin, transferrin, and gamma globulin. The unbound fraction, composed predominantly of parent drug, is cleared within minutes. The ratios of cisplatin to total free (ultrafiltrable) platinum in the plasma vary considerably between patients and range from 0.5-1.1 after a dose of 100 mg/m^2. Three hours after a bolus injection and two hours after the end of a 3-hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of 5 days or more.

Following cisplatin dose of 20-120 mg/m^2, the concentrations of platinum are highest in liver, prostate, and kidney; somewhat lower in bladder, muscle, testicle, pancreas, and spleen; and lowest in bowel, adrenal, heart, lung, cerebrum, and cerebellum. Platinum is present in tissues for as long as 180 days after the last administration. Maximum red blood cell concentrations of platinum are reached within 90-150 minutes after a 100 mg/m^2 dose of cisplatin and decline in a biphasic manner with a terminal half-life of 36-47 days.

Only a small portion of the drug is excreted by the kidneys during the first 6 hours after administration. Over a dose range of 40-140 mg/m^2 given as a bolus injection or as infusions varying in length from 1 hour to 24 hours, 10-40% of the administered platinum is excreted in the urine within 24 hours. Over 5 days following administration of 40-100 mg/m^2 doses given as rapid, 2-3 hours, or 6-8 hour infusions, a mean of 35-51% of the dosed platinum is excreted in the urine, mostly covalently bound to protein and peptides. Mean urinary recoveries of platinum of about 14-30% of the dose are found following 5-day administrations of 20, 30 or 40 mg/m^2/day. Only a small percentage of the administered platinum is excreted beyond 24 hours post-infusion and most of the platinum excreted in the urine in 24 hours is excreted within the first few hours. The parent compound is also excreted in the urine and accounts for 13-17% of the dose excreted within one hour after administration of 50 mg/m^2. The mean renal clearance of cisplatin exceeds creatinine clearance and is 62 and 50 mL/min/m^2 following administration of 100 mg/m^2 as 2 hour or 6-7 hour infusions, respectively. The renal clearance of free (ultrafiltrable) platinum also exceeds the glomerular filtration rate indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. The renal clearance of free platinum is nonlinear and variable and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption. There is a potential for accumulation of ultrafiltrable platinum plasma concentrations whenever cisplatin is administered on a daily basis but not when dosed on an intermittent basis. No significant relationships exist between the renal clearance of either free platinum or cisplatin and creatinine clearance. Although small amounts of platinum are present in the bile and large intestine after administration of cisplatin, the fecal excretion of platinum appears to be insignificant.

Drug Interactions:
Concomitant use of cisplatin and aminoglycosides (amikacin, gentamicin, streptomycin, tobramycin) has the potential to increase the risk of nephrotoxicity. Concomitant use of anticonvulsant agents (carbamazepine, fosphenytoin, phenytoin, valproic acid) may result in subtherapeutic plasma concentrations of these agents, resulting in seizure activity. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

Adverse Reactions
Nephrotoxicity
Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28-36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. The severity of toxicity correlates directly with the amount of cisplatin administered in individual and cumulative doses. Renal toxicity may be mitigated by the administration of hydration during and after cisplatin administration and avoiding administration of concurrent nephrotoxic drugs.

Impairment of renal function has been associated with renal tubular damage, and may present with electrolyte disturbances such as hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Hypomagnesemia may be a possible permanent adverse effect of cisplatin. Decreased serum sodium concentrations have been observed within 24-72 hours following

cisplatin infusion. Chronic salt wasting and hyponatremia may persist after discontinuation of cisplatin.

Ototoxicity
Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000-8000 Hz). Hearing loss may be unilateral or bilateral and tends to become more frequent and severe with repeated cisplatin doses. Vestibular toxicity has also been reported. Ototoxic effects may be related to peak plasma concentration of cisplatin.

Ocular Toxicity
Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occur with discontinuation of therapy. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than recommended. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. Findings on fundoscopic exam include irregular pigmentation of the macular area.

Neurotoxicity
Peripheral neuropathy is a dose-limiting toxicity. The severity of neuropathy varies with dose intensity and the total cumulative dose administered. Symptoms usually develop during treatment, and persist after discontinuation of treatment, and include numbness, tingling, impairment of reflexes, vibratory sense, proprioception, and sensory ataxia.

Hematologic Toxicity
Myelosuppression occurs in 25-30% of patients. The nadir platelet count and leukocyte count occurs between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (> 50 mg/m^2). Anemia (defined as decrease of 2 g/dL) occurs at approximately the same frequency and timing as leukopenia and thrombocytopenia. Fever and infection have been reported in patients with neutropenia.

Gastrointestinal Toxicity
Cisplatin is highly emetogenic; nausea and vomiting may begin within 1 to 4 hours after treatment and may last up to 24 hours. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients despite adequate emetic control on the day of therapy. In some cases, vomiting, nausea, and/or anorexia may persist for up to 1 week after treatment.

Hepatotoxicity
Transient elevations of liver enzymes and bilirubin have been reported to be associated with cisplatin administration at the recommended doses.

Anaphylactic-Like Reactions
Anaphylactic-like reactions have been reported in patients previously exposed to platinums. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes

after drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated.

2.5 Correlative Studies Background

2.5.1 Pharmacodynamic Assessment of Drug Response

Evaluation of drug effect on DNA damage response in tumor and CTCs will be performed by immunofluorescence assays for measurement of DNA damage-repair markers, such as γH2AX, RAD51, pNbs1, and pATR.

ATR phosphorylation in response to DNA damage will be used as a marker of direct target effect. A quantitative immunofluorescence assay for pT1989-ATR will be used as a marker of ATR inhibitor activity.

Downstream from the primary biomarker are three additional biomarkers of interest:

- Histone H2AX is one of the H2A histones present in nucleosomes from normal tissues as well as cancer tissues. H2AX is phosphorylated at its C-terminus (serine 139) following DNA double-strand breaks. Phosphorylated H2AX, referred to as γH2AX, can be selectively detected using antibodies by Western blots or immunofluorescence. The levels of γH2AX are directly correlated to the amounts of double-strand breaks per cell, and can be used as a dosimeter and biomarker for DNA double-strand breaks.

- Nbs1 is an adapter protein, linking Mre11 and Rad50 to form the MRN complex involved in recognition of DNA damage and initiation of the signaling cascade in response to DNA double-strand breaks.

- Rad51 plays a central role in recognition of double-strand breaks and homologous recombination.

A multiplexed immunofluorescence assay for γH2AX, phosphorylated Nbs1, and Rad51 has recently been validated and published by the Pharmacodynamic Assay Development and Implementation Section (PADIS) at the Frederick National Laboratory for Cancer Research (FNLCR) [15]. PADIS and the National Clinical Target Validation Laboratory (NCTVL) will carry out the testing of all 4 PD biomarkers on tumor tissue and CTCs collected from this study.

2.5.2 Genomic Analysis

Genomic sequencing of patient biopsies will be performed in the laboratory of Dr. Mickey Williams, Director of the Molecular Characterization (MoCha) Laboratory, located at FNLCR. MoCha is registered under Clinical Laboratory Improvement Amendments (CLIA) for the performance of high-complexity molecular testing for clinical purposes. MoCha will perform two types of analysis: (1) exploratory (non-CLIA) whole exome sequencing (WES) analysis of tumor tissues, and (2) the CLIA-

certified Oncomine Comprehensive Assay v3 (OCAv3), a next generation sequencing (NGS) assay designed to find gene mutations within tumors (somatic mutations).

2.5.2.1 WES

To address the reality that even those patients who respond to this drug combination are likely to eventually progress, genomic (whole exome) information from consenting patients undergoing optional tumor biopsies at restaging follow-up or at the time of progression will be compared with C1D1 genomic information from those patients to investigate the development of acquired drug resistance.

2.5.2.2 OCAv3

OCAv3 is not designed to be used to find hereditary or germline mutations. The assay was originally validated for the NCI-MATCH clinical trial (NCT02465060) and is considered an investigational device limited by Federal law to investigational use. Its performance characteristics have been determined through extensive testing by the NCI-MATCH network laboratories. It has not been cleared by the US Food and Drug Administration and such approval is not required for clinical implementation.

OCAv3 can reliably identify the presence or absence of greater than 3,000 known mutations of interest (MOIs) in 161 unique genes, with results compared to the Human Reference Genome hg19. The assay identifies greater than 3,000 annotated mutations of interest (MOIs) characterized into 5 mutation types: single nucleotide variants (SNV), small insertions/deletions (indels), large (> 3 bases) insertions/deletions (large indels), copy number variants (CNV), and gene fusions. In the majority of cases, we do not know the medical significance of the genetic variants [16, 17].

This report generated from the assay is intended to provide background information to the oncology team and the patient about mutations detected within the patient's tumor. It does not determine assignment of a patient to a clinical trial; however, as MoCha is a MATCH study-designated lab (see https://ecog-acrin.org/nci-match-eay131-designated-labs), a CLIA OCAv3 report from MoCha indicating that a patient carries an eligible aMOI is sufficient for enrollment on the NCI MATCH (NCT02465060) and MPACT (NCT01827384) trials.

Mutations detected by the assay may be present only in the tumor, or in every cell of the body; this test also cannot tell whether a potential germline mutation causes or will cause a hereditary cancer syndrome. If the patient's personal and/or family history are suggestive of a hereditary cancer predisposition, it is recommended that the PI arrange for the patient to meet with a genetic counselor and, if warranted, undergo the appropriate genetic test.

A Certificate of Confidentiality has been obtained from the NIH to help protect the privacy of all study participants. Information on tumor gene variants will be stored in the patient's medical records.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed solid tumors for which standard therapy known to prolong survival has failed in the metastatic setting or for which standard therapies do not exist.

3.1.2 Tumor amenable to biopsy and willingness to undergo tumor biopsies before and after M6620 (VX-970) treatment during the expansion phase of the trial (biopsies optional during the escalation phase).

3.1.3 Patients must have completed any chemotherapy, radiation therapy, surgery, or biologic therapy ≥3 weeks (or ≥ 5 half-lives, whichever is shorter) prior to entering the study. Patients must be ≥ 2 weeks since any prior administration of a study drug in an exploratory IND/Phase 0 study and ≥ 1 week since any palliative radiation therapy. Patients must have recovered to eligibility levels from prior toxicity or adverse events.

3.1.4 Age ≥18 years of age.

3.1.5 ECOG performance status ≤ 2 (see Appendix A).

3.1.6 Life expectancy > 3 months.

3.1.7 Patients must have normal organ and marrow function as defined below:

– absolute neutrophil count	≥1,500/mcL
– hemoglobin	≥ 10 g/dL
– platelets	≥100,000/mcL
– total bilirubin	≤1.5 X institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤1.5 X institutional upper limit of normal (OR ≤ 3X ULN in the setting of liver metastases)
– creatinine	≤1.5X institutional upper limit of normal
	OR
– creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.8 The effects of M6620 (VX-970) and veliparib on the developing human fetus are unknown. For this reason and because cisplatin is known to be teratogenic, women of child-bearing potential and men 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 after completing study treatment. 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 for 6 months after completion of administration of study agents.

3.1.9 HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with M6620 (VX-970). In addition, these subjects are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.1.10 Patients must be able to swallow whole tablets or capsules. Nasogastric or G-tube administration is not allowed. Any gastrointestinal disease which would impair ability to swallow, retain, or absorb drug is not allowed.

3.1.11 Ability to understand and the willingness to sign a written informed consent form.

3.1.12 During the expansion phase of the protocol, patients must have disease amenable to biopsy and be willing to undergo pre- and post-treatment biopsies.

3.1.13 Patients must have ≥10.0 g/dL Hb and no blood transfusion in the past 28 days to receive Veliparib.

3.2 Exclusion Criteria

3.2.1 Patients who are receiving any other investigational agents.

3.2.2 Patients with known active brain metastases or carcinomatous meningitis are excluded from this clinical trial. Patients whose brain metastatic disease status has remained stable for ≥ 4 weeks following treatment of brain metastases are eligible to participate at the discretion of the principal investigator.

3.2.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active untreated infection, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.4 Patients required to be on any of the concomitant medications listed in Appendix B are excluded.

3.2.5 Pregnant women and women who are breastfeeding are excluded from this study because the effects of the study drugs on the developing fetus are unknown.

3.2.6 Patients who have had prior platinum-based therapy who have > Grade 1 neurotoxicity or ototoxicity at the time of enrollment will not be permitted on study.

3.2.7 Patients with a seizure history will not be permitted on protocol due to association of veliparib with seizure activity in animal toxicology studies at higher doses. Patients on anticonvulsant medications will not be permitted on study due to the potential to lower plasma levels of anticonvulsants and risk for seizure activity.

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

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

3.4 Screening Evaluation

3.4.1 Histologic confirmation of primary tumor tissue or of known recurrence will be required from each participant to confirm diagnosis. Pathology reports from outside institutions will be accepted.

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

3.4.3 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to enrollment. MRI evaluation of site of disease may be performed in lieu of CT evaluation at the discretion of the principal investigator if it is the opinion of the investigator that this modality would provide a more accurate assessment of disease than a CT would, for a given site.

3.4.4 Laboratory Evaluation: Baseline laboratory data are to be obtained within 8 days prior to enrollment:

- Hematological Profile: CBC with differential.
- Biochemical Profile: albumin, total bilirubin, BUN, calcium, creatinine, SGOT [AST], SGPT [ALT], magnesium, potassium, and sodium.
- Coagulation Profile: PT, PTT, INR required within 1 week prior to all biopsies, and may also be performed as clinically indicated.
- Serum or urine pregnancy test for female participants of childbearing potential.

4 REGISTRATION PROCEDURES

4.1 NCI Clinical Center Patient Registration Process

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) and through the Theradex Interactive Web Response System (IWRS) within 24 hours after signing consent. Access IWRS through https://iwrs.theradex.com under the "Patient" tab utilizing your CTEP-IAM Username and Password. A registration Eligibility Checklist from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via

encrypted email to the NCI Central Registration Office (HOIS; ncicentralregistration-l@mail.nih.gov). After confirmation of eligibility at the Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail. Patient enrollment data entered in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.
Please note that it is very important for all registrars to acquire encrypted e-mail from NIH Help Desk, since the verification of registration includes patient's information.

Off Protocol Therapy and Off-Study Procedure: Authorized staff must notify the Central Registration Office (CRO) when a patient is taken off protocol therapy and when a patient is taken off-study. The Participant Status Updates Form from the Web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to the NCI Central Registration Office (HOIS; ncicentralregistration-l@mail.nih.gov).

4.2 Participating Site Patient Registration

Authorized staff must register an eligible candidate through the Theradex Interactive Web Response System (IWRS). Access IWRS through https://iwrs.theradex.com under the "Patient" tab utilizing your CTEP-IAM Username and Password. Patient enrollment data entered in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

Off-Study Procedure: Authorized staff must update the patient status in Medidata Rave when a patient is taken off study.

4.3 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

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

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

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

5 TREATMENT PLAN

This is an open-label Phase I trial evaluating the combination of M6620 (VX-970), an ATR inhibitor, veliparib, an oral PARP inhibitor, and cisplatin in patients with refractory solid tumors.

Reported adverse events and potential risks for M6620 (VX-970), veliparib, and cisplatin are described in Section 7. Appropriate dose modifications for M6620 (VX-970), veliparib, and cisplatin are described in Section 6.

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, and laboratory evaluations must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.4), the results from these screening evaluations may be used as baseline measurements. If >8 days have passed since the screening evaluations, the medical history, physical examination, and laboratory evaluations must be repeated prior to starting protocol therapy.

History and physical examination can be done up to 3 days before the start of a new cycle prior to treatment with cisplatin on day 1. Patients will also be examined on day 8 or 9 (± 1 day due to scheduling conflicts) of each cycle. Each cycle is 21 days (± 1 day due to scheduling conflicts).

Labs (CBC with differential; serum chemistries) will be performed as follows (±1 day for all dates):

- Cycle 1
    - Day 1 prior to treatment (or within 8 days prior to treatment)
    - Day 2 prior to M6620 (VX-970)
    - Day 8 prior to prescribing veliparib for week 2
    - Day 9 prior to M6620 (VX-970)

  - Day 15 (may be performed by patients' home oncologist)
- Cycle 2 and beyond
  - Day 1 prior to treatment
  - Week 2 prior to first IV treatment
  - Day 15 (optional and may be performed by patients' home oncologist)

CT scans will be performed at baseline (within 28 days prior to start of protocol therapy), and repeat-imaging scans will be performed every 2 cycles (every 3 cycles for patients on study for more than one year, 4 cycles for patients on study more than 3 years). MRI evaluation of site of disease may be performed in lieu of CT evaluation at the discretion of the principal investigator if it is the opinion of the investigator that this modality would provide a more accurate assessment of disease than a CT would for a given site.

ECG will be performed at baseline (within 8 days prior to start of protocol therapy), within approximately 1 hour after the end of M6620 (VX-970) infusion during cycle 1 only, and as clinically indicated.

The starting dose will start at dose level 1 per dosing schema below. Intra-patient dose escalation will be allowed.

Once the MTD is established, additional patients will be enrolled to the expansion phase as described in Section 13.1.

5.1 Agent Administration

5.1.1 M6620 (VX-970) Administration

M6620 (VX-970) will be administered intravenously, over one hour (± 10 minutes) on days 2 and 9 of each 21-day cycle (or on days 1 and 8 of any cycle in which cisplatin is not administered). M6620 (VX-970) should not come in contact with 0.9% Sodium Chloride due to incompatibility. 5% dextrose in water solution must be used for IV line priming and flushing. Infuse using an infusion set containing low-sorption or non-PVC, DEHP-free tubing and an in-line 0.2 micron filter.

5.1.2 Veliparib administration

Veliparib will be administered orally on days 1 through 3 and days 8 through 10 of each 21-day cycle. Veliparib should be administered before cisplatin and M6620 (VX-970).

5.1.3 Cisplatin administration

Cisplatin will be administered at 40 mg/m^2 intravenously over one hour (± 10 minutes), via central or peripheral access on day 1 (and day 8 on DL3 and higher) of each 21-day cycle. As of ***Amendment I*** (12/7/2017), patients who have been on trial for at least 6 cycles may have cisplatin administration held or discontinued while continuing on trial at the discretion of the PI, Dr. [redacted] to address the potential for cumulative neurotoxicity observed with extended cisplatin treatment.

- Prior to cisplatin administration, at least 500 mL of 0.9% sodium chloride with KCl 10 mEq/L and magnesium sulfate 4 mEq/L injection should be administered over at least 60 minutes. Following administration of cisplatin, at least an additional 500 mL of 0.9% sodium chloride with KCl 10 mEq/L and magnesium sulfate 4 mEq/L injection should be administered over at least 60 minutes.
- Patients will additionally receive pre-medication with anti-emetics. The following regimen is recommended for initial antiemetic prophylaxis; administration of steroids will be at the discretion of the investigator:
  - Dexamethasone 12 mg orally at least 60 minutes prior to cisplatin on day 1 (and day 8 on DL 3 and above) of each 21-day cycle.
  - Aprepitant 125 mg orally given at least 60 minutes prior to cisplatin on day 1 (and day 8 on DL 3 and above) of each 21-day cycle, followed by 80 mg orally daily for days 2 and 3 (and days 9 and 10 on DL 3 and higher)*
  - Ondansetron 8 mg orally given at least 60 minutes prior to cisplatin on day 1 (and day 8 on DL 3 and above) of each 21-day cycle, and continued every 8 hours for days 1-5 (and days 8-12 on DL 3 and higher)

For patient convenience, pre-medications can alternatively be given intravenously 30 minutes prior to therapy.

*A single 150 mg dose of fosaprepitant IV may be given prior to cisplatin in lieu of the oral aprepitant, or another anti-emetic may be used if aprepitant is not tolerated.

Dosing Schema:

Dose Level	Veliparib (PO q12 hours ± 1 hour)	M6620 (VX-970) (IV Days 1/2 and 8/9)	Cisplatin (IV Day 1 or Days 1 and 8)
-2	20 mg days 1-3, 8-10	40 mg/m^2	40 mg/m^2 day 1
-1	40 mg days 1-3, 8-10	60 mg/m^2	40 mg/m^2 day 1
1	100 mg days 1-3, 8-10	90 mg/m^2	40 mg/m^2 day 1
2	100 mg days 1-3, 8-10	140 mg/m^2	40 mg/m^2 day 1

3	100 mg days 1-3, 8-10	120 mg/m^2	40 mg/m^2 days 1, 8
4	100 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
5	150 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
6	200 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
7	300 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8
8	400 mg days 1-3, 8-10	210 mg/m^2	40 mg/m^2 days 1, 8

Doses will be calculated based on body surface area per institutional SOP.

As of Amendment L (dated 4/22/2019), the MTD for this combination has been established as DL6.

5.2 Intra-patient Dose Escalation

Intra-patient dose escalation is permitted ONLY if: **a)** there is no toxicity > grade 1 that is possibly, probably, or definitely related to the study drugs after one cycle at the patient's initially assigned dose level (subsequent cycles may be delayed up to 14 days past the end of the previous 21-day cycle to allow for toxicities to resolve), **b)** higher doses have been evaluated and completed without DLT, and **c)** disease has not progressed. Doses may be escalated by one dose level for every subsequent cycle, provided conditions a–c are met, up to the last evaluated dose level NOT associated with DLT.

Intra-patient dose reductions: If a patient experiences DLT during a cycle, the dose will be reduced by one level (if there is a lower dose level) for the next cycle, provided toxicity has recovered to ≤ Grade 1 within 14 days after completing a 21-day cycle, and the patient's disease is stable or responding. If a patient is dose reduced twice and still experiences a DLT, then the patient would be removed from the study unless the patient is experiencing clinical benefit and, at the PI's discretion, should be allowed to continue on study. If no lower dose level exists, then the patient will be removed from the study.

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.

5.3 Definition of Dose-Limiting Toxicity

Determination of dose-limiting toxicity (DLT) will be based on toxicities observed in the first cycle of therapy. Dose escalation will proceed within each cohort according to the following scheme. DLT is defined below:

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule

0 out of 3	Enter 3 patients at the next dose level.
≥ 2	Dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

Dose limiting toxicity (DLT) is defined as an adverse event that is related (possibly, probably, or definitely) to administration of study drugs and fulfills one of the following criteria.

5.3.1 Grade ≥ 3 Non-Hematological Toxicity

Grade ≥ 3 non-hematological toxicity thought to be related to study medications will be considered dose-limiting with the following clarifications:

Diarrhea Grade 3 will only be considered dose-limiting if it is refractory to treatment as outlined in Section 5.3.2, Supportive Care Guideline, and unable to be corrected to Grade 2 or less within 24 hours. Bloody or Grade 4 diarrhea will be dose-limiting.

Vomiting Grade 3 will only be considered dose-limiting if it is refractory to anti-emetic therapy and unable to be corrected to Grade 2 or less as outlined in Section 5.3.1.

Nausea Grade 3 will only be considered dose limiting if symptoms and severity persist beyond 48 hours despite continuation of anti-emetics.
Rise in creatinine to Grade 3, not corrected to Grade 1 or less within 48 hours with IV fluids will be considered dose-limiting. All Grade 4 rises in creatinine will be dose limiting.

Grade ≥ 3 metabolic toxicities unable to be corrected to Grade 1 or baseline within 48 hours (hypocalcemia, hypercalcemia, hypomagnesemia, and hyponatremia) will be considered dose limiting. For hypokalemia or hyperkalemia, grade ≥ 2 toxicities unable to be corrected to grade 1 or less within 48 hours will be considered dose limiting.

Grade 4 metabolic toxicities that are symptomatic will be considered dose limiting regardless of duration or ability to correct.

5.3.2 Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding.

5.3.3 Grade 4 neutropenia ≥ 5 days or febrile neutropenia will be considered dose limiting.

5.3.4 Any degree of leukopenia in the absence of grade 4 neutropenia ≥ 5 days, or lymphopenia will not be considered dose limiting.

5.3.5 Any degree of alopecia will not be considered dose limiting.

5.3.6 Grade 3 fatigue of greater than 1 week duration.

5.3.7 Failure to tolerate 100% of the dosing in the first cycle.

5.4 General Concomitant Medication and Supportive Care Guidelines

The predominant toxicity observed in clinical and non-clinical toxicology studies was hematologic. Weekly blood counts and chemistry panels will be obtained prior to treatment each week. If any weekly evaluation demonstrates grade 2 neutropenia or thrombocytopenia, treatment will proceed but a repeat hematology assessment will be obtained within 48 hours for interval evaluation. Platelet count must improve to Grade 1 or better and neutrophil count must improve to Grade 2 or better on repeat hematology assessment prior to the next cycle.

All patients will be provided with the best available supportive care. All concomitant medications should be documented prior to initiation of treatment, and be periodically reviewed with the patient. Because there is a potential for interaction of M6620 (VX-970) and 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 PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. M6620 (VX-970) is metabolized by cytochrome P450 (CYP) 3A4 isoenzyme (CYP3A4); exposure to M6620 (VX-970) may be affected by concomitantly administered drugs that are strong inhibitors or inducers of CYP3A4. Veliparib is metabolized by CYP1A1, 2D6, 2C19, and 3A4; it is not known whether its metabolism is affected by drugs that are strong inhibitors or inducers of these enzymes. To date, no clinically significant pharmacokinetic drug-drug interaction has been reported for Veliparib. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

M6620 (VX-970) is a moderate inhibitor of P-gp and BCRP. Use caution when administered with substrates of P-gp and BCRP.

M6620 (VX-970) absorbs in the UV-visible radiation spectrum and is widely distributed including skin, so patients receiving M6620 (VX-970) should take protective measures to minimize sun exposure.

To minimize the possibility of phlebitis, M6620 (VX-970) should be administered through a large-bore catheter into a large-caliber peripheral vein or through central venous access. The intravenous infusion site should be monitored closely for the development of erythema, induration, purulence, tenderness, or warmth.

5.4.1 Nausea/Vomiting

As cisplatin is known to be highly emetogenic, patients will receive pre-medication with the following anti-emetics prior to administration of cisplatin (steroids at the discretion of the investigator):

- Dexamethasone 12 mg orally at least 60 minutes prior to cisplatin on day 1 (and day 8 on DL 3 and higher) of a 21-day cycle, every 21 days
- Aprepitant 125 mg orally given at least 60 minutes prior to cisplatin on day 1 (and day 8 on DL 3 and above) of each 21-day cycle, followed by 80 mg orally daily for days 2 and 3 (and days 9 and 10 on DL 3 and higher)
- Ondansetron 8 mg orally given at least 60 minutes prior to cisplatin on day 1 (and day 8 on DL 3 and above) of each 21-day cycle, and continued every 8 hours for days 1-5 (and days 8-12 on DL 3 and higher)

For patient convenience, pre-medications can alternatively be given intravenously 30 minutes prior to therapy. A single 150 mg dose of fosaprepitant IV may be given prior to cisplatin, in lieu of the 3 days of oral aprepitant, or another anti-emetic may be used if aprepitant is not tolerated.

If the patient is well and beyond the first cycle, steroid dose reduction may be considered at the discretion of the investigator.

The addition of dopamine receptor antagonists or benzodiazepines will be at the discretion of the investigator. Vomiting will be considered refractory if it does not resolve to ≤ Grade 1 within 24 hours. Nausea ≤ Grade 2 will be considered refractory if symptoms and severity persist past 48 hours after cisplatin dosing despite continuation of anti-emetics.

5.4.2 Diarrhea

If diarrhea develops and does not have an identifiable cause other than study agents, anti-motility agents (e.g., loperamide, diphenoxylate/atropine) with be given after the first unformed stool, with continuation until the first formed stool. Diarrhea will be considered refractory if it does not resolve within 24 hours to ≤ Grade 1 with the above measures. If the patient develops blood or mucous in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, patient will receive IV fluids and antibiotics as medically indicated.

5.4.3 Seizures

Seizures were seen in some animal toxicology studies for veliparib, although at doses higher than those anticipated in this study. In the phase I single agent trial, seizures were seen at 400-500 mg BID. Seizures were successfully treated with lorazepam, which will be considered the drug of first choice for controlling seizures, should they occur on this study. Any seizure occurring in a patient on this study will be considered a DLT.

5.4.4 Neutropenia

To reduce the risk of severe myelosuppression events, a complete blood count (CBC) should be performed on weeks 1 and 2 of each cycle prior to cisplatin or M6620 (VX-970) treatment and again on days 2, 9, and 15 of the first cycle. Pegfilgrastim should be avoided as it requires 14 days between dosing and the next administration of chemotherapy. Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

5.4.5 Anemia

Symptomatic anemia should be treated with red blood cell transfusion as clinically indicated, and is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (http://www.asco.org).

5.4.6 Thrombocytopenia

Thrombocytopenia will be closely monitored on study. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be considered for a platelet count $\leq 25{,}000/mm^3$. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions will be administered as clinically indicated.

5.4.7 Acute hypersensitivity reaction/severe infusion reaction

Patients should be monitored during M6620 (VX-970) infusion for these reactions, which may include loss of consciousness and/or hemodynamic instability, including hypotension. In the event of one of these reactions, the infusion should be stopped immediately and standard supportive measures should be applied according to the presentation. This may include administration of fluids and epinephrine.

5.5 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Pregnancy
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.6 Duration of Follow Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Toxicities considered to be possibly, probably, or definitely related to the study drugs that have not resolved or stabilized by Day 30 post-treatment will be followed until stabilization or resolution via phone calls as clinically indicated.

5.7 Criteria for Removal from Study

Patients will be removed from study for one of the following reasons: completed 30-day follow up period or toxicities are unresolved but stabilized, patient enrolls on another protocol, or patient receives standard of care. The reason for study removal and the date the patient was removed must be documented in the medical record and communicated by fax to the NCI Central Registration Office per Section 4.

6 DOSING DELAYS/DOSE MODIFICATIONS

Toxicities should have resolved to ≤ Grade 2 (Grade 1 for some hematologic toxicities) prior to starting the next cycle. Treatment may be delayed for a maximum of 3 weeks beyond the actual cycle length of 21 days for toxicities that develop and do not resolve as defined above. Beyond 3 weeks, the patient may remain in the study at the discretion of the PI unless noted otherwise. Treatment may be delayed for a maximum of ± 1 day during a cycle due to unavoidable scheduling conflicts. If treatment is held during a cycle, that week's treatment will be omitted for the cycle and treatment will proceed with the following week's treatment as scheduled (e.g., if Day 2 M6620 (VX-970) treatment is held, the next treatment will be Day 9). Missed doses of veliparib will not be made up and will be documented in the patient's diary (see Appendix C). This applies starting with cycle 2 and beyond. If this occurs during cycle 1, the patient will be considered not evaluable and will need to be replaced on study.

6.1 Dose Modifications

Dose modifications are defined below:

6.1.1 Grade 2 drug-related toxicity: The dose of cisplatin will be reduced to 30 mg/m^2 without a concomitant dose reduction in M6620 (VX-970) or veliparib for any Grade 2 ototoxicity, neurotoxicity, or persisting Grade 2 rise in creatinine. A second recurrence of Grade 2 nephrotoxicity, ototoxicity, or neurotoxicity despite dose reduction will result in discontinuation of treatment. Treatment will not be held for Grade 2 hematologic toxicities.

Grade 3-4 drug-related non-hematologic toxicities attributed to all 3 drugs: Treatment will be held until toxicities recover to ≤ Grade 2 or baseline prior to re-initiating treatment at the next lower dose level. If electrolyte abnormalities do not resolve to

grade 2 or less within 48 hours, dose reduction will be required. Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment and symptoms and severity persist beyond 48 hours for nausea and vomiting, or beyond 24 hours for diarrhea (See Section 5.2).

6.1.2 Grade 3 drug-related hematologic toxicities:

Treatment will be held for a maximum of 3 weeks until hematologic toxicities, except leucopenia in the absence of Grade 3 or higher neutropenia, have resolved to ≤ Grade 1 prior to re-initiating treatment at a lower dose level. See also Section 6.2.

6.1.3 Grade 4 Drug-related Hematologic Toxicities: Treatment will be held for a maximum of 3 weeks until hematologic toxicities, except leucopenia in the absence of Grade 4 neutropenia, have resolved to ≤ Grade 1 prior to re-initiating treatment at a lower dose level. See also Section 6.2.

6.1.4 Anaphylactic reaction attributed to cisplatin: Symptoms have included facial edema, wheezing, tachycardia, and hypotension during or within a few minutes after drug administration. Treatment will be held and supportive measures implemented including administration of epinephrine 1:1000 (1 mg/mL) 0.3 mg SQ/IM, and intravenous fluid support for hypotension. Treatment may not be restarted.

6.1.5 Infusional reaction attributed to M6620 (VX-970): Symptoms may include pruritis, flushing, shortness of breath, chest tightness, dizziness, headache, increased or decreased blood pressure, loss of consciousness, and increased heart rate.

Severity of Symptoms	
Mild transient reaction	Give diphenhydramine HCl 25 mg to 50 mg IV, continue treatment, close monitoring of vitals q 5 min. for 15 min. after onset of symptoms.
Mild to moderate persistent reaction	**Stop treatment;** give dexamethasone 10 mg IV and diphenhydramine HCl 25 mg to 50 mg IV; may resume treatment after recovery of symptoms; premedication indicated for subsequent drug administration: pre-medication indicated prior to re-initiation: dexamethasone 12 mg PO and diphenhydramine HCl 25 mg to 50 mg PO approximately 4 to 6 hours prior to re-challenge
Severe symptoms (e.g., hypotension requiring pressor therapy or IV fluids, angioedema, respiratory distress requiring bronchodilator therapy, or generalized urticaria)	**Stop treatment;** give dexamethasone 10 mg IV and diphenhydramine HCl 25 mg to 50 mg IV; add bronchodilators as needed; patients may not receive further treatment; the patient will be taken off study.

6.2 Agent-specific Dose Modifications: Veliparib

To date, four cases of grade 4 myelodysplastic syndrome (MDS) and two cases of leukemia secondary to oncology therapy (one grade 4 and one grade 5) were observed on CTEP-sponsored studies utilizing veliparib. It is possible veliparib contributed to these

adverse events; it is also possible that prior therapy with platinum or alkylating agents contributed to the development of MDS or leukemia.

If a patient is taking veliparib in combination with other therapies, but develops bone marrow findings consistent with acute myeloid leukemia (AML)/MDS or severe persistent anemia requiring transfusion to maintain ≥10 g/dL hemoglobin, the patient may be allowed to continue the other therapies if they are experiencing clinical benefit and the toxicity is not related to the other therapies, based on the opinion of the treating investigator, and after discussion with the Principal Investigator. Patients who develop MDS/AML on treatment should discontinue ABT-888 treatment and be managed appropriately.

In addition, patients should be monitored for persistent myelosuppression, including anemia, thrombocytopenia, and neutropenia that does not recover to normal or grade 1 between courses of treatment, as per Good Clinical Practice. If peripheral blood counts do not recover to normal or are persistently abnormal, the patient should be evaluated for the possible development of AML/MDS using a bone marrow aspirate with cytogenetics. veliparib therapy should be held and discontinued if AML/MDS is documented. A complete history of prior therapy should be documented, particularly prior platinum-based or alkylating agent therapies. Documentation of germline BRCA mutation (*gBRCA*m) status, if known, should be recorded.

Management of neutropenia and thrombocytopenia

CTCAE Grade	Definition	Veliparib Dose
1-2	ANC >1.0 G/L or Platelet count >50 G/L	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 3 weeks; appropriate supportive treatment and causality investigation.
3-4	ANC <1.0 G/L or Platelet count <50 G/L	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 3 weeks. Upon recovery, veliparib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one veliparib dose level.

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events

Use of hematopoietic agents

Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor

(G-CSF) is not recommended. Aranesp, Epogen and Procrit may not alleviate fatigue or increase energy, and should not be used in patients with uncontrolled hypertension. The package inserts for these agents should be consulted.

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

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Dose modifications for hematologic toxicity

Patients who have veliparib held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery; these data should be recorded in eCRF as extra laboratory examinations. If counts do not improve to CTCAE Grade 1 or better despite drug cessation for 3 weeks, patients should be referred to a hematological oncologist for further assessment. A bone marrow analysis should be considered.

For AEs that are unrelated to the study drug, study drug may be withheld for up to 3 weeks at the discretion of the treating Investigator.

Management of anemia

CTCAE Grade	Definition	ABT-888 Dose
2	Hb <10 but ≥8 g/dL	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue veliparib or interrupt dose for a maximum of 3 weeks. If repeat Hb <10 but ≥8 g/dL, dose interrupt until Hb ≥10 g/dL for maximum of 3 weeks and upon recovery dose reduce per the schema.
3	Hb <8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt veliparib until improved to Hb ≥10 g/dL. Upon recovery, dose reduce veliparib.

BID = twice daily; Hb = hemoglobin

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

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

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

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

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred to a hematological oncologist for further investigations. Bone marrow for evaluation and cytogenetics should be considered at this stage according to standard hematological oncology practice. Veliparib should be discontinued if blood counts do not recover to CTCAE Grade ≤1 within 3 weeks of dose interruption.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 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.

Version 2.4, May 13, 2018[1]

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 Dehydration		***Anorexia (Gr 2)*** ***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	Seizure	***Headache (Gr 3)***
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.

7.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for M6620 (VX-970) (NSC 780162)

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. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for M6620 (VX-970).

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

Version 1.4, April 30, 2019[1]

Adverse Events with Possible Relationship to M6620 (VX-970) (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS	
Diarrhea	***Diarrhea (Gr 2)***
Nausea	***Nausea (Gr 2)***

Adverse Events with Possible Relationship to M6620 (VX-970) (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	***Fatigue (Gr 2)***
IMMUNE SYSTEM DISORDERS	
Anaphylaxis	
INFECTIONS AND INFESTATIONS	
Urinary tract infection	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Infusion related reaction	***Infusion related reaction (Gr 2)***
INVESTIGATIONS	
Alanine aminotransferase increased	***Alanine aminotransferase increased (Gr 2)***
Aspartate aminotransferase increased	***Aspartate aminotransferase increased (Gr 2)***
Blood bilirubin increased	
Creatinine increased	
Lymphocyte count decreased	***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hyperglycemia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
Tumor pain	
NERVOUS SYSTEM DISORDERS	
Dizziness	
Headache	***Headache (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Pruritus	
Rash maculo-papular	
VASCULAR DISORDERS	
Flushing	

[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.

Adverse events reported on M6620 (VX-970, NSC 780162) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that M6620 (VX-970, NSC 780162) caused the adverse event:

CARDIAC DISORDERS - Palpitations
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Colonic obstruction; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (lower respiratory tract infection); Otitis externa; Sepsis; Soft tissue infection
INVESTIGATIONS - GGT increased; Hemoglobin increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression)
NERVOUS SYSTEM DISORDERS - Lethargy; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Atelectasis; Dyspnea
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: M6620 (VX-970) 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.

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP Web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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.

7.4 Expedited Adverse Event Reporting

7.4.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Expedited Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). 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). These requirements are briefly outlined in the tables below (Section 7.4.2).

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.

For participating sites: The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 24 hours of PI awareness of the event. The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

7.4.2 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, unless as noted below. Attribution to treatment or other cause must be provided.

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

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 CTEP-AERS 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 reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted 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

7.4.3 Protocol-specific expedited AE reporting exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (i.e., CTEP-AERS). These are any grade lymphopenia, any grade alopecia, Grade 2 electrolyte (sodium, potassium, phosphorous, magnesium) abnormalities, Grade 2 anemia, Grade 2 hypoalbuminemia, Grade 2 hyperglycemia, Grade 2 INR, Grade 2 PTT, and Grade 2 hyperuricemia will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

7.4.4 Pregnancy, Fetal Death, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed for patients who became pregnant on study, and faxed along with any additional medical information to **301-230-0159.** The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

Pregnancy

- Because patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, DCTD/DCP is requesting that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3** "***Pregnancy, puerperium and perinatal conditions - Other (pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.
- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

Pregnancy loss

• Pregnancy loss is defined in CTCAE as "Death in utero."
• Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
• A Pregnancy loss should NOT be reported as a Grade 5 event under

the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.

Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.
- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

7.4.5 NIH-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

Definitions

Adverse event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section 7.3.3.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Suspected adverse reaction
Suspected adverse reaction means any adverse event for which there is a *reasonable possibility* that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse reaction
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Serious
An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

Serious Adverse Event
An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

Disability
A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Protocol Deviation (NIH Definition)
Any change, divergence, or departure from the IRB-approved research protocol.

Non-compliance (NIH Definition)
Failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

Unanticipated Problem
Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.5 NIH-IRB and Clinical Director Reporting Requirements

7.5.1 NIH-IRB and NCI Clinical Director Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NIH-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All protocol deviations
- All unanticipated problems
- All non-compliance

Reports for **serious** events must be received by the NIH IRB within 7 days of PI awareness via iRIS. Reports for **not serious** events must be received by the NIH IRB within 14 days of PI awareness via iRIS.

7.5.2 NIH-IRB Requirements for PI Reporting at Continuing Review

System	CTCAE	Grade	# of Events	Total #	Attribution	Serious?	Unexpected?

Organ Class	Term		since last CR	of Events	to Research		

The protocol PI will report to the NIH-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

7.5.3 NIH-IRB Reporting of IND Safety Reports

Only IND Safety Reports that require a sponsor-recommended change to the protocol or the consent form or in the opinion of the PI increase risks to study participants will need to be reported to the NIH IRB.

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 via CTEP-AERS. Three options are available to describe the event:

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

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

7.7 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 reporting unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational drugs administered in this study can be found in Section 7.

8.1 M6620 (VX-970) (NSC 780162)

Other Names: VRT-0768079, MSC2527093A, VX-970

Chemical Name: 5-(4-(isopropylsulfonyl)phenyl)-3-(3-(4-((methylamino)methyl)phenyl)isoxazol-5-yl)pyrazin-2- amine

Classification: ATR inhibitor **CAS Registry Number:** 1232416-25-9

Molecular Formula: $C_{24}H_{25}N_5O_3S$ **M.W.:** 463.55 Da

Mode of Action: Ataxia telangiectasia mutated and Rad3-related (ATR) kinase is an apical regulator of checkpoint pathways triggered by DNA damage. The DNA damage response (DDR) is regulated by ATR kinase and ataxia telangiectasia mutated (ATM) kinase, which are recruited to distinct DNA damage structures. M6620 (VX-970) disrupts ATR-mediated DNA damage response signaling and leads to sustained accumulation of DNA damage in cancer cells co-treated with DNA-damaging agents.

Description: The drug substance for M6620 (VX-970) is the free base.

How Supplied: M6620 (VX-970) is supplied by Merck KGaA/EMD Serono, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 200 mg vials containing a sterile solution (20 mg/mL). M6620 (VX-970) solution for injection is a yellow liquid formulated in 20% betadex sulfobutyl ether sodium (w/v) and 86 mM acetate buffer, 10 mL total volume, supplied in clear glass vials in cardboard boxes with foam inserts.

Preparation: M6620 (VX-970) solution for injection must be diluted with 5% dextrose in water solution prior to administration. Do not use 0.9% Sodium Chloride due to incompatibility with M6620 (VX-970). To prepare the infusion solution add the dose volume of M6620 (VX-970) to a non-polyvinyl chloride (non-PVC), di(2-ethylhexyl) phthalate (DEHP)-free EVA infusion bag containing 5% dextrose in water. Gently invert the IV bag 5-10 times to mix the solution. Confirm the solution is clear and free of precipitates and/or particulates. The final concentration must be between **0.075 mg/mL to 1 mg/mL**. Place the IV bag into an opaque cover to protect from light.

Storage: Store intact vials protected from light inside cardboard boxes at room temperature, 25°C (77°F), with excursions allowed between 15 and 30°C (59 and 86°F).

If a storage temperature excursion is identified, promptly return M6620 (VX-970) to between 15 and 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing of the intact vials is on-going**.** Prepared solutions must be protected from light and used within 4 hours from time of preparation if stored at room temperature or 24 hours if stored refrigerated (2-8°C).

Route of Administration: Intravenous (IV) infusion.

Method of Administration: Prior to administration the solution should be given one hour at ambient temperature to warm up if stored refrigerated following preparation. Infuse over 60 minutes using an infusion set containing low-sorption or non-PVC, DEHP-free tubing and an in-line 0.2 micron filter. 5% dextrose in water solution must be used for IV line priming and flushing. M6620 (VX-970) should not come in contact with 0.9% Sodium Chloride due to incompatibility. The infusion time may be extended beyond 60 minutes (as tolerated) but no more than 90 minutes if standard procedures to limit symptoms of an infusion reaction are insufficient or if the total volume of the infusion exceeds 600 mL. To minimize the possibility of phlebitis, M6620 (VX-970) should be administered through a large bore catheter into a large caliber peripheral vein or central venous access.

Patient Care Implications: Monitor for infusion site reactions, irritation, and phlebitis. M6620 (VX 970) absorbs in the UV-visible radiation spectrum and is widely distributed including skin, so patients receiving M6620 (VX-970) should take protective measures to minimize sun exposure.

Women of childbearing potential and men should use appropriate contraception while on study drug and for 6 months after discontinuation of M6620 (VX-970).

Potential Drug Interactions: M6620 (VX-970) is primarily metabolized by CYP3A4. M6620 (VX-970) has a low potential to inhibit CYP1A2, 2C9, 2C19, 2D6, and 3A4, and a moderate potential to reversibly inhibit CYP2E1. The potential for M6620 (VX-970) to induce CYP450 enzymes is low. Concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided.

M6620 (VX-970) is a weak/moderate inhibitor of UGT1A1, UGT1A14, UGT1A9, UGT2B15, and UGT2B17. UGT2B7, UGT1A3, and UGT1A6 were weakly or not inhibited. M6620 (VX-970) is predicted to not inhibit significantly the metabolic clearance of SN-38 (active metabolite of irinotecan) at therapeutic exposures.

M6620 (VX-970) is a moderate inhibitor of P-gp and BCRP. Use caution when administered with substrates of P-gp and BCRP transporters.

1/2019 ew

8.2 Veliparib (NSC 737664)

Other Names:	ABT-888, A-861695.0
Chemical Name:	1*H*-Benzimidazole-7-carboxamide, 2-[(2*R*)-2-methyl-2-pyrrolidinyl]-
Classification:	Poly (ADP-ribose) polymerase (PARP) Inhibitor
CAS Registry No.	912444-00-9
Mode of Action:	Veliparib is an inhibitor of poly(ADP-ribose) polymerase (PARP), a nuclear enzyme that recognizes DNA damage and facilitates DNA repair.
Molecular Formula:	$C_{13}H_{16}N_4O$
Molecular Weight:	244.29
Description:	White to light yellow solid
Solubility:	Freely soluble at 37 °C at a pH < 6.9, soluble at pH 6.9 to 7.1, and slightly soluble at pH > 7.1
How Supplied:	AbbVie supplies and DCTD distributes Veliparib. Veliparib capsules are available in 10 mg, 20 mg, 40 mg, 50 mg, and 100 mg immediate release capsules. The inactive ingredients are microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. It may contain FD&C blue#1, FD&C yellow #6, or FD&C yellow #5. The capsules are packaged in HDPE bottles, and each HDPE bottle contains 16 capsules or 64 capsules. Veliparib capsules may be repackaged from the supplied HDPE bottles into amber (or other low-actinic) child resistant pharmacy dispensing bottles. Expiration will be 30 days from the repackaging date (or the original retest date, whichever is earlier) when stored at 15°C to 25°C (59°F to 77°F).
Storage:	Capsules should be stored in the original container at 15° to 25°C (59° to 77°F).
Route of Administration:	Oral
Method of administration	Administer Veliparib orally without regards to meals; the capsules should not be crushed or chewed. If a dose is vomited, it may be re-administered if whole/intact capsules are observed in vomitus.
Potential Drug Interaction	Nonclinical studies suggest ABT-888 is a substrate of P-gp, OCT2, and MATE1/MATE2K transporters. Co-administration of ABT-888 with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K

may result in a decrease of ABT-888 renal clearance and an increase in ABT-888 plasma concentration. Therefore, use caution when administering ABT-888 with strong inhibitors of P-gp, OCT2, and MATE1/MATE2K. At high dose (e.g., 400 mg BID), ABT-888 may inhibit OCT1 in the liver and MATE1/MATE2K in the kidney.

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

Availability Veliparib is an investigational agent supplied to investigators by DCTD, NCI. Veliparib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and DCTD, NCI.

8.3 Cisplatin

Other Names:	cisplatinum
Chemical Name:	cis-diamminedichloroplatinum(II)
Classification:	DNA crosslinking agent
CAS Registry No.:	15663-27-1
Molecular Formula:	(SP-4-2)-diamminedichloroplatinum
Mechanism of Action:	Cisplatin is a DNA crosslinking agent that forms intra- and interstrand crosslinks with DNA, interfering with DNA replication and repair.
How Supplied:	Cisplatin is commercially available in amber, multiple-dose vials containing 50, 100, or 200 mg cisplatin in solution. Each milliliter of solution contains 1 mg of cisplatin and 9 mg sodium chloride in water for injection.

Storage:	Intact vials and reconstituted solution must be maintained at room temperature. Store intact vials at 15° - 25°C (59° - 77°F). Do not refrigerate cisplatin in vials or after dilution. Cisplatin that remains in an amber vial after initial entry is stable for 28 days if protected from light or for 7 days under fluorescent room light. Large-volume solutions do not need to be protected from light if used within 6 hours after preparation. For longer time periods, light protection is recommended. Light protection is required for intensive lighting conditions; e.g., direct sunlight exposure. Although cisplatin slowly degrades to trichloroaminoplatinate (TCAP) on exposure to ambient lighting conditions, solution pH is the predominant factor affecting cisplatin stability. Solutions with pH > 4.3 (especially > 6.3) were associated with loss of cisplatin and a more rapid formation of TCAP.
Stability:	Vials bear the manufacturer's expiration date. Cisplatin dilution to 0.05 or 0.5 mg/mL with 0.9% normal saline yields a solution that is stable for at least 24 hours at room temperature.
Preparation:	Cisplatin will be diluted in 100 mL 0.9% sodium chloride injection, USP, for intravenous administration over 60 minutes on Day 1 (and Day 8 from DL3 and higher) of a 21-day cycle.
Route of Administration:	Cisplatin is administered intravenously on Day 1 (and Day 8 for DL3 and higher) of a 21-day cycle.
Method of administration:	Prior to cisplatin administration, at least 500 mL of 0.9% sodium chloride with KCl 10 mEq/L and magnesium sulfate 4 mEq/L injection should be administered over at least 60 minutes. Following administration of cisplatin, at least an additional 500 mL of 0.9% sodium chloride with KCl 10 mEq/L and magnesium sulfate 4 mEq/L injection should be administered over at least 60 minutes.
Availability:	Commercially available.

8.4 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/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov

- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday

8.5 Agent Ordering

NCI-supplied agents may be requested by the responsible investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), 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 investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an "active" account status, a "current" password, and an active registration status. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.6 Agent Accountability

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

8.6.1 Investigator Brochure Availability

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

9 CORRELATIVE/SPECIAL STUDIES

We plan to evaluate the effect of the combination of M6620 (VX-970), veliparib, and cisplatin on markers of DNA damage, such as γH2AX, RAD51, pNbs1, and pATR, in tumor biopsies and circulating tumor cells (CTCs). For patients on the expansion cohort, two biopsies will be obtained, one on C1D1 after administration of cisplatin and again on C1D9, 2-5 hours after the day 9 dose of M6620 (VX-970), with a third progression or restaging follow-up biopsy optional. Biopsies are mandatory for patients on the expansion phase. Based on the availability of tissue and various histologies, additional markers of DNA damage will be evaluated.

9.1 Pharmacodynamic Assays

Evaluation of drug effect on DNA damage response in tumor and CTCs will be performed by immunofluorescence assays for measurement of DNA damage-repair markers, such as γH2AX, RAD51, pNbs1, and pATR.

Histone H2AX is one of the H2A histones present in nucleosomes from normal tissues as well as cancer tissues. H2AX is phosphorylated at its C-terminus (serine 139) following DNA double-strand breaks. Phosphorylated H2AX, referred to as γH2AX, can be selectively detected using antibodies by Western blots or immunofluorescence. The levels of γH2AX are directly correlated to the amounts of double-strand breaks per cell, and can be used as a dosimeter and biomarker for DNA double-strand breaks.

Nbs1 is an adapter protein, linking Mre11 and Rad50 to form the MRN complex involved in recognition of DNA damage and initiation of the signaling cascade in response to DNA double-strand breaks.

Rad51 plays a central role in recognition of double-strand breaks and homologous recombination.

ATR phosphorylation in response to DNA damage will be used as a marker of direct target effect. A quantitative immunofluorescence assay for pT1989-ATR will be used as a marker of ATR inhibitor activity.

9.1.1 Laboratory Contact (NCI only)

At least 24 hours prior to tumor biopsy or blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10:
E-mail (preferred): NCIPK-PDsupport@mail.nih.gov, Pager (preferred): 102-12798
Phone: (240) 858-3963 Fax: 301-480-5871. For biopsies, tubes pre-labeled with the information specified in Section 9.1.4, biopsy date, and site of tissue biopsy will be provided. Initial processing and shipping of the samples will be completed as described below.

9.1.2 Tumor Biopsies

Biopsies will be optional during the escalation phase but mandatory during the expansion phase. Biopsies will be collected at the following time points:

- On C1D1 after administration of cisplatin

- On C1D9, 2-5 hours after the dose of M6620 (VX-970)

An optional third biopsy may also be collected, either at restaging follow-up (on day 1 (± 2 days) of the cycle following any restaging at which a 10-19% increase in tumor volume is observed, according to RECIST criteria, for patients on study 4 or more cycles) or at the time of disease progression (a 20% or more increase in tumor volume by RECIST).

9.1.2.1 Biopsy Procedure

Serial tumor biopsies will be obtained by the Interventional Radiology team by a percutaneous approach, a dermatologist for skin lesions, or an ENT for lesions that are easily biopsiable through ENT exam. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and the biopsy team, an attempt for biopsy will be made. Because approximately 20% of tumor biopsies collected on research trials are not usable due to the presence of stroma or normal and/or necrotic tissue and paired biopsies are necessary for analysis, up to 5 core biopsies 18-gauge in diameter and ≥1 cm in length, or equivalent, will be obtained during each procedure to try and ensure adequate tumor content and quality. If possible, the lesion from which each biopsy is taken will be documented. Acceptable biopsy procedures are:

- Percutaneous biopsy with local anesthetic.
- Excisional cutaneous biopsy with local anesthetic
- Other biopsy with local anesthetic and/or sedation that has been shown to have a risk of severe complications < 2%

The use of imaging to facilitate biopsies will be decided by members of the biopsy team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant, as determined by the investigators and the biopsy team. The clinical, radiologic, dermatologic, ENT, and pharmacodynamic members of the research team will meet monthly to review the adequacy of the biopsy specimens for analysis.

C1D1 and C1D9 tumor biopsies are optional during the escalation phase and mandatory during the expansion phase (the progression/restaging follow-up biopsy is always optional). Baseline biopsies will be performed following patient enrolling on study. If an initial attempt at biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study, receive study medication, and other correlative studies will be performed.

9.1.2.2 Solid Tumor Biopsy Processing

- All biopsy specimens should be collected, placed in pre-chilled cryogenic vials, and flash frozen in liquid nitrogen within 2 minutes of collection per DCTD SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf)

- See Appendix G for the collection and shipment procedures for all biopsy samples.

- **C1D1 and C1D9 biopsies** should be transferred to PADIS on dry ice, where they are stored at -80°C, or colder, and subsequently processed within 7-10 days for analysis or as directed by the Principal Investigator. Biopsy samples will be analyzed for γH2AX, Rad51, pNbs1, and pATR as described above; any additional tissue will be flash-frozen and kept for future analysis in the Frederick National Laboratories CR Biorepository in liquid nitrogen freezers. Additional studies, if performed, will be conducted following an amendment to the current protocol.

- **Restaging follow-up or progression biopsies** should be processed as follows:
  - As the first priority, two cores, or equivalent tissue from dermatology or ENT biopsy, should be flash frozen as described above and transferred on dry ice to Dr. Mickey Williams' laboratory (MoCha) at the Frederick National Laboratory for Cancer Research (FNLCR).

    Following processing, one tissue section will be stained with H&E for histopathological examination by a designated pathologist. The remaining biopsy tissue will be extracted for nucleic acids. DNA will be assessed for quantity and quality by spectroscopy (OD 260/280) and a PCR-based amplification quality assessment test. All specimens that meet necessary quantity and quality will be sequenced using a targeted sequencing assay.

  - Any remaining tissue collected (up to 5 cores or equivalent) will be transferred to PADIS on dry ice and stored for analysis of γH2AX, Rad51, pNbs1, and pATR.

  - *Note: Per the discretion of the PI, restaging follow-up or progression biopsies may be used for other analyses, including analyses carried out as a part of other DTC clinical trials, providing that the tissue is collected per SOP for those analyses.*

9.1.2.3 Optional Archival Tissue Submission for Additional Studies

Patients may choose to submit an additional, archival tumor tissue specimen that has been collected within 3 months prior to patient registration if the patient has not received any intervening cancer therapy since collection of the specimen and the tissue was collected and processed according to SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf), including flash-freezing in liquid nitrogen, minimal cold ischemia time (< 5 minutes), and shipment on dry ice. **Archival tissue**

submissions do not fulfill the requirement for a baseline (C1D1) biopsy because the baseline biopsy must be collected after the C1D1 cisplatin administration; however, qualifying archival tissue submissions will be analyzed for the same PD biomarkers as C1D1 and C1D9 biopsies to provide additional context for interpreting PD changes after drug administration.

Please send an email to FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) to advise that archival tissue is being prepared for shipment. State "P9771 PD Specimens Ready for Shipment" in the subject line. If needed, FNLCR PD Central Receiving can be contacted directly at 301-846-1951 or 301-846-6747.

9.1.3 Blood Collection for CTC Studies (Optional)

Whole blood (at least 7.5 mL) will be collected aseptically by venipuncture or from a venous port into one 10 mL CellSave preservative tube. Prior to CTC collection, each participating site should e-mail a request for specimen collection and shipping materials from NCIPDSupportPADIS@mail.nih.gov . See Appendix G for the collection procedure for CTC samples for pharmacodynamic studies.

At the NCI only, whole blood (at least 7.5 mL) will be collected aseptically by venipuncture or from a venous port into one 10 mL Streck tube (catalog number 218962). One 10 mL RareCyte tube (catalog number 24-1070-005) is also acceptable. Tubes must be inverted 8 times to ensure adequate mixing of the additive.

Blood samples for CTCs will be collected at the following times:

- at baseline
- on cycle 1 day 2 prior to administration of M6620 (VX-970)
- on cycle 1 day 2, 8 hours (± 30 minutes) after the start of M6620 (VX-970) administration
- on cycle 1 day 8 prior to administration of veliparib/cisplatin administration
- on cycle 1 day 9 prior to M6620 (VX-970) administration,
- on cycle 2 day 1 prior to veliparib/cisplatin administration
- on cycle 2 day 2 prior to M6620 (VX-970) administration
- on cycle 2 day 2, 10 hours (± 2 hours) after the start of M6620 (VX-970) administration*
- on the first day of every subsequent cycle prior to veliparib/cisplatin administration
- at the time of restaging follow-up biopsy or progression biopsy, if applicable

***At the NCI only:** CTC collection on cycle 2 day 2 is fixed at 7:00pm (± 30 minutes) in order to make the timing of the procedure more feasible and convenient for study participants. The time elapsed between M6620 (VX-970) administration and blood collection will be recorded.

Testing and data analysis will be performed by Dr. Bob Kinders (PADIS/FNLCR).

9.1.4 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. Information about each specimen (e.g., blood, tumor biopsy, per specific protocol) will be recorded on a PK/PD collection worksheet.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
400 series: CTCs
500 series: tumor biopsies

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

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

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following

receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

9.2 Exploratory Genomic Analyses

As of **Amendment L** (dated 4/22/2019), the MoCha laboratory at FNLCR will investigate the occurrence of tumor genomic alterations potentially associated with acquired drug resistance for only those patients who agree to undergo an optional progression or restaging follow-up biopsy.

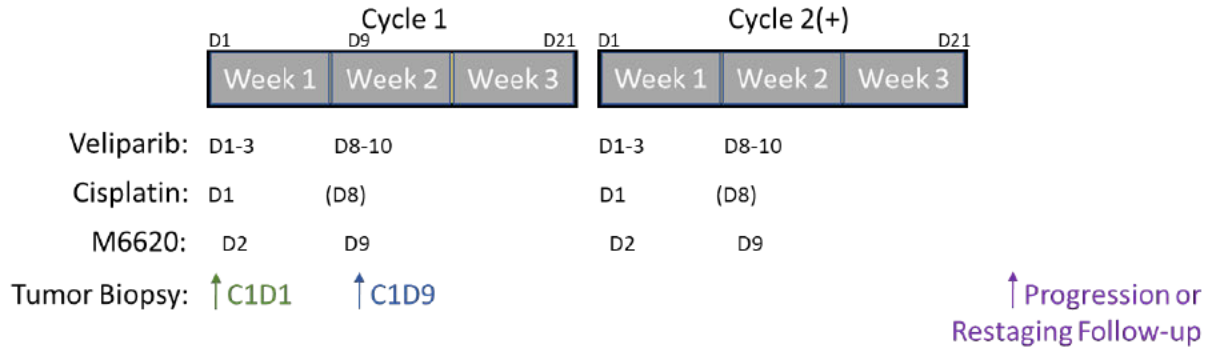
9.2.1 Optional Restaging Follow-Up and Progression Biopsies

With patient consent, tumor tissue collected at the (optional) restaging follow-up or progression biopsy may be analyzed by the CLIA-certified OCAv3 assay and results will be returned to patients in the form of the Oncomine report. If additional tumor tissue is available after the OCAv3 analysis, exploratory, non-CLIA certified genomic analyses such as WES may be conducted but the results will not be returned to patients or used for clinical decision making (Figure 5). *Note: Per the discretion of the PI, restaging follow-up or progression biopsies may be used for other analyses, including analyses carried out as a part of other DTC clinical trials, providing that the tissue is collected per SOP for those analyses.*

9.2.2 Cycle 1 Day 1 and 9 Biopsies

For only those patients who have undergone the optional restaging follow-up or progression biopsy and consented to genomic analyses, tumor biopsy tissue collected at C1D1 will be used for exploratory WES analyses **if** there is sufficient tissue remaining after PD biomarker analyses have been completed (Figure 5). Remaining C1D9 biopsy tissue may also be used for exploratory WES analysis after PD biomarker analyses have been completed if there is not sufficient C1D1 tissue available. Tissue availability will be tracked in real time using Labmatrix. Although the MoCha Laboratory is CLIA-certified, these sequencing studies will not be done per CLIA specifications and these data will not be returned to the patients or used for clinical decision making.

Figure 5. Summary of Planned Genomic Analyses.



	C1D1 Tumor Biopsy	C1D9 Tumor Biopsy	Progression or Restaging Follow-up Biopsy* (optional)
Collection Information:	All tissue flash frozen	All tissue flash frozen	All tissue flash frozen
First Priority Assay:	PD assays	PD assays	CLIA OCAv3 assay
Second Priority Assay:	WES	WES	WES
Third Priority Assay:			PD assays
Reporting to Patients:	None	None	Oncomine report

**Note: Per the discretion of the PI, restaging follow-up or progression biopsies may be collected per SOP to be used for analyses other than those listed here, including analyses carried out as a part of other DTC clinical trials.*

9.3 Human Data Sharing Plan

What data will be shared?
We will share human data generated in this research for future research as follows:
X De-identified data in an NIH-funded or approved public repository

X Identified data in BTRIS (automatic for activities in the Clinical Center)
X De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?
Data will be shared through:
X An NIH-funded or approved public repository: clinicaltrials.gov
X BTRIS (automatic for activities in the Clinical Center)
X Approved outside collaborators under appropriate individual agreements
X Publication and/or public presentations

When will the data be shared?
X At the time of publication or shortly thereafter

10 STUDY CALENDAR

Eligibility screening evaluations are to be conducted within 8 days prior to enrollment, with the exception of informed consent and diagnostic imaging, which must be done within 28 days prior to enrollment. Baseline history, physical examination, laboratory evaluations, and ECG are to be conducted within 8 days prior to the start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations, values from the screening evaluations may be used as baseline measurements; if > 8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and ECG must be repeated prior to starting protocol therapy. Baseline imaging scans must be done within 28 days prior to the start of protocol therapy. Start of next cycle may be changed by 1 day or delayed for up to 1 week to accommodate scheduling conflicts. Treatments within a cycle may be delayed ± 1 day to accommodate scheduling conflicts. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle.

Study Procedure	Pre-Study Eligibility Screen	Study Treatment						
		Cycle 1			Cycle 2 and subsequent cycles			Off Treatment
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
M6620 (VX-970)[a]		**X**	**X**		**X**	**X**		
Veliparib[b]		**X**	**X**		**X**	**X**		
Cisplatin[c]		**X**			**X**			
Informed consent	**X**							
Demographics	**X**							
Medical history	**X**	**X**[l]						
Concomitant meds	**X**	**X**----------**X**						
Physical exam[d]	**X**	**X**[l]	**X**		**X**	**X**		**X**
Vital signs[d]	**X**	**X**[l]	**X**		**X**	**X**		**X**
Height[d]	**X**							
Weight[d]	**X**	**X**[l]	**X**		**X**	**X**		**X**
Performance status[d]	**X**	**X**[l]	**X**		**X**	**X**		**X**
ECG[e]	**X**	**X**						
CBC w/diff, plts[f]	**X**	**X**[l]	**X**	**X**	**X**	**X**	**optional**	**X**
Serum chemistry[f]	**X**	**X**[l]	**X**	**X**	**X**	**X**	**optional**	**X**
PT, INR, PTT[g]		**X**	**X**					
β-HCG[h]	**X**							
Adverse event evaluation	**X**	**X**----------**X**						
Tumor measurements[i]	**X**	**X**[l]	Tumor measurements are repeated per Section 11.1 Documentation (radiologic) must be provided for patients removed from study for progressive disease.					**X**
Tumor biopsy[j]		**X**	**X**					
Circulating Tumor Cells[k]	**X**	**X**	**X**		**X**			

a. M6620 (VX-970) will be administered intravenously as a 1-hour infusion ± 10 minutes on days 2 and 9 of a 21-day cycle (or on days 1 and 8 of any cycle in which cisplatin is not administered).
b. Veliparib will be administered orally q12 hours ± 1 hour on days 1 through 3 and 8 through 10 of a 21-day cycle. Veliparib should be administered before cisplatin and M6620 (VX-970).
c. Cisplatin will be administered intravenously as a 1-hour infusion ± 10 minutes on day 1 of a 21-day cycle (days 1 and 8 for patients on dose level 3 and higher). As of ***Amendment I*** (12/7/2017), patients who have been on trial for at least 6 cycles may have cisplatin administration held or discontinued while continuing on trial at the discretion of the PI, Dr. [redacted]
d. Physical examination, including vitals, weight, and performance status, will be performed at the Clinical Center at the start of each cycle of treatment (up to 3 days before the start of a new cycle) and on day 8 or 9 (±1 day) of each cycle. Weight will be used to calculate doses per institutional SOP. Height will be performed prior to enrollment and will not need to be repeated

prior to each treatment.
e. ECG for eligibility screening and at baseline (within 8 days prior to enrolling or starting study drug, respectively), within approximately 1 hour after the end of M6620 (VX-970) infusion during cycle 1, and as clinically indicated.
f. Serum chemistry (albumin, total bilirubin, calcium, creatinine, phosphorus, magnesium, potassium, sodium, SGOT [AST], SGPT [ALT]); CBC w/diff, and platelets should be performed for eligibility screening and at baseline (within 8 days prior to enrollment or starting treatment, respectively), and prior to treatment on days 2, 8, 9, and 15 (±1 day for all) of cycle 1. For all subsequent cycles, these labs should be performed prior to treatment on day 1 (±1 day) and prior to the first IV treatment on week 2 of the cycle (day 8 or 9, ±1 day). C1D1 values need to re-meet eligibility criteria. C1D15 labs may be obtained by the patient's local physician and day 15 labs in subsequent cycles are optional.
g. PT, INR, PTT required within 1 week prior to all biopsies, and may also be performed as clinically indicated.
h. Serum or urine pregnancy test (women of childbearing potential) within 8 days prior to enrollment and as clinically indicated.
i. Radiologic examination (CT scan or MRI) will be performed for eligibility screening and at baseline (within 28 days prior to enrolling or starting study drug, respectively) and then every 2 cycles (every 3 or 4 cycles for patients on study for more than one or three years, respectively).
j. Tumor biopsies will be obtained after the administration of cisplatin on C1D1 and again on C1D 9 2-5 hours after the day 9 dose of M6620 (VX-970). Tumor biopsies are optional during the escalation phase and mandatory during the expansion phase.
k. Circulating tumor cells (optional) will be drawn as defined in Section 9.1.3.
l: Eligibility screening results may be used for these baseline measurements if conducted within 8 days (for medical history, physical exam, vital signs, weight, performance status ECG, serum chemistry, and CBC) or 28 days (for tumor measurements) prior to the start of protocol therapy.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated for response every 6 weeks (every 2 cycles; every 3 cycles for patients on study for more than one year or every 4 cycles for more than three years). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with the combination of M6620 (VX-970), veliparib, and cisplatin.

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

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

11.1.2 Disease Parameters

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

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

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be

those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.3 Guidelines for Evaluation of Measurable Disease

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

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

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

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

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

As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.2 Response Criteria

11.2.1 Evaluation of Target Lesions

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

11.2.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.2.3 Evaluation of Best Overall Response

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

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

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

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.3 Duration of Response

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

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

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

12 DATA REPORTING/REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

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.

12.2 Data Reporting

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 ctms@theradex.com for additional support with Rave and completion of CRFs.

Note: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via the monitoring method identified above.

12.2.2 Responsibility for Data Submission

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. 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. Guidelines 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.

12.3 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix F.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

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: E-mail: ncicteppubs@mail.nih.gov

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

12.5 Genomic Data Sharing Plan

The NIH Genomic Data Sharing (GDS) Policy does not apply to this protocol as the genomic analysis will be performed will be for no more than 30 patient samples; therefore, this study does not meet GDS criteria, and a GDS plan is not warranted.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This Phase I study will use a standard 3+3 design with a slight modification as outlined in Section 5.3. Accrual will not proceed to a higher dose level until all patients have been treated at the current dose level, and the last patient treated has been observed for at least one cycle. The MTD dose for the combination of M6620 (VX-970), veliparib, and cisplatin is defined as the dose level at which no more than 1 of 6 patients experience a DLT during the first cycle of the treatment, and the dose level below that at which at least 2 (of ≤ 6) patients have DLT as a result of the drugs. Patients will receive cisplatin intravenously on day 1 (and day 8 from DL3 onwards; at the discretion of the PI, Dr. [redacted] after cycle 6), M6620 (VX-970) intravenously on days 1/2 and 8/9, and veliparib orally q12 hours ± 1 hour on days 1-3 and 8-10 of each 21-day cycle.

Once the MTD is established, up to 15 additional patients will be enrolled to the expansion phase of the trial at the MTD. Mandatory tumor biopsies will be obtained in the expansion phase to assess for pharmacodynamic endpoints. With up to 15 patients and a tumor biopsy QA criteria failure rate of 50% with respect to paired (pre- and post-dose) biopsies, we have an 85% likelihood of having at least 6 usable PD samples, and 95% likelihood of having at least 5 usable samples.

13.2 Sample Size/Accrual Rate

We plan to accrue up to 55 patients in this study. To allow for some patients who may have only evaluable and not measurable disease, the accrual ceiling is set at 60. It is anticipated that 2-3 patients may be enrolled per month onto this study. It is expected that 12-18 months will be required to accrue the number of patients necessary to complete the trial.

13.3 Secondary Endpoints

- To assess the effect of the combination of M6620 (VX-970), veliparib, and cisplatin on markers of DNA damage and apoptosis.
- To assess the antitumor activity of the combination

14 HUMAN SUBJECTS PROTECTIONS

14.1 Justification for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information

hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Due to lack of knowledge of the effects of the combination of M6620 (VX-970), veliparib, and cisplatin on the fetus or infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with unstable or serious medical conditions are excluded due to the possibility that the combination of M6620 (VX-970), veliparib, and cisplatin may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events to M6620 (VX-970), veliparib, and cisplatin. HIV-positive patients are excluded from the study per Section 3.1.9.

14.1.1 Participation of Children

This study includes patients 18 years of age and older. Because insufficient dosing or adverse event data are currently available on the use of combination of M6620 (VX-970), veliparib, and cisplatin in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials. Studies will be performed in patients <18 years of age when it is appropriate to do so.

14.2 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 5 and Section 6. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.3 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record. Patients will not be consented by telephone.

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

Adults who are unable to provide initial informed consent are excluded from participation on this study. All patients > 18 years old will be offered the opportunity to assign a substitute decision

maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form, so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

14.3.1 Participation of subjects unable to give consent

At the NCI only: Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation, all subjects ≥ age 18 at the NCI only will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

14.3.2 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative, and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using the Short Form process). Preferably, someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of use of the Short Form. The Short Form process will be used no more than 5 times per language, after which the full consent document will be translated into that language.

14.4 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

The research component of this study required to obtain 3 CT tumor biopsies confers radiation exposure at an effective dose of 2.4 rem. This dose is below NIH RSC guidelines of less than 5.0 rem per year in adults, and represents a slightly greater than minimal risk to patients.

14.5 Patient Advocate

The patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #:**
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:
M6620 (VX-970) interacts with specific enzymes in the liver or other tissues like the gut and certain transport proteins that help move drugs in and out of the cell.

	Explanation
CYP isoenzymes	The enzyme in question is **CYP3A4**. M6620 (VX-970) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.
Protein transporters	The proteins in questions are **P-gp and BCRP**. M6620 (VX-970) is a moderate inhibitor of these proteins and may affect drugs that are moved in and out of cells/organs by these transport proteins.

Veliparib (ABT-888) is cleared from the body by certain specific drug transporter proteins.

- The transporters in question are **P-gp, OCT2, and MATE1/MATE2K.** Co-administration of veliparib (ABT-888) with other drugs that inhibit P-gp, OCT2, or MATE1/MATE2K may result in decreased veliparib (ABT-888) clearance by the kidneys and as a result, an increase in veliparib (ABT-888) concentration in the blood.
- Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated medical reference
- Kidney function plays an important role in the clearance of veliparib (ABT-888). Veliparib (ABT-888) levels may therefore be affected by drug-associated kidney toxicities or kidney diseases. Caution should be used when concomitantly administering veliparib (ABT-888) with oxalipaltin, carboplatin, cisplatin, and topotecan in patients with pre-existing kidney impairment.

These are the things that you need to know:
The study drugs M6620 (VX-970) and veliparib (ABT-888) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-

counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

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 inhibitors or inducers of CYP3A4, P-gp, OCT2, and MATE1/2K, and substrates of P-gp and BCRP.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Make sure your doctor knows to avoid certain prescription medications.
- 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.

Version *Feb/2019*

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE EMERGENCY INFORMATION	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE DRUG INTERACTIONS	NIH NATIONAL CANCER INSTITUTE
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	Carry this card with you at all times M6620 (VX-970) and veliparib (ABT-888) interact with specific enzymes in your liver or other tissues like the gut and transport proteins that help move drugs in and out of cells and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):**	**Use caution and avoid the following drugs if possible:** • ***Oxaliplatin, carboplatin, cisplatin, and topotecan (in patients with pre-existing kidney impairment)***	Your healthcare providers should be aware of any medicines that are strong inhibitors/inducers of CYP3A4, P-gp, OCT2, MATE1/2K or substrates of P-gp or BCRP. • Strong inhibitors or inducers of CYP3A4 should be avoided. • Strong inhibitors of P-gp, BCRP, OCT2, or MATE1/MATE2K should be used with caution. • Substrates of P-gp and BCRP should be used with caution. **Before prescribing new medicines,** your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. Version Feb/2019	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov

APPENDIX C: PATIENT STUDY CALENDAR AND DIARY

The study drugs are given over a 21-day period of time called cycles. The 21-day treatment cycle will be repeated as long as you are tolerating the medications and your cancer is either stable or getting better.
The chart below shows what will happen to you during cycle 1 and future cycles after you sign the consent form and start the study. Each cycle is numbered. The left-hand column shows the day in the cycle, and the right-hand column tells you what will happen on that day.

Day	What to do and what will happen to you
Before starting study drug	• Check in at _____ *[name of outpatient clinic]* • Get routine blood tests • Pregnancy test for women who are able to become pregnant • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT or MRI scan will be done • Research blood samples will be drawn
Cycle 1, Day 1	• Admitted to _____ *[name of clinical center]* • Get routine blood tests • Research blood samples will be drawn • Receive the first dose of veliparib (ABT-888) by mouth • Receive the first dose of cisplatin through a vein • Tumor biopsies will be taken for some patients
Cycle 1, Day 2	• Get routine blood tests • Receive the first dose of M6620 (VX-970) through a vein • Tumor biopsies will be taken for some patients 2 to 5 hours after receiving M6620 (VX-970) • Research blood samples will be drawn • Continue to take veliparib (ABT-888) by mouth twice a day about 12 hours apart for a total of 3 days
Cycle 1, Days 8-10	• Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests • Research blood samples will be drawn • Take veliparib (ABT-888) by mouth twice a day about 12 hours apart for 3 days • Receive cisplatin through a vein on day 8 • Receive M6620 (VX-970) through a vein on day 9 • Tumor biopsies will be taken for some patients 2 to 5 hours after receiving M6620 (VX-970)

Day	What to do and what will happen to you
Cycle 1, Day 15	• Get routine blood tests at your clinical center or by your home physician
Cycle 2, Day 1	• Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests • Research blood samples will be drawn • Start taking veliparib (ABT-888) by mouth twice a day about 12 hours apart for days 1 through 3 • Receive cisplatin through a vein
Cycle 2, Day 2	• Research blood samples will be drawn • Receive M6620 (VX-970) through a vein
Cycle 2, Days 8-10	• Check in at _____ *[name of outpatient clinic]* • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • Get routine blood tests • Continue taking veliparib (ABT-888) by mouth twice a day about 12 hours apart on days 8 through 10 • Receive cisplatin through a vein on day 8 • Receive M6620 (VX-970) through a vein on day 9
Cycle 2, Day 15	• Get routine blood tests at your clinical center or by your home physician (optional)

Cycle 3, and onward	• Check in at _____ *[name of outpatient clinic]*
	• Have a history taken of how you feel and undergo a physical examination by a Health Care Provider
	• Get routine blood tests
	• CT scan to determine how your tumor is responding to the treatment will be done every 6 weeks (every 2 cycles, or every 3 cycles if you have been on study for more than one year, every 4 cycles if on study for more than 3 years)
	• Research blood samples will be drawn before Cycle 3 treatment
	  • Cisplatin will be given through a vein on Day 1 and 8 of each cycle
	  • M6620 (VX-970) will be given through a vein on Day 2 and 9 of each cycle
	  • veliparib (ABT-888) will be taken orally twice a day about 12 hours apart on days 1 through 3 and 8 through 10 of each cycle

Study Diary

Patient Name: _____ _____

Instructions:

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

Dose of veliparib (ABT-888) (number of capsules):

Time of dosing: Take veliparib (ABT-888) capsules twice each day (morning and evening, about 12 hours apart) on days 1 to 3 and 8-10

Cycle number: _____
Start date: _____

Patient Signature: _____

Date	**Day**	**Time taken** AM	PM	**Comments:** Side effects/missed dose
	1			
	2			
	3			
	4	*No veliparib (ABT-888) taken today*		
	5	*No veliparib (ABT-888) taken today*		
	6	*No veliparib (ABT-888) taken today*		
	7	*No veliparib (ABT-888) taken today*		
	8			

	9			
	10			
	11	*No veliparib (ABT-888) taken today*		
	12	*No veliparib (ABT-888) taken today*		
	13	*No veliparib (ABT-888) taken today*		
	14	*No veliparib (ABT-888) taken today*		
	15	*No veliparib (ABT-888) taken today*		
	16	*No veliparib (ABT-888) taken today*		
	17	*No veliparib (ABT-888) taken today*		
	18	*No veliparib (ABT-888) taken today*		
	19	*No veliparib (ABT-888) taken today*		
	20	*No veliparib (ABT-888) taken today*		
	21	*No veliparib (ABT-888) taken today*		

APPENDIX D: PD SAMPLE COLLECTION WORKSHEETS AT THE NCI

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 1				
CTEP Protocol P9771 **Dose level:** **Patient ID:**	**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**			**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 1	**Prior to drug administration**	**PD 400** 10 mL Streck x1 Label tube: sample number, date and time	**Morning of drug administration**		

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 2				
CTEP Protocol P9771 **Dose level:** **Patient ID:**	**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**			**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 2	**Prior to M6620 (VX-970) administration**	**PD 401** 10 mL Streck x1 Label tube: sample number, date and time			
Start time of M6620 (VX-970) administration:					
Day 2	**8 hr (± 30 min) after start of M6620 (VX-970) administration**	**PD 402** 10 mL Streck x1 Label tube: sample number, date and time			

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 8				
CTEP Protocol P9771 **Dose level:** **Patient ID:**	**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**		**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 8	**Prior to veliparib + cisplatin administration**	**PD 403** 10 mL Streck x1 Label tube: sample number, date and time			

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 1 DAY 9				
CTEP Protocol P9771 **Dose level:** **Patient ID:**	**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**		**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 9	**Prior to M6620 (VX-970) administration**	**PD 404** 10 mL Streck x1 Label tube: sample number, date and time			

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 2 DAY 1				
CTEP Protocol P9771 **Dose level:** **Patient ID:**	**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**		**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 1	**Prior to veliparib + cisplatin administration**	**PD 405** 10 mL Streck x1 Label tube: sample number, date and time			

Date:	PD BLOOD SAMPLE COLLECTION SHEET: CYCLE 2 DAY 2				
CTEP Protocol P9771 **Dose level:** **Patient ID:**	**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**		**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**		**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 2	**Prior to M6620 (VX-970) administration**	**PD 406** 10 mL Streck x1 Label tube: sample number, date and time			
Start time of M6620 (VX-970) administration:					
Day 2 (at participating sites	**10 hr (± 2 hr) after start of M6620 (VX-970) administration**	**PD 407** 10 mL Streck x1 Label tube: sample number, date and time			
Day 2 (at NCI only)	**7:00 pm (± 30 min)**	**PD 407** 10 mL Streck x1 Label tube: sample number, date and time			

Date:	PD BLOOD SAMPLE COLLECTION SHEET: EACH SUBSEQUENT CYCLE DAY 1				
CTEP Protocol P9771 **Dose level:** **Patient ID:** **Cycle number: _____**		**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**		**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 1	**Prior to veliparib + cisplatin administration**	**PD 40X** 10 mL Streck x1 Label tube: sample number, date and time			

Date:	PD BLOOD SAMPLE COLLECTION SHEET: ON THE DAY OF RESTAGING FOLLOW_UP OR PROGRESSION BIOPSY				
CTEP Protocol P9771 **Dose level:** **Patient ID:** **Cycle number: _____**		**Veliparib Dose:** **M6620 (VX-970) Dose:** **Cisplatin Dose:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 301-451-1169**		**Research Nurse:** Phone: **PI:** [redacted] Phone: [redacted]
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 1	**Prior to veliparib + cisplatin administration**	**PD 40X** 10 mL Streck x1 Label tube: sample number, date and time			

APPENDIX E: INFORMED CONSENT FORM TEMPLATE

Study Title: Phase I Study of Veliparib (ABT-888), an Oral PARP Inhibitor, and M6620 (VX-970), an ATR Inhibitor, in Combination with Cisplatin in Patients with Refractory Solid Tumors

Introduction

We invite you to take part in this research study.

First, we want you to know that:

Taking part in this research study is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with family, friends or your personal physician or other health professional.

Why is this study being done?

The purpose of this study is to test the safety of a combination of 3 drugs (M6620 (VX-970), veliparib (ABT-888), and cisplatin) to find out the doses of these drugs that can be safely given to humans and to learn if these drugs have activity against tumors. Although we hope this experimental therapy will decrease the size of your tumor, we cannot promise or predict the benefits of the treatment at this time. The drugs used in this study have known side effects that will be reviewed with you by your medical team before you sign this consent form.

Cisplatin is currently approved by the US Food and Drug Administration (FDA) for the treatment of patients with bladder, ovarian, and testicular cancers in combination with other chemotherapy agents. Veliparib (ABT-888) and M6620 (VX-970) are not approved by the FDA. Combining veliparib (ABT-888) and M6620 (VX-970) with cisplatin is thought to block proteins that are known to be important for cancer cell growth.

We are also studying the genes in your tumor to help us understand how your tumor responds to these 3 drugs. Blood, tissue, and tumor cells contain genes that are made up of DNA and serve as the “instruction book” for each cell in the body. We know that variations in some tumor genes play an important role in how cancers respond to drugs. Determining whether different tumor gene

variations affect how veliparib (ABT-888), M6620 (VX-970), and cisplatin work against tumors will help scientists understand why some patients might stop responding to these drugs.

Why are you being asked to take part in this study?

You are being asked to take part in this research study because you have advanced cancer that has progressed after receiving standard treatment, or for which no effective therapy exists. We hope that this combination of study drugs will slow down the growth of your cancer.

How many people will take part in this study?

Up to 60 patients will take part in this study at multiple sites around the US.

What will happen if I take part in this study?

If you are accepted and you choose to take part, you will begin receiving veliparib (ABT-888) and cisplatin on the first day, followed by M6620 (VX-970) on the second day. Cisplatin and M6620 (VX-970) are given as an infusion through a vein. The drugs are given in cycles, and each cycle is 21 days (3 weeks) long.

- Cisplatin is given the first day of each cycle and on day 8 for some patients, for at least the first 6 cycles
- M6620 (VX-970) is given on day 2 and day 9 of each cycle (or day 1 and day 8 if no cisplatin is given during that cycle)
- Veliparib (ABT-888) is given orally twice a day on days 1 through 3 and days 8 through 10 of each cycle

Each patient may receive a different dose based on when he or she entered the study. Your dose of study drugs may be decreased by the study doctor if you are not tolerating it well, or increased if you are tolerating it well.

Most of the exams, tests, and procedures you will have are part of your regular care such as a complete medical history, blood tests, and scans to measure your tumors. We would also do a pregnancy test in women who are able to become pregnant. The team will also give you a chart describing the tests and procedures that will be done each day during the study.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- **Clinic visit:** to ask how you are feeling and to evaluate you with a physical examination during week 1 and 2 of each cycle before you receive treatment.
- **Vital signs and physical examinations:** will be performed during the clinic visits.
- **Blood tests:** Measurement of your white blood cells, red blood cells, platelets, blood sugar, electrolytes, and of how your liver and kidneys work will be done during the first two days of the first week of each cycle, the second week before you receive treatment every cycle, and the

third week of the first cycle (this third week visit can be done with your home physician). About 1 tablespoon (15 mL) of blood will be drawn per visit.

- **CT scans** or other imaging tests such as MRI (an examination using magnetic field and radio waves) that detect your tumor will be done before the study and every 6 weeks while you are receiving study drugs. This is done so that any benefit of the treatment can be determined, and if your cancer is not responding to the treatment, the study team can tell you and discuss other treatment options (discussed further below).
- **EKGs** (a recording of the heart's electrical activity) to check for signs of possible damage to your heart.

You will also have tests and procedures done because you are in the study to see how the study drugs are affecting your body. If you develop any side effects, you may be asked to visit more often. You will be asked to keep a diary to record the exact time you took veliparib (ABT-888), and to report any side effects you may have. If you miss a dose or vomit the dose, please make a note of this in your diary and contact your team immediately to receive further instructions. Please bring the study diary with you to each clinic visit.

Tests and procedures being done to see how the drug is affecting your body:

- **Research blood tests:** We will also be collecting blood samples from some patients to find out the effects of the drug on any tumor cells in the blood. Blood samples will be collected from patients at the beginning of the study, and prior to receiving study drugs on days 1, 2, and 9 of cycle 1, days 1 and 2 of cycle 2, and on day 1 of cycle 3 and every subsequent cycle. The total blood for all these tests will be up to 2 tablespoons (about 30 mL).

- **Tumor Biopsy:** You may be asked to undergo imaging-directed biopsy of your tumor (removal of a small bit of tissue for microscopic examination) once on day 1 and again on day 9 in the first cycle only. We are collecting biopsy samples to study the effects of study drugs on your tumor and to search for any gene variations in your tumor that may help us understand how it responds to these drugs. Biopsies are an important part of this trial and are done for research purposes. Biopsies are optional in the early part of this study (called the dose escalation phase) but mandatory at a certain point in the study called the expansion phase.

  If you decide not to have biopsies collected, you will still receive study drugs and other tests that are part of the study and detailed above. However, at the expansion phase, willingness to undergo tumor biopsies will be required for taking part in this study. We will tell you if biopsies are required before you decide to take part in the study.

  No more than three biopsy procedures will be performed during the study. After the first biopsy, if you decide not to have further biopsies, you will still receive study drugs and have other tests that are part of the study. You will be asked to sign a separate consent form for each biopsy procedure.

  Tumor biopsies are only collected by trained personnel. Biopsies are collected using a small needle under imaging guidance (CT, MRI, or ultrasound as deemed appropriate by the interventional radiologist performing the biopsy). Imaging helps the specialized radiologist know that the needle has been placed into the tumor mass.

Typical risks of biopsy collection include, but are not limited to, bleeding, infection, pain, and scarring. If you experience any complications from the biopsy, medical care will be offered to you. You will be counseled in more detail about biopsies, and you will be asked to sign a separate consent form that will describe the procedures and risks at that time. Your safety is the most important thing at all times. If upon attempting the first biopsy, no tissue can be obtained or it has caused you harm, further biopsies will not be done. After you are enrolled in this study, if for any reason the biopsies cannot be done safely, you may still receive the study drugs but the biopsies will not be done.

The biopsies are for research purposes and will not benefit you. They might help other people in the future. Even if you sign "yes" to have biopsies, you can change your mind at any time. Please read each sentence below and think about your choice. After reading the sentence, circle the initial answer that is right for you:

Have you been informed regarding what phase of the study you will be in?

Escalation phase_____ Expansion phase_____ Initials _____

I agree to have the tumor biopsies for the escalation phase of the research study (optional).
Yes ____ No ____ Initials_____

I agree to have the tumor biopsies for the expansion phase of the research study (mandatory).
Yes ____ No ____ N/A _____ Initials_____

Optional Tumor Genomic Sequencing

Targeted Sequencing—If your cancer looks like it is getting worse, you may choose to have another, optional tumor biopsy before leaving the study and have a targeted genomic sequencing test done on this tumor tissue in a clinically approved laboratory. You and your doctor will receive the results of this test, and the results will be in your electronic medical record. Your doctor will discuss these results with you and tell you about any gene variations that might make you able to take part in targeted therapy clinical trials in the future, such as the NCI MATCH (NCT02465060) and MPACT (NCT01827384) trials.

Exome Sequencing—If you choose to have the optional, third tumor biopsy, we are also requesting your permission to perform exome sequencing on your tumor biopsies and link this information to information from your medical history. You are not required to agree to exome sequencing to take part in this trial. Your tumor tissue contains genes, which are made up of DNA (**d**eoxyribo**n**ucleic **a**cid) and serve as the "instruction book" for the cells that make up our bodies. Exome sequencing will determine the exact order of the base pairs (DNA building blocks) in your tumor. We know that variations in the base pairs of some tumor genes play an important role in how cancers respond to drugs. Information about your gene variations combined with information from your medical history may help us understand how your tumor responds to the study drugs and why it has stopped responding.

If you agree, we will identify gene variants in your tumor biopsy samples collected at the beginning and end of treatment with exome sequencing, but this information will be for research purposes only and we will not give you any individual results from this sequencing or add this information to your medical records. This is because it will probably take a long time for this project to produce health-related information that we will know how to interpret accurately. However, we will tell you if we find that you have a communicable disease that we are required by law to report.

I agree to allow genomic sequencing for research purposes:

Yes ____ No ____ Initials_____

How long will I be in this study?

You will stay in the study as long as you are tolerating the drugs and your tumors are either stable or getting better, but you can choose to leave the study at any time.

For some study procedures, we will need you to come to _____ *[name of center]*.

Stopping Therapy
You can decide to stop at any time. If you decide to stop for any reason, it is important to let your study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to include your medical information in the study. Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Your study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB, or FDA

Follow-up
You will be followed for 30 days after taking the last dose of study drugs. We will call you between days 27- 30 to ask about any side effects that were ongoing when you stopped therapy, or any new side effects that might be related to the study therapy. If you have side effects that might be related to the study drugs that have not gotten better after 30 days, we will call you every 2 weeks until the side effects have become stable or gotten better. The follow-up period will end if you enroll in another study or start receiving standard therapy.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- you may choose to have the usual approaches described above

- you may choose to take part in a different study, if one is available
- you may continue your standard care as usual (see table below), and not take part in this study
- or you may choose not to be treated, but you may want to receive comfort care to relieve symptoms

Please talk to your doctor about these and other options. Your doctor may decide that it is not safe for you to receive a particular treatment or you have the right to refuse a treatment, but before you decide to take part in this study you should discuss all available treatment options with your local doctor.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in the study?

If you choose to take part in this study, there is a risk that the treatment may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The agents used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.
- Your study doctor will give you a drug interactions handout and wallet card that lists possible interactions.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

- Some patients on this study have had low platelet counts and low red and white blood cell counts in their blood, possibly due to this drug combination. These conditions can cause bruising, bleeding, slow blood clotting after an injury, tiredness, weakness, shortness of breath, and can keep your body from fighting off infections.

Risks and side effects related to **veliparib (ABT-888)** may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving ABT-888 (veliparib), more than 20 and up to 100 may have:
• Nausea • Tiredness • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ABT-888 (veliparib), from 4 to 20 may have:
• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low • Belly pain • Constipation, diarrhea, vomiting • Weight loss, loss of appetite • Dehydration • Dizziness, headache • Changes in taste • Rash

RARE, AND SERIOUS In 100 people receiving ABT-888 (veliparib), 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • A new cancer resulting from treatment of earlier cancer • Seizure • Blood clot which may cause swelling, pain, shortness of breath

Risks and side effects related to **M6620 (VX-970)** may include:

POSSIBLE, SOME MAY BE SERIOUS

- Anemia which may require blood transfusion
- Diarrhea, nausea, vomiting
- Tiredness
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Infection, especially when white blood cell count is low which may cause painful and frequent urination
- Bruising, bleeding
- Pain in tumor
- Dizziness, headache
- Itching, rash
- Flushing

While taking M6620 (VX-970), you should take protective measures to minimize sun exposure.

Risks and side effects related to **cisplatin** may include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving cisplatin, more than 20 and up to 100 may have:
• Nausea, vomiting • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require blood transfusions • Bruising, bleeding • Kidney damage which may cause swelling, may require dialysis • Hearing loss including ringing in ears

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cisplatin, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Confusion • Difficulty with balance

RARE, AND SERIOUS In 100 people receiving cisplatin, 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy later in life • Seizure

Risks associated with genomic sequencing:

Privacy Risks

Your privacy is very important to us and we will use many safety measures to protect your privacy. Your research samples will be stored with a coded identifier, not your name. Any personal data about you will also be stored in a sequence computer database with that code identifier. All information that can directly link you to the tissue or personal information will not be shared with investigators using your specimens for research. This includes information that contains your name, medical record number, date of birth, or address.

There are protections in place that restrict who can see the results of your genetic tests. However, there remains a risk someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen.

Genetic variant results that we return to you will become part of your medical record at the NIH. In spite of all of the safety measures that we will use, we cannot guarantee that your identity will ever become known. For instance, if you or a family member releases information about you or your involvement in this study, or an insurer, employer, or other person obtains your written consent to receive information from your NIH medical record, your identity, information about your enrollment in this study and genetic variant results may be included in a release of your medical records.

Protections against misuse of genetic information

Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

There are state and federal laws that protect against genetic discrimination. There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA also does not apply to members of the United States military, to veterans obtaining health care through the Veteran's Administration or the Indian Health Service. GINA does not forbid insurance medical underwriting based on your current health status, including your cancer. GINA also does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. However, your cancer diagnosis will often be considered more important that genetic information about risk for developing another condition when evaluating you during medical underwriting.

Emotional and psychological risks

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond. *A*lthough your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your

testing results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you and your partner will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include using at least two of the following:

- abstinence
- tubal ligation
- barrier methods (condoms)
- hormonal (birth control pills, injections, or implants)
- intrauterine device (IUD)
- vasectomy

Also, if you are a woman taking hormonal birth control, please tell your study doctor or nurse. Some patients on this study may be given medication to control the side effects of nausea and vomiting that can make some forms of hormonal birth control stop working or work less well. You may need to use an alternative form of birth control during this time.

Potential Risks Related to Blood Samples

Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually last only a few minutes.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drugs' effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in this study. If you decide to take part, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical

care from our institution if you are eligible and choose to participate in another trial. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.
Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.

- Designated investigators from other cancer centers participating in this study, including MD Anderson Cancer Center and Dana-Farber Cancer Institute.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

Certificate of Confidentiality
To help us protect your privacy, the NIH has obtained a Certificate of Confidentiality from the Department of Health and Human Services. The Certificate is designed to prevent us from being forced to disclose identifying information for use in any federal, state, or local civil, criminal, administrative, legislative, or other court proceeding, even if faced with a court subpoena. You should understand, however, that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. We may not withhold information if you give your insurer or employer or a law enforcement agency permission to receive information about your participation in this project. This means that you and your family must also actively protect your own privacy.
The Certificate does not prevent us from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. Such disclosures will be made as described below.
The research team may share your information with:

- The Department of Health and Human Services (HHS), to complete federal responsibilities for audit or evaluation of this project;
- Public health agencies, to complete public health reporting requirements;
- NIH representatives, to complete NIH responsibilities for oversight of this study;

- Your primary care physician if a medical condition that needs urgent attention is discovered;
- Appropriate authorities to the extent necessary to prevent serious harm to yourself or others.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The NCI will supply the study agents veliparib (ABT-888) and M6620 (VX-970) at no charge while you take part in this study. Even though it is unlikely, there is a possibility that at some point the supply of study agents may run out, necessitating taking you off-study. The NCI will not provide cisplatin free-of-charge, so you or your health plan may need to pay for cisplatin and the personnel who give it to you.

[If applicable, inform the patient of any tests, procedures or agents for which there is no charge. The explanation, when applicable, should clearly state that there are charges resulting from performance of the test or drug administration that will be billed to the patient and/or health plan. For example, "The NCI is supplying (drug) at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the (drug)."]

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237). You may also visit the NCI Web site at http://cancer.gov/.

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature
I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX F: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP Form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
- The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
- The Coordinating Center must be designated on the title page.
- Central registration of patients is required. The procedures for registration must be stated in the protocol.
- Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
- Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
- Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP (see Section 8.4). Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX G: PROCEDURE FOR SAMPLES FOR PHARMACODYNAMIC STUDIES

Collection of Biopsies

Materials for shipping biopsy specimens will not be provided. Core needle biopsies and biopsies from dermatologic and ENT lesions should be collected, placed in pre-chilled cryogenic vials, flash frozen in liquid nitrogen within 2 minutes of collection, and shipped on dry ice. Refer to SOP 340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf) for detailed instructions on core needle biopsy collection and handling, including the sample shipping manifest, batch record, and instructions for requesting FedEx labels. Sample handling SOPs are still in development for biopsies collected from dermatologic and ENT lesions; please contact FNLCR PD Central Receiving (NCI_PD_Support@mail.nih.gov, 301-846-1951, or 301-846-6747) for additional instructions regarding these tissue types.

Participating site **biopsy samples will shipped via FedEx to:**

Attention: [redacted]
NCI-F/FNLCR
1073 Beasley Street, [redacted]
Fort Detrick
Frederick, MD 21701
Phone: [redacted]

At the NCI only, **biopsy samples will be shipped via courier to:**

Attn: [redacted]
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
[redacted]
Frederick, MD 21702
Phone: [redacted]

Isolation of CTCs

Prior to CTC collection, each participating site should e-mail a request for specimen collection and shipping materials from NCI_PD_Support@mail.nih.gov**.** Allow at least six business days for receipt of the blood shipment containers; a confirmation e-mail with the expected shipping date will be sent. Blood (at least 7.5 mL) will be collected aseptically by venipuncture or from a venous port into one 10 mL CellSave preservative tube; the collected blood samples are stable for up to 48 hours at room temperature (15˚C to 30˚C) prior to processing.

Participating site **CTC samples will be shipped to:**

Attention: [redacted]
NCI-F/FNLCR
1073 Beasley Street, [redacted]

Fort Detrick
Frederick, MD 21701
Phone: [redacted]

***At the NCI only,* CTC samples will be shipped via courier to:**

Attn: PADIS CTC Laboratory
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
[redacted]
Frederick, MD 21702
Phone: 301.846.4711

E-mail NCIPDSupportPADIS@mail.nih.gov prior to shipping CTC samples with expected arrival date/time and a description of contents. All shipments should include a description of contents on the outside label/shipping slip, and a detailed packing slip should be included with the samples. Because of the 48-hour window of CTC sample stability, CTC samples should be shipped to arrive when specified below:

Collection Day	Day/time samples **must** arrive at PADIS
Monday	Wednesday (early morning)
Tuesday	Thursday (early morning)
Wednesday	Friday (early morning)
Thursday	Friday (early morning)
CTC samples may not be collected on Fridays	
Saturday	Monday (early morning)
Sunday	Tuesday (early morning)