SUMMARY OF CHANGES – Protocol

For Protocol Amendment #13 to:

NCI Protocol #: 10191
Local Protocol #: Dana-Farber/Harvard Cancer Center Protocol #19-715

NCI Version Date: August 24, 2024
Protocol Date: August 24, 2024

Please provide a list of changes from the previous CTEP approved version of the protocol. The list shall identify by page and section each change made to a protocol document with hyperlinks to the section in the protocol document. All changes shall be described in a point-by-point format (i.e., Page 3, section 1.2, replace 'xyz' and insert 'abc'). When appropriate, a brief justification for the change should be included.

Protocol Changes (from version May 4, 2021)

#	Section	Comments
1.	Header Title Page	1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy: Protocol Cover Page: Page Number(s): __1____ Version Date: _22 August, 2024_____
2	Biomarker Table	Added DirectHRD assay to Biomarker Table
3	2.5.2	Added description of DirectHRD to "Tumor profiling from circulating free DNA (cfDNA)"
4	7.4.3	Updated AE Reporting Table
5	9.7.2	Added 50 x whole genome sequencing to exploratory correlative studies

"**Biomarker Table**"

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-Based Biomarkers							
1	Whole Exome Sequencing	NGS CLIA: No	Integrated For identification of homologous recombination deficiency (baseline) and mediators of resistance (progression)	DNA from Metastatic biopsy tissue	Pre-study and at the time of progression	M (baseline) O (progression)	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams, Ph.D. mickey.williams@nih.gov
2	RAD51 focus formation	IHC CLIA: N	Exploratory Functional assessment of HRD	Slides from Metastatic biopsy tissue	Pre-treatment	M (baseline)	Center for DNA Damage and Repair, Dana-Farber Cancer Institute (DFCI) Bose Kochupurakkal, Ph.D. bose_kochupurakkal@dfci.harvard.edu Center for DNA Damage and Repair, Dana-Farber Cancer Institute (DFCI) Geoffrey Shapiro geoffrey_shapiro@dfci.harvard.edu BWH Specialized Histopathology Services Core, Dana-Farber Cancer Institute (DFCI) Jon Aster jaster@partners.org

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
3	ATM/p-KAP1 IHC	IHC CLIA: N	Exploratory Functional assessment of HRD	Slides from Metastatic biopsy tissue	Pre-treatment	M (baseline)	Center for DNA Damage and Repair, Dana-Farber Cancer Institute (DFCI) Bose Kochupurakkal, Ph.D. bose_kochupurakkal@dfci.harvard.edu Center for DNA Damage and Repair, Dana-Farber Cancer Institute (DFCI) Geoffrey Shapiro geoffrey_shapiro@dfci.harvard.edu BWH Specialized Histopathology Services Core, Dana-Farber Cancer Institute (DFCI) Jon Aster jaster@partners.org
4	RNAseq	NGS CLIA: No	Exploratory Assessment of RB functional status	RNA from Metastatic biopsy tissue	Pre-study and at the time of progression	M (baseline) O (progression)	NCLN Genomics Laboratory Mickey Williams, Ph.D mickey.williams@nih.gov (analysis by Leigh Ellis, Cedars Sinai leigh.ellis@cshs.org)
Blood-Based Biomarkers							
1	Whole Exome Sequencing	NGS CLIA: No	Integrated Germline Control	DNA from blood in cfDNA Streck tube	Pre-treatment	M	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Mickey Williams, Ph.D. mickey.williams@nih.gov

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial (Integral, integrated, or Exploratory) AND Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
1	Ultra low-pass whole genome sequencing (ULP-WGS) and prostate cancer-specific targeted sequencing from cfDNA	0.1 x pass whole genome sequencing and targeted NGS CLIA: N	Exploratory To qualify plasma for whole exome sequencing and to determine if genetic alterations detected in the tumor specimen can also be detected in cfDNA.	Plasma	Arm B: C1D1, C4D1, and every 3 cycles thereafter and at end of study . Arm A/crossover: C1D1, C4D1, and every 3 cycles while on carbo+/- docetaxel, then C1D1 [crossover], C4D1 [crossover], and every 3 cycles thereafter while on carbo+M6620 and at end of study.	M	Center for Cancer Precision Medicine, Dana-Farber Cancer Institute / Brigham & Women's Hospital / Broad Institute Eliezer Van Allen, M.D. eliezerm_vanallen@dfci.harvard.edu
1	DirectHRD	50 x whole genome sequencing from cfDNA and 15 x from germline CLIA: N	Exploratory To assess homologous recombination repair deficiency in cfDNA	Plasma	Arm B: C1D1, C4D1, and every 3 cycles thereafter and at end of study . Arm A/crossover: C1D1, C4D1, and every 3 cycles while on carbo+/- docetaxel, then C1D1 [crossover], C4D1 [crossover], and every 3 cycles thereafter while on carbo+M6620 and at end of study.	M	Broad Institute Viktor Adalsteinsson, PhD viktor@broadinstitute.org

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

NCI Protocol #: 10191

Local Protocol #: Dana-Farber/Harvard Cancer Center Protocol #19-715

ClinicalTrials.gov Identifier: NCT03517969

TITLE: A Phase 2 Study of M6620 (VX-970, berzosertib) in Combination with Carboplatin compared with Docetaxel in Combination with Carboplatin in Metastatic Castration-Resistant Prostate Cancer

Study Disease: Prostate Cancer 10036910

Corresponding Organization: LAO-MA036 / Dana-Farber/Harvard Cancer Center

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LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-MD017/ JHU Sidney Kimmel Comprehensive Cancer Center LAO **PARTICIPATION LIMITED TO:** **CO070 /** University of Colorado Hospital
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NCI-Supplied Agent(s): M6620 (VX-970, berzosertib), NSC# 780162
Other Agent(s): carboplatin, NSC# 241240, commercial; docetaxel, NSC# 628503, commercial

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

Protocol Type / Version # / Version Date: Amendment 13 / Version #18 / 24 August, 2024
**Protocol types: Original, Revision, or Amendment*

SCHEMA

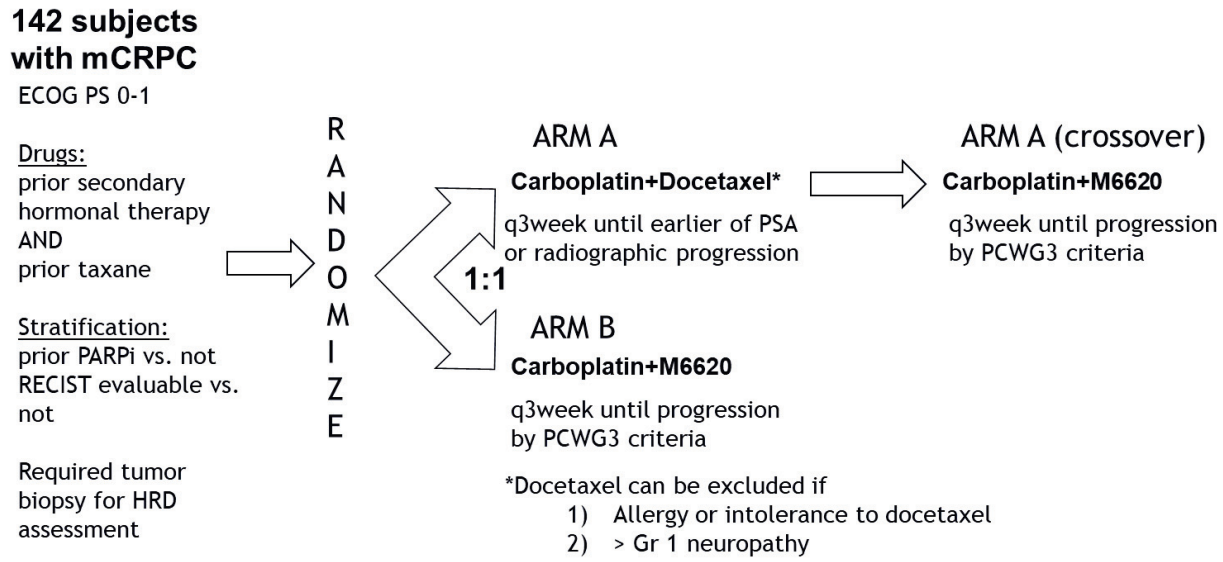

142 subjects with mCRPC
ECOG PS 0-1
Drugs:
prior secondary hormonal therapy AND
prior taxane
Stratification:
prior PARPi vs. not
RECIST evaluable vs. not
Required tumor biopsy for HRD assessment
RANDOMIZE
1:1
ARM A
Carboplatin+Docetaxel*
q3week until earlier of PSA or radiographic progression
ARM A (crossover)
Carboplatin+M6620
q3week until progression by PCWG3 criteria
ARM B
Carboplatin+M6620
q3week until progression by PCWG3 criteria
*Docetaxel can be excluded if
1) Allergy or intolerance to docetaxel
2) > Gr 1 neuropathy

TABLE OF CONTENTS

SCHEMA 3

1. OBJECTIVES 7
   - 1.1 Primary Objectives 7
   - 1.2 Secondary Objectives 7
   - 1.3 Exploratory Objectives 7

2. BACKGROUND 7
   - 2.1 Study Disease – Prostate Cancer 7
   - 2.2 M6620 (VX-970, berzosertib) 9
   - 2.3 Carboplatin 15
   - 2.4 Rationale 16
   - 2.5 Correlative Studies Background 17

3. PATIENT SELECTION 20
   - 3.1 Eligibility Criteria 20
   - 3.2 Exclusion Criteria 22
   - 3.3 Inclusion of Women and Minorities 24

4. REGISTRATION PROCEDURES 24
   - 4.1 Investigator and Research Associate Registration with CTEP 24
   - 4.2 Site Registration 25
   - 4.3 Patient Registration 28
   - 4.4 General Guidelines 29

5. TREATMENT PLAN 29
   - 5.1 Agent Administration 29
   - 5.2 General Concomitant Medication and Supportive Care Guidelines 33
   - 5.3 Crossover 34
   - 5.4 Duration of Therapy 35
   - 5.5 Duration of Follow Up 35

6. DOSING DELAYS/DOSE MODIFICATIONS 36

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 40
   - 7.1 Rave-CTEP-AERS Integration 40
   - 7.2 Comprehensive Adverse Events and Potential Risks List (CAEPR) 42
   - 7.3 Adverse Event Characteristics 46
   - 7.4 Expedited Adverse Event Reporting 46
   - 7.5 Routine Adverse Event Reporting 49
   - 7.6 Pregnancy 49
   - 7.7 Secondary Malignancy 49
   - 7.8 Second Malignancy 49

8. PHARMACEUTICAL INFORMATION....50
8.1 M6620 (VX-970, berzosertib) (NSC 780162)....50
8.2 Carboplatin....54
8.3 Docetaxel....55

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES....57
9.1 Collection of Specimens....57
9.2 Specimen Procurement Kits and Scheduling....58
9.3 Specimen Tracking System Instructions....58
9.4 Specimen Collection....62
9.5 Shipping Specimens from Clinical Site to the EET Biobank....64
9.6 Integrated Correlative Study – Whole Exome Sequencing....66
9.7 Exploratory/Ancillary Correlative Studies....67

10. STUDY CALENDAR....69

11. MEASUREMENT OF EFFECT....70
11.1 Antitumor Effect – Solid Tumors....70
11.2 PSA Response....78

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS....78
12.1 Study Oversight....78
12.2 Data Reporting....78
12.3 Data Quality Portal....81
12.4 CTEP Multicenter Guidelines....81
12.5 Collaborative Agreements Language....81
12.6 Genomic Data Sharing Plan....83

13. STATISTICAL CONSIDERATIONS....83
13.1 Study Design/Endpoints....83
13.2 Sample Size/Accrual Rate....84
13.3 Analysis of Primary Endpoint....85
13.4 Analysis of Secondary/Exploratory/Correlative Endpoints....86
13.5 Reporting and Exclusions....87

REFERENCES....87

APPENDIX A PERFORMANCE STATUS CRITERIA....91

APPENDIX B CTEP MULTICENTER GUIDELINES....92

APPENDIX C PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD....93

APPENDIX D - BIOASSAY TEMPLATES....95

APPENDIX E PROCEDURE FOR COLLECTION OF BIOPSY TISSUE.....101

APPENDIX F -TISSUE BIOPSY VERIFICATION 103

1. OBJECTIVES

1.1 Primary Objectives

The primary objective of this study is to assess the difference in response rate (either achievement of PSA reduction of greater than 50% or radiographic response by RECIST 1.1) of the combination of M6620 (VX-970, berzosertib) and carboplatin as compared to the combination of docetaxel and carboplatin.

1.2 Secondary Objectives

A secondary objective is to assess the difference in time to PSA progression by Prostate Cancer Working Group 2 (PCWG2) criteria[1] of the combination of M6620 (VX-970, berzosertib) and carboplatin as compared to the combination of docetaxel and carboplatin. In addition, we plan to describe radiographic progression-free survival and progression-free survival by PCWG3 criteria[2] in both arms of the study. We will assess the relationship with homologous recombination deficiency (HRD) detected from baseline tumor biopsy with response to the combination of M6620 (VX-970, berzosertib) and carboplatin and the combination of docetaxel and carboplatin. We also plan to describe the safety and adverse events from the combination of M6620 (VX-970, berzosertib)+carboplatin as well the combination of docetaxel+carboplatin.

1.3 Exploratory Objectives

Exploratory objectives include comparison of overall survival in the two arms of the study. In addition, we will explore response rate, time to PSA progression, radiographic progression-free survival, and progression-free survival by PCWG3 criteria in patients who initially receive docetaxel+carboplatin after crossover to M6620 (VX-970, berzosertib)+carboplatin. We also plan to assess the relationship with homologous recombination deficiency (HRD) detected from baseline circulating free DNA (cfDNA) with response to the combination of M6620 (VX-970, berzosertib) and carboplatin and the combination of docetaxel and carboplatin, and describe alterations seen in cfDNA (and optional tumor biopsy) at end of study.

2. BACKGROUND

2.1 Study Disease – Prostate Cancer

Prostate cancer is the most common non-cutaneous malignancy in men in the United States, and despite significant progress in management and treatment of this disease, prostate cancer is the third most common cause of cancer death in men in the United States.[3] The vast majority of these deaths is in patients with metastatic dissemination of their cancer and in whom their disease has become resistant to medical or surgical castrating therapies. While genetic and molecular alterations in metastatic castration-resistant prostate cancer (mCRPC) have been well characterized,[4] there has been limited progress in translating these findings into novel therapeutic strategies for these patients. Specifically, there has been limited clinical benefit derived from

molecularly targeted agents (other than those targeting signaling through the androgen receptor) in mCRPC, and there is a paucity of validated predictive biomarkers to guide clinical management in these patients. Recently, Mateo, et al.[5] demonstrated that olaparib, an inhibitor of Poly (ADP-ribose) polymerase (PARP), has clinical activity in mCRPC, with clinical responses enriched in the population of patients identified by next generation sequencing to have homozygous deletions, deleterious mutations, or both in DNA-repair genes – 14 of the 16 patients (88%) found to have one of these aberrations experienced a response to olaparib. This study has been transformative to our understanding of therapeutic vulnerabilities in mCRPC, having demonstrated both that targeting defects in DNA repair pathways can lead to clinical benefit in these patients, and that sequencing-based biomarkers can provide predictive information for the likelihood of response to therapy.

However, there are multiple limitations in applying these findings broadly in clinical practice. The sequencing-based biomarker in this study was primarily obtained from biopsy of a metastatic lesion, which is a cumbersome and expensive process to apply broadly in the community. The alterations implicated in conferring sensitivity to olaparib in the Mateo study were predominantly BRCA2, ATM, FANCA, BRCA1, PALB2 and HDAC2 – however the degree to which these alterations were causal to the sensitivity remain unclear. In reality, hundreds of genes are involved in the response to and repair of DNA damage, and capturing and interpreting these data to understand the phenotypic relevance is a major challenge (e.g. whether specific alterations are truly pathogenic, and whether the presence of multiple hypomorphic or heterozygous mutations in combination can confer sensitivity). The overall response rate in the unselected population of patients in this study was 33%, with 12 of 49 patients (24%) remaining on study treatment for greater than 6 months.
The FDA initially granted breakthrough therapy designation to olaparib in patients with *BRCA1*, *BRCA2* or *ATM* mutations based on the TOPARP-A study[5], and subsequently the Phase III PROfound study[6] demonstrated improvement in radiographic progression-free survival, objective response rate and overall survival of olaparib compared to potent AR pathway inhibitor (ARPI) abiraterone or enzalutamide in patients with these mutations who progressed on the other ARPI agent. However, the degree to which patients with *ATM* mutations respond to PARP inhibitors remains unclear. Rucaparib was granted FDA breakthrough therapy designation in patients with *BRCA1* or *BRCA2* mutations based on results of the TRITON2 study[7], but in this study 0 of 18 patients with an *ATM* mutation responded to rucaparib. In other studies of olaparib, Marshall et al.[8] reported responses in 0 of 6 patients with *ATM* mutation, and the TOPARP-B study[9] reported 2 of 19 patients with PSA or radiographic response in this population (the remaining 5 "responders" with *ATM* mutations in this study were based on CTC conversion, which is not a commonly used criterion for clinical response in prostate cancer studies). The TOPARP-B study did demonstrate responses in patients with *PALB2* mutations, but limited benefit in patients with mutations in *CDK12* and in a basket of "other" genes involved in DNA damage repair. Thus, better biomarkers to predict response and resistance to PARP inhibitors are needed, and alternative therapeutic approaches are required for patients unlikely to respond to PARP inhibitor monotherapy.

One such targeted approach is through inhibiting the enzymatic activity of the Ataxia telangiectasia and Rad3 related (ATR) serine/threonine kinase. ATR is activated by replication

protein A (RPA)-coated single-stranded DNA (ssDNA), a nucleoprotein structure commonly generated at sites of DNA damage and stressed replication forks.[10] Whereas a related kinase ATM is primarily involved in the response to DNA double-stranded breaks, ATR responds to a wide range of DNA damage and DNA replication problems. Thus, ATR inhibition is selectively toxic in cells with loss of genes involved in homologous recombination (HR) repair (ATM, XRCC1) and NER (ERCC1), but also in cells reliant on alternative lengthening of telomeres (ALT) as well as cells with high levels of replication stress induced by oncogenes (e.g. Ras isoforms, Myc, Cyclin E) and hypoxia. Replication stress can be induced exogenously, such as through treatment with chemotherapeutics.[11] This study seeks to assess the anti-tumor activity of the ATR inhibitor M6620 (VX-970, berzosertib) in combination with carboplatin in patients with metastatic castration-resistant prostate cancer.

2.2 M6620 (VX-970, berzosertib)

M6620 (VX-970, berzosertib) is a highly potent and selective ATP-competitive inhibitor of ATR, with an inhibition constant (Ki) <0.3 nmol/L (nM)[12]. In comparison, M6620 (VX-970, berzosertib) was >100-fold weaker inhibitor of ATM (Ki=34 nM) and >1000-fold less effective against other closely related kinases, such as DNA-dependent protein kinase (DNA-PK) (Ki>4 mcM), mTOR (Ki>1 mcM), and PI3K-gamma (Ki=0.22 mcM).[13] Overall, M6620 (VX-970, berzosertib) selectivity was >50-fold higher for ATR than for 290 of 291 kinases tested and >25-fold over FLT4[12]. A cellular 50% inhibition of ATR was attained at a M6620 (VX-970, berzosertib) concentration (IC_{50}) of 0.019 mcM, demonstrating >100-fold greater selectivity against ATR compared to ATM or DNA-PK (IC_{50} of 2.6 mcM or 18.1 mcM, respectively).[13]

Effect of M6620 (VX-970, berzosertib) on DDR signaling and DNA damage

M6620 (VX-970, berzosertib) potentiated the activity of multiple DNA-damaging agents in numerous cancer cell lines from a range of indications[12]. Concurrent treatment of cancer cell lines with M6620 (VX-970, berzosertib) and various DNA-damaging agents led to sustained M6620 (VX-970, berzosertib)-dose-dependent decreases in levels of chemotherapy-induced CHK1pS^{345}, a major substrate of ATR[13,14]. In the presence of DNA damage, primarily DSBs, histone H2AX is phosphorylated at serine 139 to produce γH2AX (H2AXpS^{139}). Although all three DDR regulatory kinases, ATM, ATR, and DNA-PK phosphorylate H2AX to γH2AX, they are variably activated during different DNA-damage repair mechanisms (*e.g.*, HR repair, non-homologous end joining [NHEJ] repair, base excision repair due induced by stalled replication forks, *etc.*)[15]. In addition, for efficient DNA-damage repair, the DDR regulatory kinases must be able to access damaged sites in the chromatin environment. ATM has been shown to phosphorylate the heterochromatin protein KAP1 at serine 824 (KAP1pS^{824}) in response to DNA damage[16]. Exposure of lung cancer cell lines as well as primary tumors to M6620 (VX-970, berzosertib) in combination with DNA-damaging agents enhanced levels of the DNA-damage markers, *i.e.*, γH2AX and KAP1pS^{824}, as compared to DNA-damaging agent alone[14]. Sequential treatment of cells with DNA-damaging agent followed 15 h later by M6620 (VX-970, berzosertib) resulted in an initial inhibition of phospho-CHK1 (for 1 to 2 h)[12]. However, over time, phospho-CHK1 re-appeared despite continued exposure to M6620 (VX-970, berzosertib). The rebound of phospho-CHK1 has been attributed to non-specific phosphorylation by an

undefined kinase. However, despite the transient inhibition of phospho-CHK1, the sustained accumulation of the DNA damage markers was observed. Together these data suggest that disruption of ATR-mediated DDR signaling by M6620 (VX-970, berzosertib) leads to sustained accumulation of DNA damage in cancer cells exposed to DNA-damaging agents. It has been suggested that the failure to repair chemotherapy-induced DNA damage in the presence of M6620 (VX-970, berzosertib) is the driver of enhanced cytotoxicity in cancer cells. These data support using the DNA-damage markers as pharmacodynamic markers of M6620 (VX-970, berzosertib) activity.

M6620 (VX-970, berzosertib)-mediated radiosensitivity of pancreatic ductal adenocarcinoma cells was associated with inhibition of HR repair[13]. M6620 (VX-970, berzosertib) caused increased persistence of γH2AX levels both *in vitro* and *in vivo*. Adding M6620 (VX-970, berzosertib) to gemcitabine and ionizing radiation (IR) dramatically enhanced antitumor effects, with early and late apoptosis and abrogation of IR-induced G2 checkpoint in cell culture experiments. It has been suggested that by promoting strong S-phase arrest, chemoradiation may further increase dependence of tumor cells on ATR-mediated homologous recombination (HR) repair of DNA double strand breaks (DSBs) and for survival.

Nonclinical studies

In vitro antitumor activity

In the absence of exogenous DNA-damaging agents, M6620 (VX-970, berzosertib) demonstrated stronger antiproliferative effects against cancer cell lines tested (HCT116, NCI-H23, and HT29 with IC_{50s} of 35, 48, and 170 nM, respectively) than against noncancerous cells (*e.g.*, fibroblasts or mammary epithelial cells (IC_{50}=200 -1100 nM)[12]. However, M6620 (VX-970, berzosertib) caused potent cytotoxicity only in the colorectal (CRC) cell line, HCT116, with 50% effective concentration (EC_{50}) of 61 nM. This suggests that certain cancer cells may be particularly reliant on ATR for survival even in the absence of an exogenous DNA-damaging agent.

In the cell proliferation assay with the HCT116 cell line, M6620 (VX-970, berzosertib) synergized with cisplatin (cross-linking agent), gemcitabine (anti-metabolite), irinotecan (topoisomerase I inhibitor), and etoposide (topoisomerase II inhibitor)[12]. The most dramatic response was observed in combination with cisplatin (a 20-fold lower IC_{50} compared to the IC_{50} of cisplatin alone). Preliminary data from cell proliferation studies with M6620 (VX-970, berzosertib) + carboplatin suggests >10-fold reduction in carboplatin IC_{50} for two non-small cell lung cancer (NSCLC) cell lines (H23 and HT1299) tested.

The M6620 (VX-970, berzosertib) impact on chemotherapy-induced cytotoxicity was further examined against a panel of 37 lung cancer cell lines (including squamous NSCLC and small cell lung cancer [SCLC] histotypes) and 15 pancreatic cancer cell lines[12]. Most lung cancer cell lines responded well to M6620 (VX-970, berzosertib) in combination with cisplatin (84% of cell lines) or gemcitabine (76% of cell lines), demonstrating ≥3-fold reduction in the IC_{50} compared to the cytotoxic agent alone.[12,14,17] Enhanced sensitivity was also observed with etoposide (53% of cell lines), irinotecan (49% of cell lines) and oxaliplatin (39% of cell lines). M6620 (VX-970,

berzosertib) hypersensitized (caused >10-fold reduction in IC_{50}) about 40% of cell lines to cisplatin[14]. Marked synergy between the two agents was also seen against four of seven human NSCLC primary tumors tested *in vitro*. The greatest antitumor synergistic effect was demonstrated by tumors with poor response to cisplatin alone. Similarly, most pancreatic cancer lines responded well to combination of M6620 (VX-970, berzosertib) with cisplatin or gemcitabine: antitumor IC_{50} was ≥3-fold lower for the M6620 (VX-970, berzosertib) + cytotoxic agent in >70% of cell lines as compared to IC_{50} of cytotoxic agent alone.[12]

In addition, significant radiosensitization effects by M6620 (VX-970, berzosertib) were observed against two human pancreatic cancer cell lines with mutant KRAS and mutant p53 (MiaPaCa-2 and PSN1) (P<0.05), but not against non-cancerous fibroblast cell lines[13]. In addition, M6620 (VX-970, berzosertib) profoundly sensitized pancreatic tumor cells to gemcitabine-based chemoradiation.

Impact of defective ATM signaling on sensitivity of cells to M6620 (VX-970, berzosertib) in combination with a cytotoxic agent (cisplatin, gemcitabine, irinotecan, oxaliplatin, or etoposide) was examined in isogenic matched lung cancer cells (wild-type p53 A549 versus A549 transfected with p53 shRNA), using a cell viability assay.[12,14] Loss of p53 promoted sensitivity to ATR inhibition in combination with all five cytotoxic agents in contrast with the effects in the p53 wild-type A549. M6620 (VX-970, berzosertib) also synergized with cisplatin resulting in cytotoxicity in ATM-null primary skin fibroblasts, but no cytotoxicity was observed against ATM wild-type fibroblasts.[12] This suggests that the functional status of the ATM pathway is a contributing factor in the cellular response to the inhibition of ATR.

Of note, the response/p53 status relationship was unclear in the panel of heterogeneous cancer cell lines exposed to M6620 (VX-970, berzosertib) + chemotherapy[14]. Although not significant, there was a trend of causality between response and p53 status (P=0.08) for M6620 (VX-970, berzosertib) combined with cisplatin. Furthermore, no clear relationship between cellular response to M6620 (VX-970, berzosertib) + cisplatin and p53 status was observed in seven primary lung tumors.

<u>*In vivo* antitumor activity</u>

The *in vivo* activity of M6620 (VX-970, berzosertib) was tested in multiple mouse xenograft models derived from human lung cancer cell lines and primary human tumor cells[12,14]. M6620 (VX-970, berzosertib) potentiated antitumor effects of cisplatin, gemcitabine, irinotecan, and IR in a dose- and schedule-dependent manner. Antitumor efficacy correlated with inhibition of phospho-CHK1 and an increase in DNA-damage markers. This supports ATR inhibition as a primary mechanism of action for M6620 (VX-970, berzosertib). Single-agent M6620 (VX-970, berzosertib) had no significant effect on tumor growth in the experimental models. M6620 (VX-970, berzosertib) was generally well tolerated at efficacious doses in combination with DNA-damaging agents. Some body weight loss and enhanced changes in specific peripheral blood cell populations were observed with intensive and sustained dosing of M6620 (VX-970, berzosertib) in combination with cisplatin. This effect could be attributed to an increased growth arrest, which was observed *in vitro* in normal cells for combinations of M6620 (VX-970, berzosertib)

with DNA-damaging agents. This effect was reversed when ATR activity was restored. M6620 (VX-970, berzosertib) sensitized pancreatic tumor xenografts to the cytotoxic effects of gemcitabine-based chemoradiation[13]. The combination treatment was effective even at gemcitabine doses with no single-agent activity. M6620 (VX-970, berzosertib) administered in combination with gemcitabine + IR was well tolerated.

In the sequence/schedule-optimization studies, M6620 (VX-970, berzosertib) was administered intravenously (IV) at 20 mg/kg (either as a single injection or as two 10 mg/kg injections 3 days apart) before (-2 h) or after cytotoxic agent (+12, 24, or 48 h) in human pancreatic cancer and NSCLC xenograft mouse models[12]. M6620 (VX-970, berzosertib) effectively enhanced antitumor activity of gemcitabine or cisplatin when administered 12 to 24 h after a cytotoxic agent. M6620 (VX-970, berzosertib) administered before cytotoxic drug or greater than 48 h after a DNA-damaging agent had no impact on tumor growth compared to the effect of cytotoxic agent alone.

A therapeutic dose for humans has been estimated based on the efficacious exposure achieved at 20 mg/kg/week of M6620 (VX-970, berzosertib) (given either as a single IV injection or as two IV injections of 10 mg/kg per week) 12-24 h after cytotoxic agent (gemcitabine or cisplatin) in mice[12]. The target M6620 (VX-970, berzosertib) plasma exposure, which corresponded to this dose, was an area under the concentration-time curve (AUC) of 4080 ng×h/mL/week. Allometry predicts that a human dose of 2.5 mg/kg (100 mg/mg^2) will be sufficient to achieve this exposure.

Nonclinical Pharmacokinetics

In all nonclinical species (the mouse, rat, dog, and monkey), M6620 (VX-970, berzosertib) exhibited a high volume of distribution (V_d); tissue exposure, including tumor, was high[12]. In rats, no accumulation or retention was observed in tissues and the elimination half-lives ($t_{1/2}$) were similar across all tissues and whole blood. The whole blood $t_{1/2}$ was 11.6 h in rats and 9.8 h in dogs. M6620 (VX-970, berzosertib) was extensively bound to plasma proteins; the free fraction of M6620 (VX-970, berzosertib) was only 2.1% in human blood.

M6620 (VX-970, berzosertib) is primarily eliminated by oxidative metabolism, with a cytochrome 450 (CYP) 3A4 isoform being the principle isoform responsible[12]. Strong inducers or inhibitors of CYP3A4 may alter M6620 (VX-970, berzosertib) kinetics and blood levels. Based on its minimal inhibition or induction effects on CYPs, M6620 (VX-970, berzosertib) is expected to have a low potential for drug-drug interactions. M6620 (VX-970, berzosertib) metabolites were excreted 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 of M6620 (VX-970, berzosertib) following IV administration was 26 and 13 mL/min/kg in the rat and dog, respectively.

Nonclinical Safety Pharmacology

An manual patch-clamp human ether-a-go-go-related gene (hERG) assay demonstrated moderate

inhibition of the hERG channel[12]. However, a telemetry dog study did not demonstrate any cardiovascular (CV) effects at exposures greatly exceeding the target human exposure.

Nonclinical Toxicology

A severely toxic dose defined as causing a death in 10% of animals (STD_{10}) in rats was 30 mg/kg/day administered IV over 3 h[12]. The highest non-severely toxic dose (HNSTD) in dogs was 20 mg/kg/day 3 h IV. M6620 (VX-970, berzosertib) had no cardiovascular liabilities, was not genotoxic in 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, berzosertib) absorbs in the ultraviolet (UV) spectrum and has high tissue distribution in rats.

M6620 (VX-970, berzosertib) has yet not been assessed in developmental and reproductive toxicity studies[12]. However, M6620 (VX-970, berzosertib) inhibits DNA-damage repair and will be administered in conjunction with cytotoxic chemotherapy, thus the potential for teratogenicity should be considered high.

Clinical Studies

Preliminary clinical data for M6620 (VX-970, berzosertib) have been derived from company-sponsored clinical studies evaluating M6620 (VX-970, berzosertib) in combination with various DNA-damaging agents, *e.g.*, gemcitabine, cisplatin, or carboplatin[12]. To test M6620 (VX-970, berzosertib) single-agent PK, a single IV dose of M6620 (VX-970, berzosertib) alone, ranging from 18-210 mg/m^2, was administered 7-14 days before M6620 (VX-970, berzosertib) was combined with a DNA-damaging agent. Combination of M6620 (VX-970, berzosertib) and a DNA-damaging agent were administered on a once-weekly schedule, with M6620 (VX-970, berzosertib) being dosed 24 h after a DNA-damaging agent. M6620 (VX-970, berzosertib) doses evaluated in combination with a DNA-damaging agent ranged from 90-240 mg/m^2 IV.

Clinical Pharmacokinetics

Clinical PK have been evaluated both in whole blood and plasma[12]. Mean exposure (AUC) profiles were similar in whole blood and plasma. Overall, the C_{max} was 1.3-fold greater in whole blood than in plasma. The results suggest that plasma is an appropriate matrix to characterize the M6620 (VX-970, berzosertib) PK. The terminal elimination $t_{1/2}$ was approximately 17 h across all doses. In the M6620 (VX-970, berzosertib) single dose studies, M6620 (VX-970, berzosertib) exposures (C_{max} and $AUC_{0-\infty}$) increased in a dose-proportional manner. Collectively, the data suggest that co-administration of gemcitabine, cisplatin, or carboplatin 24 hours before M6620 (VX-970, berzosertib) administration did not appear to affect the PK of M6620 (VX-970, berzosertib).

Clinical Efficacy

Preliminary analysis demonstrated objective responses for M6620 (VX-970, berzosertib) used in combination with a DNA-damaging agent(s) in treatment of patients with solid tumors[12]: A summary of preliminary activity is as follows:

- M6620 (VX-970, berzosertib) + gemcitabine in advanced solid tumors: Among 48 patients, 4 (one each NSCLC, head and neck cancer, breast cancer, and unknown primary cancer) had partial response (PR) and 29 patients had stable disease (SD). In an additional cohort of 18 patients with advanced NSCLC, 3 had PRs and 15 had SD.
- M6620 (VX-970, berzosertib) + cisplatin in advanced solid tumors: Among 26 patients, 4 (1 each $BRCA2^+$ ovarian cancer, epithelioid mesothelioma, TNBC, neuroendocrine prostate cancer) had PRs, and 15 patients had SD. In an additional cohort of 18 patients with advanced TNBC, 7 had PR and 6 had SD.
- M6620 (VX-970, berzosertib) + carboplatin in advanced solid tumors refractory to standard therapy: Among 21 evaluable patients, 1 had PR (ovarian cancer) and 14 had SD.
- M6620 (VX-970, berzosertib) + carboplatin or M6620 (VX-970, berzosertib) + cisplatin in platinum-resistant advanced SCLC: There were no objective responses observed among nine evaluable patients and 4 had SD.
- M6620 (VX-970, berzosertib) + gemcitabine + cisplatin in advanced solid tumors: Of 7 evaluable patients, 1 had PR (CRC) and 4 had SD.
- M6620 (VX-970, berzosertib) + carboplatin + paclitaxel in advanced solid tumors refractory to standard therapy: Among 8 evaluable patients, 2 had PR (1 each adenosquamous carcinoma of the cervix and melanoma) 3 had SD.

Safety summary from studies with M6620 (VX-970, berzosertib) as single agent or in combination with cytotoxic therapy[12]

Infusion-related reactions (local or systemic), nausea, and vomiting are considered adverse drug reactions (ADRs) for M6620 (VX-970, berzosertib), and myelosuppression events are considered ADRs for M6620 (VX-970, berzosertib) in combination with carboplatin.

- Systemic infusion-related reactions to M6620 (VX-970, berzosertib) may include signs or symptoms such as pruritus, flushing, chills/rigors, urticaria/rash, headache, bronchospasm/dyspnea, and hypotension or hypertension, among others.

- Some systemic infusion-related reactions to M6620 (VX-970, berzosertib) have been serious, including those described as acute hypersensitivity reactions. In almost all cases, these reactions occurred within minutes of the second exposure to M6620 (VX-970, berzosertib) and they included hypotension and mental status changes. All subjects fully recovered with standard care procedures.

- Local infusion-related reactions to M6620 (VX-970, berzosertib), sometimes described as infusion site reactions, may include signs or symptoms such as infusion site erythema, swelling, or pain. To minimize the possibility of phlebitis, M6620 (VX-970, berzosertib) should be administered through a large-bore catheter into large-caliber peripheral vein or central venous access.

- Nausea and vomiting have occurred commonly in patients receiving M6620 (VX-970, berzosertib) monotherapy. Many of the affected subjects experienced these events on the same day as M6620 (VX-970, berzosertib) was administered, and there was some suggestion of a dose response.

- Hematologic AEs in subjects who received M6620 (VX-970, berzosertib) in combination with carboplatin have included neutropenia, thrombocytopenia, and febrile neutropenia.

- M6620 (VX-970, berzosertib) has not been assessed in developmental and reproductive toxicity studies at this stage of development. However, M6620 (VX-970, berzosertib) inhibits DNA-damage repair and it will be administered in conjunction with cytotoxic chemotherapy; thus, the potential for teratogenicity should be M6620 (VX-970, berzosertib) considered high. Patients on M6620 (VX-970, berzosertib) studies must take stringent measures to avoid fathering or bearing children while on study drug and for 6 months after discontinuation of M6620 (VX-970, berzosertib). Refer to the M6620 (VX-970, berzosertib) clinical study protocols for specific contraceptive requirements.

Guidance on prior and concomitant medications[12]

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

The following list of potent CYP3A4 inhibitors and inducers is not exhaustive:

- Potent CYP3A4 inhibitors: clarithromycin, itraconazole, ketoconazole, hepatitis C virus and human immunodeficiency virus protease inhibitors, nefazodone, posaconazole, telithromycin, voriconazole.

- Potent CYP3A4 inducers: carbamazepine, rifampin, phenobarbital, phenytoin, St. John's wort.

2.3 Carboplatin

Platinum compounds have demonstrated clinical responses in castration-resistant prostate cancer, suggesting their clinical utility in this setting. In an unselected population, a Phase III trial of satraplatin in combination with prednisone demonstrated improved PFS as compared to placebo in combination with prednisone, but with no OS benefit seen.[18] A wide range of clinical responses have been reported to platinum compounds (cisplatin, carboplatin and satraplatin) in the literature,[19] with the highest response rates generally seen in combination with other chemotherapeutics in chemotherapy-naïve patients. The response rate to carboplatin combinations is ~20% overall in patients who progressed on docetaxel, and carboplatin in combination with docetaxel is a common regimen in taxane-refractory patients[20]. Recently, a

higher response rate has been demonstrated for carboplatin in combination with cabazitaxel[21]: PSA > 50% reduction was 60% for carboplatin plus cabazitaxel vs. 44% for cabazitaxel alone; radiographic partial response rate was 52% (17/33) for carboplatin plus cabazitaxel vs. 14% (5/35) for cabazitaxel alone. However, while these early data are promising, this is not considered a standard regimen at this point and is thus not yet universally covered by insurance.

Carboplatin use has previously been described in patients with "anaplastic" or "aggressive variant" prostate cancer.[22] More recently, carboplatin has been shown to be an active agent in cancers with homologous recombination repair deficiency, with demonstrated activity in prostate cancer patients with known inherited BRCA2 mutations.[23,24] However, now that olaparib has demonstrated responses in patients with mCRPC with alterations in genes involved in homologous recombination repair, PARP inhibitors have already been incorporated in clinical practice for off-label use and are often preferentially prescribed over carboplatin at centers where detection of these alterations is feasible. Nonetheless, many questions remain in the utility of PARP inhibitors, including a better understanding of patients likely to respond, the proper sequencing/combination of this agent with others, and mechanisms of resistance.

A variety of mechanisms have been proposed for how tumors that are resistant to PARP inhibition could remain sensitive to platinum agents, including loss of 53BP1, which leads to increased double strand break resection and thus leads to resistance to PARP inhibition in Brca1-null cells, but maintenance of sensitivity to DNA-crosslinking agents[25]; BRCA1 mutations that lead to defects in alternate DNA repair pathways such as nucleotide excision repair but retain proficiency in homologous recombination repair[26]; and mutation of other genes involved in nucleotide excision repair such as ERCC6 and ERCC4.[27] As such, carboplatin remains a relevant agent in mCRPC and may lead to clinical responses even in patients who progress on a PARP inhibitor.

2.4 Rationale

ATR inhibition is selectively toxic in cells with high levels of replication stress induced by oncogenes (e.g. Ras isoforms, Myc, Cyclin E), hypoxia, and exogenous administration of chemotherapeutics. In particular, platinum compounds increase replication stress by modifying DNA to produce intra- and inter-strand crosslinks between nucleotide bases. Intra-strand crosslinks induce DNA lesions in the template strand as well as misincorporate nucleotides, while inter-strand crosslinks induce defects in DNA unwinding—the very first step of DNA replication. These crosslinks will delay the progression of replication forks and enhance replicative stress. In pre-clinical studies, ATR inhibitor M6620 (VX-970, berzosertib) is synergistic with a variety of DNA damaging agents in cancer cell lines, but the synergy was found to be most pronounced with cisplatin.[14] In addition, M6620 (VX-970, berzosertib) was found to enhance the therapeutic efficacy of cisplatin in patient-derived lung tumor xenografts.

We conjecture that the combination of carboplatin with M6620 (VX-970, berzosertib) would provide clinical benefit to patients with metastatic castration-resistant prostate cancer with homologous recombination deficiency (even those who received prior PARP inhibitor) and a larger group of patients without HRD due to alternate mechanisms of action of carboplatin and

the synergistic activity of M6620 (VX-970, berzosertib) with platinum compounds related to induction of replication stress.

The recommended Phase II dose of M6620 (VX-970, berzosertib) in combination with carboplatin was informed by Part B of Study VX13-970-002 (Study 002). Initial results of this study were reported at the 2016 ASCO Annual Meeting.[28] M6620 (VX-970, berzosertib) was tolerated as a single agent with mostly grade 1/grade 2 toxicities and no dose-limiting toxicities (DLTs), and the recommended Phase 2 dose of the single agent was 240 mg/m^2. Among 11 treated patients, a patient with ATM loss colorectal cancer had RECIST complete response (19 months+) and 4 pts had RECIST stable disease (SD). In the combination of M6620 (VX-970, berzosertib) + carboplatin, dose escalation was limited by neutropenia and/or thrombocytopenia. The recommended Phase 2 dose of the combination was carboplatin AUC 5 day 1 and M6620 (VX-970, berzosertib) 90 mg/m^2 days 2,8 of a 21 day cycle. Among 15 patients treated with the combination, a patient with germline BRCA1 mutant and platinum-refractory, PARP inhibitor-resistant ovarian cancer with a somatic Y220C TP53 mutation had RECIST partial response for 6 months and 8 pts had RECIST SD. We will thus compare the response rate of this combination against a standard docetaxel + carboplatin combination regimen[20] in patients with metastatic CRPC.

2.5 Correlative Studies Background

2.5.1 Whole exome sequencing through Molecular Characterization (MoCha) laboratory at the Frederick National Laboratory for Cancer Research

Mandatory pre-treatment tumor biopsy specimens will be submitted for whole exome sequencing through the Molecular Characterization (MoCha) laboratory at the Frederick National Laboratory for Cancer Research. We plan to assess for the presence of homologous recombination repair deficiency as detected by a bone fide deleterious mutation or deletion in a gene known to be involved in homologous recombination repair from a fresh tumor biopsy. In addition, whole exome sequencing using the same assay will be performed from optional end of study tumor biopsies to assess for mediators of resistance.

This analysis is critical to understanding the relationship of response to carboplatin +/- M6620 (VX-970, berzosertib) with DNA damage repair defects detected in patients with metastatic CRPC. Specifically, we would hypothesize that:

1. Patients with HRD who are previously untreated with PARPi or carboplatin would be expected to respond to either docetaxel+carboplatin or M6620 (VX-970, berzosertib) + carboplatin.
2. Patients with HRD who were previously treated with PARPi and are found to have a secondary mutation in a gene involved in an alternate DNA damage repair pathway (such as nucleotide excision repair)[27] would be expected to respond to docetaxel+carboplatin or M6620 (VX-970, berzosertib)+carboplatin.
3. Patients with HRD who were previously treated with PARPi and are found to have a reversion mutation in the gene originally conferring HRD (and thus no longer possessing an HRD phenotype) would not be expected to respond to docetaxel+carboplatin but could

respond to the combination of M6620 (VX-970, berzosertib)+carboplatin due to synergistic activity related to induction of replication stress.

4. Patients without HRD or other DNA damage repair defects would not be expected to respond to docetaxel+carboplatin but could respond to the combination of carboplatin+M6620 (VX-970, berzosertib) due to synergistic activity related to induction of replication stress.

Genetic alterations detected from end of study circulating free DNA or the optional end of study biopsy would allow us to understand mechanisms of resistance to carboplatin+M6620 (VX-970, berzosertib) and thus design therapeutic strategies based on these mechanisms.

2.5.2 Tumor profiling from circulating free DNA (cfDNA)

DNA derived from tumor tissues can be detected in circulating free DNA (cfDNA) isolated from plasma from patients with metastatic cancer. We plan to perform whole genome sequencing at 0.1x coverage, termed ultra-low pass whole genome sequencing (ULP-WGS). The sequencing information derived from ULP-WGS can be used to identify copy number alterations (CNA) in the tumor using ichorCNA[29], a probabilistic model that is an adaptation of TITAN.[30] While other algorithms for assessing copy number changes from cfDNA have been described[31,32], ichorCNA has the advantage of accounting for mixtures of cell populations to assess for subclonal events, while also estimating the fraction of DNA derived from tumor cells rather than normal tissues.

Our model can also use ULP-WGS to estimate the fraction of circulating free DNA derived from tumor rather than normal tissues ("tumor fraction") based on an assumption that the cancer cells derive from a common precursor and thus have at least one truncal copy number alteration (other alterations being subclonal). We estimate the lower limit for detection of tumor derived DNA by this method to be approximately 3%. The tumor purity estimated by ULP-WGS using ichorCNA demonstrates close concordance with that estimated from whole exome sequencing using a different method for deriving tumor fraction from somatic DNA alterations called ABSOLUTE[33], thus validating this method for quantification.

This exploratory analysis will allow us to assess for the relationship of copy number alterations detected in cfDNA (particularly deletions in ATM and BRCA2) and tumor fraction at baseline with response to therapy. Changes in tumor fraction with treatment and then resistance to therapy could serve as an additional biomarker of response and resistance.

In addition, we plan to perform targeted next generation sequencing from circulating free DNA at baseline, at crossover (for patients randomized to arm A), and at end of study. We have designed a custom bait set specifically for prostate cancer including allowing for identification of SSNVs in all genes known to be recurrently mutated in metastatic prostate cancer[34], genes involved in DNA damage repair[35], as well as sequencing of intronic and intergenic regions of genes known to be translocated or have complex structural alterations in prostate cancer (AR[36], ERG, TMPRSS2, ETV1, ETV4, SLC45A3, RAF1, PTEN, MSH2, MSH6[37]). This analysis will allow us to determine if genetic alterations detected in pre- and post-treatment tumor specimens

can be detected in cfDNA. This analysis may also allow us to better sample global tumor burden better than a single biopsy due to tumor heterogeneity. In addition, longitudinal monitoring of cfDNA from patients while on study will allow us to monitor clonal dynamics over time.

Whole genome sequencing from cfDNA can be used to assess homologous recombination repair deficiency using an algorithm called DirectHRD.[38] DirectHRD is a whole-genome sequencing (WGS) scar-based classifier that makes use of a specific type of genomic scar–a small, microhomology deletion (mhDel) believed to be the direct evidence of microhomology-mediated end joining in the absence of HR due to its superior classification power and low error rate in next generation sequencing (NGS).[39] We have demonstrated that DirectHRD is 10x more sensitive than state-of-the-art methods and can detect HRD at >=1% tumor fraction using 50x WGS of cell-free DNA.

2.5.3 RAD51 focus formation assay

Homologous recombination (HR) repair deficiency confers sensitivity to platinum-based chemotherapeutic agents and inhibitors of poly(ADP-ribose) polymerase (PARP). To date, the identification of tumors with impaired HR has relied on genomic features, including mutational signature, LOH-based HRD assays or gene expression analyses defining 'BRCAness'. These tests analyze history of the tumor rather than providing a functional assessment of HR status at the time of diagnosis. Therefore, development of a functional assay for HR status in tumors is essential to make accurate treatment decisions.

We have described a RAD51-based immunohistochemical (IHC) assay that identifies HR status (Kochupurakkal BS, et al. AACR 2017 Abstract #2796). The presence or absence of RAD51 foci in cell lines and PDX models correlated with olaparib sensitivity and not with BRCA mutation status. Therefore, tumors that are HR-deficient and PARP inhibitor-sensitive are characterized by either high RAD51 nuclear staining without foci, or absence of RAD51 staining. We thus plan to assess RAD51 focus formation from biopsy specimens from patients participating in this trial to understand if this assay could serve as a superior or complementary biomarker to HRD+ status (by genomic characterization) in predicting for response to carboplatin in combination with docetaxel or M6620 (VX-970, berzosertib).

2.5.4 ATM and p-KAP1 Immunohistochemistry

The Ataxia Telangiectasia Mutated (ATM) and Ataxia telangiectasia and Rad3 related (ATR) serine/threonine kinases are both involved in the response to DNA damage, though ATM is primarily involved in the response to double strand breaks (DSBs) in DNA while ATR is involved in the response to a wide range of perturbations leading to DNA damage and replication defects. These kinases appear to share a synthetic lethal relationship, as cells deficient in ATM expression have been shown to be sensitive to ATR inhibition in mantle cell lymphoma[40], CLL[41] and gastric cancer[42,43] models. In cell lines, the majority of cell lines sensitive to the ATR inhibitor BAY-1895344 were characterized by mutations in the ATM pathway.[44]

We have demonstrated that ATM-deficient human fibroblasts cell lines are sensitive to ATR

inhibition, and this sensitivity can be reversed by complementation with wild-type ATM. We have also demonstrated in gastric cancer cell lines that ATM deficiency predicts for sensitivity to ATR inhibition, and we developed an immunohistochemistry assay for ATM demonstrating in 208 primary gastric tumors that ATM expression is absent in 11% of samples with very low expression in 26%.[43] As ATM alterations are highly enriched in mCRPC compared with locoregional prostate cancer[45,46], targeting ATM alterations through inhibition of ATR is a promising therapeutic strategy in mCRPC.[47]

KAP1 (KRAB [Kruppel-Associated Box Domain]-Associated Protein 1) is a protein that in humans is encoded by the *TRIM28* gene. KAP1 is phosphorylated by ATM in response to DNA damage.[16,48] Unpublished data from the laboratory of Dr. Alan D'Andrea suggests that high basal levels of p-KAP1 (which is an indicator of DNA replication stress) in unirradiated tissue may also predict for sensitivity to an ATR inhibitor.

2.5.5 RNA-Seq for RB loss of function

Recent data from patients with mCRPC identified RB genetic aberrations as the strongest predictor of poor outcome.[49] Currently there is no therapeutic option to provide durable response in patients with RB loss-of function (LOF). The laboratory of Dr. Leigh Ellis has completed a genome-scale CRISPR-Cas9 pooled selection screen to identify genes that are required for proliferation or survival of an Rb-deficient prostate cancer cell line derived from an Rb-deficient mouse model. The results from this screen have identified the ATR repair pathway as a vulnerability of RB-deficient cells. RB function may be a better predictor of M6620 (VX-970, berzosertib) response than genomic RB loss, so RNA sequencing from pre-treatment tumor specimens would allow us to identify patients with decreased RB function due to a signature score derived from target gene expression. The Ellis lab has received funding through an RO1 application to the NCI to assess whether RB functional status, at the DNA and/or functional level, can predict superior response to ATR inhibition combined with carboplatin compared to carboplatin combined with docetaxel.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed prostate cancer (code 10036910) with progressive disease at the time of study entry by either

- Sequence of at least 2 rising PSA values at a minimum of 1-week intervals
- Radiographic progression per RECIST1.1 for soft tissue and/or per PCWG3[2] for bone, with or without PSA progression.

3.1.2 Patients must have metastatic disease by bone scan or other nodal or visceral lesions on CT or MRI and a castrate level of testosterone (<50ng/dL) and evaluable for disease response by either

- Baseline PSA ≥ 2.0 ng/mL OR
- Measurable disease per RECIST 1.1

NOTE: Subjects must maintain a castrate state. If they have not had an orchiectomy, they must continue to receive LHRH or GnRH agonists or antagonists unless intolerant.

3.1.3 At least 2 prior treatments for prostate cancer (in either hormone sensitive or castration-resistant disease) as follows:

- Past progression or intolerance to at least one secondary hormonal therapy (abiraterone, enzalutamide, galeterone, apalutamide, darolutamide, orteronel, seviteronel or equivalent)
- Past progression or intolerance to taxane-based chemotherapy

3.1.4 Age ≥18 years. Children are excluded from this study as prostate cancer is a disease of adults

3.1.5 ECOG performance status ≤1 (Karnofsky ≥70%, see Appendix A).

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

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- hemoglobin ≥9 g/dL (transfusion permitted)
- platelets ≥150,000/mcL (without transfusion or growth factor in prior 28 days)
- total bilirubin ≤1.5 × institutional upper limit of normal, unless the subject has known or suspected Gilbert's syndrome
- AST(SGOT)/ALT(SGPT)≤2.5 × institutional upper limit of normal or ≤5 × upper limit of normal if presence of liver metastases
- creatinine clearance ≥40 mL/min/1.73 m^2

3.1.7 Prior treatment with mTOR inhibitors, cytostatic TKI, or biologic therapies allowed

3.1.8 Prior treatment with PARP inhibitors permitted.

3.1.9 Patients with allergy or intolerance to docetaxel or Grade 2 neuropathy are allowed on study, but if randomized to Arm A will receive carboplatin as a single agent (AUC 5) rather than docetaxel+carboplatin. They must be fit for carboplatin chemotherapy as determined by the treating investigator.

3.1.10 Presence of a lesion (bone or soft tissue) amenable to image-guided percutaneous biopsy adequate for next generation sequencing (NGS), and planned to undergo core biopsy after trial registration but prior to cycle 1 day 1 of therapy. Confirmation of adequacy of this biopsy material for NGS is NOT required for initiation of therapy. If elective biopsies are not being performed at the treating institution due to preparations or precautions related to COVID-19, this requirement can be waived on discussion with the trial PI.

3.1.11 The effects of M6620 (VX-970, berzosertib), carboplatin and docetaxel on the developing human fetus are unknown. For this reason and because DNA-damage response inhibitors and chemotherapeutic agents are known to be teratogenic, men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while 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 6 months after completion of carboplatin and M6620 (VX-970, berzosertib) administration.

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

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to planned cycle 1 day 1 of study treatment. Patients on an oral anti-neoplastic such as an oral hormonal agent, PARP inhibitor or oral experimental agent should discontinue >=14 days prior to planned cycle 1 day 1 of study treatment.

3.2.2 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1), except for Grade 2 anorexia, alopecia, neuropathy, and fatigue, for which resolution is not required.

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Patients with known brain metastases or leptomeningeal disease should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to M6620 (VX-970, berzosertib) or carboplatin. (Patients with allergy to docetaxel will be allowed on study, but docetaxel will be excluded from their treatment regimen.)

3.2.6 Subjects receiving treatment with ototoxic or nephrotoxic medications that cannot be discontinued at least 7 days before first dose of carboplatin and for the duration of the study. Inadvertent or short-term use on study will not cause a subject to be ineligible. If a short course of therapy with nephrotoxic or ototoxic medication is anticipated and required, carboplatin should be discontinued until 7 days after this course is completed. Patients on continuous medications that are potentially nephrotoxic who have had no evidence of nephrotoxicity from these medications at study entry are allowed to continue those medicines on trial.

M6620 (VX-970, berzosertib) is primarily metabolized by CYP3A4; therefore, concomitant administration with strong inhibitors of CYP3A4 (*e.g*., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir) or inducers of CYP3A4 (*e.g*. rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) is prohibited. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of. APPENDIX C (Patient Drug Information Handout and Wallet Card) should be provided to patients. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

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

3.2.8 Pregnant and nursing women are excluded from this study because they do not develop prostate cancer.

3.2.9 HIV-positive participants with detectable viral load and/or CD4 count ≤300 are ineligible due to increased risk of lethal infections when treated with marrow-suppressive therapy. HIV-positive patients with undetectable viral loads and CD4 counts >300, and not on interacting antiretroviral therapy may be eligible after discussing with the principal investigator.

3.2.10 Prior treatment with platinum-containing regimen or ATR inhibitor for prostate cancer

3.3 Inclusion of Women and Minorities

Men of all races and ethnic groups are eligible for this trial. Women are not included as they do not develop prostate cancer.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN, and
- Act as the site-protocol Principal Investigator (PI) on the IRB approval

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

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

4.2 Site Registration

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

IRB Approval

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

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the

following five criteria to complete processing of the IRB/REB approval record:

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

4.2.1 Downloading Regulatory Documents

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

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *LAO-MA036*, and protocol number *10191*,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Requirements For NCI protocol # 10191 Site Registration:

- Site Initiation Visit

- Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating

site will need to complete the Theradex-led training.
- Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
- The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
- This training will need to be completed before the first patient enrollment at a given site.
- Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

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

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

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

4.2.4 Checking **Site** Registration Status

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

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

Requirements for OPEN access:

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

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

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

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

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

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

4.3.2 Special Instructions for Patient Enrollment

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

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

Detailed instructions can be found in Section **Error! Reference source not found.**.

4.3.3 OPEN/IWRS Questions?

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

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *5* days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

M6620 (VX-970, berzosertib), carboplatin and docetaxel will be administered every 3 weeks, with 21 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Arm A: Docetaxel + Carboplatin					
Agent	**Premedications; Precautions**	**Dose**	**Route*** **	**Schedule**	**Cycle Length**
Docetaxel	Corticosteroid premedication per institutional standard	60 mg/m2 administered per institutional guidelines	IV over 60 minutes (± 10 minutes)	Day 1	21 days (3 weeks)
Carboplatin	Must be administered after docetaxel Antiemetics should be administered per institution guidelines.	AUC 4 administered per institutional guidelines	IV over 30 minutes (± 25% planned infusion time)	Day 1	21 days (3 weeks)

Arm A: Carboplatin alone (for Docetaxel-ineligible)					
Agent	**Premedications; Precautions**	**Dose**	**Route*** **	**Schedule**	**Cycle Length**
Carboplatin	Antiemetics should be administered per institution guidelines.	AUC 5 administered per institutional guidelines	IV over 30 minutes (± 25% planned infusion time)	Day 1	21 days (3 weeks)

Arm B and Arm A crossover: M6620 (VX-970, berzosertib) **+ Carboplatin**					
Agent	**Premedications; Precautions**	**Dose**	**Route*** **	**Schedule**	**Cycle Length**
Carboplatin	Antiemetics should be administered per institution guidelines.	AUC 5 administered per institutional guidelines	IV over 30 minutes (± 25% planned infusion time)	Day 1	21 days (3 weeks)
M6620 (VX-970, berzosertib)	For Day 2 dose, initiate ~24 h (± 4 h) after cessation of carboplatin infusion. Premedicate with hydrocortisone 100 mg IV (or oral equivalent if intravenous	90 mg/m2 in D5W to a final concentration between 0.075 mg/ml to 1 mg/ml	IV over 60 minutes (± 10 minutes) for volumes < 600 mL. For volumes 600 – 900 mL, administer at 10	Days 2 and 9	

	formulation is unavailable or IV administration is not feasible) ~ 60 mins (± 15 min) before M6620 (VX-970, berzosertib) infusion, and 25 mg diphenhydramine IV (or oral equivalent if intravenous formulation is unavailable or IV administration is not feasible) ~ 30 min (± 10 min) before M6620 (VX-970, berzosertib) infusion		mL/min; for volumes > 900 mL, administer over 90 min.		

5.1.1 M6620 (VX-970, berzosertib)

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects. M6620 (VX-970, berzosertib) will be supplied as 20 mg/mL M6620 (VX-970, berzosertib) (in betadex sulfobutyl ether and acetate buffer) to be diluted in D5W before intravenous infusion.

M6620 (VX-970, berzosertib) solution will be constituted into the individual dosing containers by a qualified pharmacist. Details of dose preparation are listed in Section 8.1.7. Body surface area (BSA) is to be calculated per institutional standards of practice. In the event of changes in participant weight, institutional standards of practice should be followed for dose re-calculations.

The dose of M6620 (VX-970, berzosertib) will be infused intravenously over 60 minutes (± 10 minutes). When the total volume of infusion exceeds 600 mL, the infusion time may be extended beyond 60 minutes (as tolerated), but no more than 90 minutes. If the infusion volume is 600 – 900 mL, the M6620 (VX-970, berzosertib) solution should be infused at 10 mL/minute; if the volume is >900 mL then it should be infused over 90 minutes. Details of dose administration for M6620 (VX-970, berzosertib) are listed in section 8.1.1.11 Infuse 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, berzosertib) should not come in contact with 0.9% Sodium Chloride due to incompatibility.

Intravenous administration of M6620 (VX-970, berzosertib) is independent of food intake. When M6620 (VX-970, berzosertib) is given the day after chemotherapy (i.e., Day 2) infusion of M6620 (VX-970, berzosertib) should be initiated approximately 24 hours (± 4 hours) after cessation of carboplatin infusion.

To minimize the possibility of phlebitis, M6620 (VX-970, berzosertib) should be administered through a large bore catheter into a large caliber peripheral vein or central venous access. The intravenous infusion site should be monitored closely for the development of erythema, induration, purulence, tenderness, or warmth. If any subject develops phlebitis, or signs or symptoms of inflammation that may progress to phlebitis or that the patient cannot tolerate, standard measures should be employed to ameliorate these symptoms (including removal of the infusion catheter and resumption of infusion through a different vein).

Based on the observation of acute hypersensitivity in the Phase I trial, we will plan to premedicate with 100 mg hydrocortisone intravenously (or oral equivalent if intravenous formulation is unavailable or IV administration is not feasible) approximately 60 minutes (± 15 minutes) before M6620 (VX-970, berzosertib) infusion, and 25 mg of diphenhydramine intravenously (or oral equivalent if intravenous formulation is unavailable or IV administration is not feasible) approximately 30 minutes (± 10 minutes) before M6620 (VX-970, berzosertib) infusion. In addition, treatment with an H2-blocker (e.g., ranitidine) may be considered for subjects not responsive to a regimen with an H1-blocker.

If standard procedures to limit symptoms of injection site reaction, or pruritus or acute hypersensitivity are insufficient, then the infusion time may be extended beyond 60 minutes, but no more than 90 minutes.

Treatment with granulocyte colony stimulating factors is not routinely recommended for patients receiving carboplatin + M6620 (VX-970, berzosertib), however can be used if felt to be indicated per investigator discretion. Recommended timing of filgrastim (or biosimilar) is daily dosing starting the day after the second M6620 (VX-970, berzosertib) infusion (usually day 10) with last dose > 10 days prior to day 1 of the next cycle. If pegfilgrastim (or biosimilar) is preferred, this should be administered the day after the second M6620 (VX-970, berzosertib) infusion (usually day 10), and day 1 of the next cycle should be > 10 days from pegfilgrastim (or biosimilar) dose. If the day 9 M6620 (VX-970, berzosertib) dose is skipped, filgrastim/pegfilgrastim (or biosimilar) can be initiated at visit for planned day 9.

5.1.2 Carboplatin

The subject specific dose should be calculated using the modified Cockcroft-Gault method per institutional policy for AUC calculation Carboplatin should be administered per institutional standards.

When administered as sequential infusions, docetaxel should be administered before the carboplatin to limit myelosuppression and to enhance efficacy. Time interval between docetaxel and carboplatin infusions is per institutional standard.

Acceptable window for infusion: ± 25% of the planned infusion time.

Anti-emetics and supportive therapies will be administered or dispensed to subjects for use in

combination with carboplatin according to individual site SOC. Anti-emetics and growth factors can be used per institutional guidelines for standard chemotherapy. (See section 5.1.1 for recommended timing of granulocyte colony stimulating factors in relation to M6620 (VX-970, berzosertib) infusions for patients receiving carboplatin in combination with M6620 (VX-970, berzosertib)). If a participant has an infusion reaction to carboplatin, standard of care for rechallenge should be followed.

5.1.3 Docetaxel

Docetaxel should be prepared and administered per institutional standards or package insert. For one vial preparation:
1. Docetaxel vials should be stored at room temperature, 25°C (77°F), and protected from light.
2. Aseptically withdraw the required amount of docetaxel injection concentrate (20 mg/mL) with a calibrated syringe and inject into a 250 mL infusion bag of either 0.9% Sodium Chloride solution to produce a final concentration of 0.3 to 0.74 mg/mL. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel is not exceeded. Body surface area (BSA) is to be calculated per institutional standards of practice. In the event of changes in participant weight, institutional standards of practice should be followed for dose re-calculations.3. Thoroughly mix the infusion by manual rotation.
4. Attach non-PVC, DEHP-free tubing
5. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel injection concentrate or final dilution for intravenous infusion is not clear or appears to have precipitation, these should be discarded.
6. The final docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion (+/- 10 min) under ambient room temperature and lighting conditions. Docetaxel may be administered according to institutional standards or package insert.

Standard corticosteroid pre-medication per institutional standards should be administered (e.g. dexamethasone 8 mg orally twice daily the day before, day of and day after docetaxel; dexamethasone 12 mg or methylprednisolone 50 mg IV bolus prior to docetaxel)
Anti-emetics and supportive therapies will be administered or dispensed to subjects for use in combination with docetaxel according to individual site SOC. Anti-emetics and growth factors can be used per institutional guidelines for standard chemotherapy. If a participant has an infusion reaction to docetaxel or carboplatin, standard of care for rechallenge should be followed.

5.2 General Concomitant Medication and Supportive Care Guidelines

M6620 (VX-970, berzosertib) is metabolized by cytochrome P450 (CYP) 3A4 isoenzyme (CYP3A4); exposure to M6620 (VX-970, berzosertib) may be affected by concomitantly administered drugs that are strong inhibitors or inducers of CYP3A4. Because there is a potential for interaction of M6620 (VX-970, berzosertib), carboplatin and docetaxel with other concomitantly administered drugs, the case report form must capture the concurrent use of all

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

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

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

M6620 (VX-970, berzosertib) is a moderate inhibitor of P-gp and BCRP. It is a P-gp substrate but not BCRP. Based on in vitro data, there is low risk of drug-drug interaction with OATP1B3 and BCRP. Use caution when administered with sensitive substrates of OATP1B3 and BCRP.

Palliative radiation is permitted for patients on trial. Radiation should be initiated at least 14 days after carboplatin is administered (i.e. day 15 of a cycle or after). Trial therapy is to be held until radiation treatment is completed, and can be resumed at least 7 days after last fraction of radiation.

5.3 Crossover

Patients randomized to arm A who have documented PSA progression (by PCWG2 criteria[1]) or radiographic progression (by PCWG3 criteria[2]) should not receive further doses of treatment on the control arm (carboplatin+docetaxel or carboplatin alone). Patients should be re-screened for meeting eligibility criteria for the protocol and the treating investigator must feel that the patient is appropriate for continued carboplatin therapy to crossover to the experimental arm of carboplatin+M6620 (VX-970, berzosertib). If a patient required a dose reduction on the control arm, they should initiate treatment with the experimental regimen at the same dose level per Table 6-1 (e.g. if a patient required dose reduction to the -2 dose level on the control arm, they should be treated at the -2 dose level of the experimental arm at the time of crossover). If patients do not meet criteria for crossover, they will be discontinued from study, but can continue carboplatin +/- docetaxel per standard of care per investigator discretion.

PSA progression by PCWG2 criteria[1] is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later. Thus, for example if a patient has a PSA increase of 25% with an absolute increase of 2 ng/mL from nadir on labs obtained prior to C5D1, they should be advised that if this increase is confirmed prior to C6D1 then they will not receive C6D1 carboplatin +/- docetaxel treatment. In this circumstance, carboplatin +/- docetaxel should

not be administered until pre-C6D1 PSA value returns (and is administered only if PSA progression is NOT confirmed).

Cycle 1 day 1 [crossover] of carboplatin+M6620 (VX-970, berzosertib) can be scheduled as soon as eligibility is confirmed, and should be scheduled within 42 days of the last dose of carboplatin +/- docetaxel. Imaging studies should be repeated if not performed within 30 days of C1D1 [crossover].

5.4 Duration of Therapy

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

- Disease progression by PCWG3 criteria,[2] including clinical progression. Patients should not be discontinued from study therapy for PSA progression alone (but patients initially randomized to Arm A will cross over to the experimental arm at PSA progression or radiographic progression if eligible.) For patients initially randomized to Arm B, or those who cross over after PSA/radiographic progression on Arm A, PCWG3 criteria allow treatment beyond radiographic progression if the treating physician feels that the patient is continuing to derive clinical benefit from therapy, and the patient will continue until felt to be "no longer clinically benefiting" (NLCB).
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

5.5 Duration of Follow Up

An end of treatment and safety assessment should be performed 30-42 days after the last dose of study treatment to include any adverse events occurring within 30 days after the last dose of

study treatment. In the event subjects cannot be seen for the end treatment safety assessment at the site of enrollment due to the ongoing COVID-19 situation or other extenuating circumstances, safety assessments may be conducted at alternate locations if these assessments are deemed of adequate quality by the treating investigator.

Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via continued study visits or phone contact or from their general practitioner, or medical records, country/region specific cancer and/or mortality registries.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Guidelines for dose modification for toxicity are provided below. The final dose reduction or delay for each subject may be determined by the investigator and sponsor. However, these guidelines provide the minimum dose reduction or delay criteria. Patients may hold treatment up to 3 weeks (i.e. day 1 of the subsequent cycle may be delayed up to 42 days from day 1 of prior cycle) until the completion of cycle 6, then up to 6 weeks (i.e. day 1 of the subsequent cycle may be delayed up to 63 days from day 1 of prior cycle) thereafter. If day 2 or day 9 M6620 (VX-970, berzosertib) cannot be safely administered during the required window (see Section 10), then that dose will be skipped and the patient will resume treatment with day 1 of the next cycle as above. If day 1 of the next cycle cannot be safely administered within the above windows, then the subject must be discontinued from trial.

Additionally, if a subject who is responding to treatment experiences toxicity even after 2 dose reductions, the subject may continue to receive treatment if in the judgment of the investigator it is in the best interest of the subject. In this case the patient will be treated at the -3 dose level in Table 6-1. If the subject does not tolerate treatment at the -3 dose level (or -2 dose level for carboplatin alone), the subject will be discontinued from study treatment.

In case of Grade 3 or higher treatment-related toxicity (excluding fatigue or nausea/vomiting/diarrhea adequately managed by supportive care, or asymptomatic unrelated laboratory abnormalities that would not prevent safe administration of trial therapy in the opinion of the trial investigator), treatment will be interrupted and may be resumed when all toxicities have returned to Grade 2 or lower, at the discretion of the investigator at the same dose or with a dose reduction as detailed below. Dose re-escalation is allowed if an unrelated confounding

variable that contributed to the dose reduction (for example, an adverse effect of another agent that has since been discontinued) has resolved; dose re-escalation must be approved on a case-by-case basis by the principal investigator.

For the following treatment-related hematologic toxicities, once the toxicity has returned to Grade 2 or lower (Grade 1 or lower for thrombocytopenia), dosing can be resumed with 1 dose level reduction (Table 6-1). If, after 1 dose level reduction, any of the below drug-related hematologic toxicities are subsequently observed, then dosing may be resumed with 2 dose level reductions (Table 6-1). Platelet count is required to be ≥75,000/mcL to initiate a new cycle.

- o Grade 4 thrombocytopenia
- o Febrile neutropenia (growth factor support, per site protocol, may be used in lieu of dose reduction)
- o Grade 4 neutropenia lasting more than 7 days
- o Any Grade 3 or lower hematologic toxicity requiring dose delay of more than 2 weeks

For the following treatment-related non-hematologic toxicities, dosing can be resumed with 1 dose level reduction (Table 6-1).

- o Grade 3 non-hematologic toxicity (Except for fatigue or nausea, vomiting, or diarrhea adequately controlled by medication), after resolution to Grade 2 or lower.
- o Any Grade 2 or lower non-hematologic toxicity requiring dose delay of more than 2 weeks, once felt safe to resume trial therapy by the treating investigator.

If, after 1 dose level reduction, the above drug-related non-hematologic toxicities are subsequently observed, then dosing may be resumed with 2 dose level reductions (Table 6-1).

For Grade 4 treatment-related non-hematologic toxicity, treatment will be interrupted and may be resumed with 2 dose level reductions (Table 6-1) when toxicity has returned to Grade 2 or lower. If any toxicity not described above results in delay in dosing in any part of the study, but this section does not specifically mandate a dose reduction, then the doses of M6620 (VX-970, berzosertib) or chemotherapy may be reduced by 1 dose level or continued without dose reduction at the discretion of the investigator.

Of note, the toxicity profiles of docetaxel, carboplatin, and M6620 (VX-970, berzosertib) are largely overlapping so in most cases it would be difficult to ascribe a particular adverse event to a single agent. However, for non-hematologic toxicities clearly related to one agent but not the other (e.g. ototoxicity for carboplatin) dose modifications can be made independently from the other agent. Treatment day is delayed until criteria to treat are met. If a patient in Arm A needs to be discontinued from docetaxel for toxicity specifically attributable to docetaxel (i.e. new onset allergic reaction), the patient can subsequently be treated with carboplatin alone at AUC 5 – however, this would be unusual as per eligibility these patients are required to have previously tolerated docetaxel. Patients in Arm A cannot be treated with docetaxel monotherapy, and those in Arm B cannot be treated with monotherapy of either agent – if carboplatin and/or M6620 (VX-970, berzosertib) is not tolerated despite the appropriate dose reductions then the patient must be discontinued from study treatment.

Table 6-1 Guidelines for Dose Modification for Toxicity

Arm A: Docetaxel plus Carboplatin

Dose Level	**Docetaxel (mg/m^2)**	**Carboplatin** (mg·min/mL)
0	60	AUC 4
-1	45	AUC 4
-2	45	AUC 3
-3	30	AUC 3

Arm A: Carboplatin alone (for docetaxel-ineligible)

Dose Level	**Carboplatin** (mg·min/mL)
0	AUC 5
-1	AUC 4
-2*	AUC 3

*Patients who require dose reduction from carboplatin AUC 3 should be discontinued from study treatment.

Arm B and Arm A Crossover: M6620 (VX-970, berzosertib) plus Carboplatin

Dose Level	**M6620** (VX-970, berzosertib) **(mg/m^2)**	**Carboplatin** (mg·min/mL)
0	90	AUC 5
-1	90	AUC 4
-2	60	AUC 4
-3	60	AUC 3

Any patient on study treatment who develops visual symptoms should be referred for immediate ophthalmologic evaluation. Investigators should be aware of potential ocular complications of docetaxel, including cystoid macular edema.

Below are dose modification tables for the following adverse events: nausea, vomiting, diarrhea, neuropathy.

Table 6-2

Nausea	**Management/Next Dose for Arm A**	**Management/Next Dose for Arm B or Arm A Crossover**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.

Nausea	**Management/Next Dose for Arm A**	**Management/Next Dose for Arm B or Arm A Crossover**
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a delay of >3 weeks within 1st 6 cycles (or >6 weeks after 6 cycles) should go off protocol therapy. **Participants requiring > three dose reductions (or > two dose reductions for carboplatin alone) should go off protocol therapy.		
Recommended management: antiemetics.		

Table 6-3

Vomiting	**Management/Next Dose for Arm A**	**Management/Next Dose for Arm B or Arm A Crossover**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
* Participants requiring a delay of >3 weeks within 1st 6 cycles (or >6 weeks after 6 cycles) should go off protocol therapy. ** Participants requiring > three dose reductions (or > two dose reductions for carboplatin alone) should go off protocol therapy.		
Recommended management: antiemetics.		

Table 6-4

Diarrhea	**Management/Next Dose for Arm A**	**Management/Next Dose for Arm B or Arm A Crossover**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
* Participants requiring a delay of >3 weeks within 1st 6 cycles (or >6 weeks after 6 cycles) should go off protocol therapy. ** Participants requiring > three dose reductions (or > two dose reductions for carboplatin alone) should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-		

Diarrhea	**Management/Next Dose for Arm A**	**Management/Next Dose for Arm B or Arm A Crossover**
free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Table 6-5

Neuropathy	**Management/Next Dose for Arm A**	**Management/Next Dose for Arm B or Arm A Crossover**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Discontinue docetaxel and switch to carboplatin alone AUC 5. If grade 2 on carboplatin alone, can continue unless progresses to Grade 3.	No change in dose
Grade 3	Hold docetaxel until ≤ Grade 2. Resume on carboplatin alone AUC 5. If grade 3 on carboplatin alone, hold until ≤ Grade 2 and resume at one dose level lower.	Hold carboplatin until ≤ Grade 2 (may continue M6620 (VX-970, berzosertib)). Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
* Participants requiring a delay of >3 weeks within 1st 6 cycles (or >6 weeks after 6 cycles) should go off protocol therapy. ** Participants requiring > three dose reductions (or > two dose reductions for carboplatin alone) should go off protocol therapy.		
Recommended management: Gabapentin per physician discretion		

Dose delays are permitted for recovery of adverse effects of therapy as detailed above, or for inclement weather, holidays, emergencies, non-study related procedures or interventions, or other concerns regarding the health and well-being of the patient (such as concern for COVID-19 exposure) within the windows detailed in the protocol (delay of up to 3 weeks allowed in the first 6 cycles, up to 6 weeks allowed after cycle 6). Dose delays outside of permitted windows must be approved by the trial PI and IND Sponsor (DCTD NCI).

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 7.2) and the characteristics of an observed AE (Sections 7.3 and 7.4) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-

AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

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

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

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

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

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

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

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

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

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

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

7.2 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.
NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.2.1 CAEPRs for CTEP IND Agent

7.2.1.1 CAEPR for M6620 (VX-970, berzosertib)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
M6620 (VX-970, berzosertib) (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, berzosertib).

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[50]

Adverse Events with Possible Relationship to M6620 (VX-970, berzosertib) (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)***
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, berzosertib) (NSC 780162) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that M6620 (VX-970, berzosertib) (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, berzosertib) 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.

7.2.2 Adverse Event List(s) for Carboplatin

Very common side effects (>10%):

- Abdominal pain
- Anemia
- Decreased kidney function/kidney toxicity
- High blood uric acid levels
- Infection
- Abnormal liver function tests
- Electrolyte imbalance
- Low platelets
- Leukopenia
- Nausea
- Vomiting

Less common side effects (<10%):

- Allergic reaction (rash and hives)
- Bleeding
- Diarrhea
- Constipation
- Hearing impairment
- Infection
- Neuropathy (numbness or pain of the hands and/or feet)

Refer to the package insert for a comprehensive list of adverse events.

7.1.3 **Adverse Event List(s) for Docetaxel**

Likely (> 50% chance)
• Hair loss
• Fatigue
• Low white blood cell count
• Low red blood cell count

Frequent (10-50% chance)
• Low platelet count
• Soreness or weakness of muscles or joints
• Diarrhea
• Upset stomach
• Nausea or vomiting
• Mouth or throat sores
• Loss of appetite
• Elevated blood levels of liver enzymes
• Fluid retention, usually just leg swelling, but rarely fluid collection surrounding the heart or lungs that could cause difficulty breathing
• Rash or hives
• Reactions at the infusion site including redness or darkening of the skin
• Nail changes including nail pain, bleeding under the nails and rarely loss of nails numbness and tingling of fingers and toes
• The dexamethasone that needs to be taken with docetaxel may increase blood sugars which may increase thirst or urination, may cause difficulty getting to sleep, and may be associated with abnormal changes in personality or mood swings

Occasional (1-10% chance)
• Allergic reaction, which can cause difficulty breathing, irregular heartbeat, low blood pressure and be life threatening
• Continuing, long-lasting numbness, tingling or burning in the hands and feet.
• Shortness of breath
• Cough
• Infusion reaction which may cause fever, chills or rigors
• Irritation of the tear ducts, tearing of the eyes – this may be permanent
• Peeling on hands and feet
• Nosebleeds
• Taste disturbance
• Alcohol intoxication. Docetaxel contains alcohol (ethanol), which may affect the central nervous system

Rare (< 1% chance)
• Changes in vision

- Seizure
- Stevens-Johnson syndrome
- Blood clots
- Pneumonia or inflammation involving the lungs
- Heart failure, heart attack, or irregular heart rhythm
- Colitis

Refer to the package insert for a comprehensive list of adverse events.

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

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

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

7.4 Expedited Adverse Event Reporting

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

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the

24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.4.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.4.3 Expedited Reporting Guidelines

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

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

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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.

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** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes

24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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: August 30, 2024

7.4.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anemia	2	Regardless
GASTROINTESTINAL DISORDERS	Nausea	2	Regardless
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue	2	Regardless

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

7.5 Routine Adverse Event Reporting

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

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.6 Pregnancy

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

7.7 Secondary Malignancy

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. 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.

7.8 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

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

8.1 M6620 (VX-970, berzosertib) (NSC 780162)

8.1.1.1 **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

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

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

8.1.1.4 **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, berzosertib) disrupts ATR-mediated DNA damage response signaling and leads to sustained accumulation of DNA damage in cancer cells co-treated with DNA-damaging agents.

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

8.1.1.6 **How Supplied:** M6620 (VX-970, berzosertib) 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, berzosertib) 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.

8.1.1.7 **Preparation:** M6620 (VX-970, berzosertib) 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, berzosertib). To prepare the infusion solution add the dose volume of M6620 (VX-970, berzosertib) 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.

8.1.1.8 **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, berzosertib) 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.

8.1.1.9 **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).

8.1.1.10 **Route of Administration:** Intravenous (IV) infusion.

8.1.1.11 **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, berzosertib) 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. If the infusion volume is 600 – 900 mL, the M6620 (VX-970, berzosertib) solution should be infused at 10 mL/minute; if the volume is >900 mL then it should be infused over 90 minutes. To minimize the possibility of phlebitis, M6620 (VX-970, berzosertib) should be administered through a large bore catheter into a large caliber peripheral vein or central venous access.

8.1.1.12 **Patient Care Implications:** Monitor for infusion site reactions, irritation, and phlebitis. M6620 (VX 970, berzosertib) absorbs in the UV-visible radiation spectrum and is widely distributed including skin, so patients receiving M6620 (VX 970, berzosertib) should take protective measures to minimize sun exposure. M6620 (VX-970, berzosertib) is not a vesicant drug. Women of childbearing potential and men should use appropriate contraception while on study drug and for 6 months after discontinuation of M6620 (VX-970, berzosertib).

8.1.1.13 **Potential Drug Interactions:** M6620 (VX-970, berzosertib) is primarily metabolized by CYP3A4. M6620 (VX-970, berzosertib) has a low potential to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4, and a moderate potential to reversibly inhibit CYP2E1. The potential for M6620 (VX-970, berzosertib) to induce CYP450 enzymes CYP1A2, 2B6, and 3A4 at concentrations up to 6 µM is low. Concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Sensitive substrates of CYP3A4 should be used with caution.

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

M6620 (VX-970, berzosertib) is a moderate inhibitor of P-gp and BCRP. It is a P-gp substrate but not BCRP. Based on in vitro data, there is low risk of drug-drug interaction with OATP1B3 and BCRP. Use caution when administered with sensitive substrates of OATP1B3and BCRP transporters.

8.1.1.14 **Availability:**

M6620 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

M6620 (VX-970, berzosertib) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.4).

8.1.2 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational

agents for the study should be ordered under the name of one lead participating investigator at that institution.

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

8.1.3 Agent Inventory Records

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

8.1.4 Investigator Brochure Availability

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

8.1.5 Useful Links and Contacts

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

8.2 Carboplatin

8.2.1 Product description

Commercially available for injection as solution: 10 mg/mL (5 mL, 15 mL, 45 mL, 60 mL)

8.2.2 Solution preparation

Refer to package insert for complete preparation and dispensing instructions.

8.2.3 Storage requirements

Store intact vials at room temperature and protect from light.

8.2.4 Stability

Further dilution to a concentration as low as 0.5 mg/mL is stable at room temperature for 8 hours in 0.9% NaCl; stable at room temperature or under refrigeration for at least 9 days in D5W, although the manufacturer states to use within 8 hours due to lack of preservative. Multidose vials are stable for up to 14 days after opening when
stored at room temperature.

8.2.5 Route of administration

Refer to the treatment section for specific administration instructions. When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before the carboplatin to limit myelosuppression and to enhance efficacy.

8.2.6 Agent Ordering

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

8.3 Docetaxel

8.3.1 Description

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,Ntert- butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4- acetate 2-benzoate, trihydrate.

Mechanism of Action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

8.3.2 Form

Docetaxel Injection Concentrate is supplied in glass vials as non-aqueous, clear, viscous, colorless to pale yellow solution at 20mg/mL concentration. Docetaxel injection concentrate is sterile, non-pyrogenic, and is available in single-dose vials as 20 mg/mL or 80mg/4mL. One vial formulation (Injection Concentrate) Docetaxel injection concentrate (20mg/mL) requires no prior dilution with a diluent and is ready to add to the infusion solution. Docetaxel injection concentrate should be inspected visually for particulate matter or discoloration prior to preparation. If the injection concentrate is not clear or appears to have precipitation, then it should be discarded.

8.3.3 Storage and Stability

Store vials at 25°C (77°F); excursions permitted to 15°C to 30°C (36°F and 77°F). Retain in the original package to protect from bright light. Docetaxel final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. Docetaxel final dilution for infusion (in 0.9% Sodium Chloride solution or D5W), diluted to a final concentration of 0.3mg/ml to 0.74mg/ml, should be used within 4 hours (including the 1 hour intravenous administration).

8.3.4 Compatibility

Contact of the docetaxel injection concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

8.3.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once the study treatment is prepared for a participant, it can only be administered to that participant. Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended. If docetaxel injection concentrate or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If docetaxel injection concentrate or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

8.3.6 **Availability**

Docetaxel is commercially available.

8.3.7 **Preparation**

Docetaxel may be prepared according to institutional standards or package insert. Body surface area (BSA) is to be calculated per institutional standards of practice. In the event of changes in participant weight, institutional standards of practice should be followed for dose re-calculations. For one vial preparation: 1. Docetaxel vials should be stored at room temperature, 25°C (77°F), and protected from light. 2. Aseptically withdraw the required amount of docetaxel injection concentrate (20 mg/mL) with a calibrated syringe and inject into a 250 mL infusion bag of either 0.9% Sodium Chloride solution or D5W to produce a final concentration of 0.3 to 0.74 mg/mL. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel is not exceeded. 2. Thoroughly mix the infusion by manual rotation. 3. Attach non-PVC, DEHP-free tubing 3. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel injection concentrate or final dilution for intravenous infusion is not clear or appears to have precipitation, these should be discarded.

8.3.8 **Administration**

The final docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion (+/- 10 min) under ambient room temperature and lighting conditions. Docetaxel may be administered according to institutional standards or package insert.

8.3.9 **Ordering**

Docetaxel will not be provided by the sponsor. Commercial supply will be used.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Collection of Specimens

Summary of Specimen Requirements:

Time point	Specimen and Processing at Site	Send specimens to
Pre-treatment	• Tumor tissue biopsies in formalin (minimum of 4) • 10 mL blood in cfDNA Streck tube	EET Biobank
Every Third Cycle (Arm B: C1D1, C4D1, C7D1, etc.; Arm A: C1D1, C4D1, etc. then C1D1[crossover],	• 10 mL blood in cfDNA Streck tube	EET Biobank

C4D1[crossover], etc.)		
Off Study	• Tumor tissue biopsies in formalin (minimum of 4) [optional] • 10 mL blood in cfDNA Streck tube	EET Biobank

*For new biopsies, the Tissue Biopsy Verification Form (Appendix G) and a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank. When completed, upload the corresponding pathology report to Rave and send a copy to the EET Biobank.

9.2 Specimen Procurement Kits and Scheduling

9.2.1 Specimen Kits

EET Biobank Kits for shipment can be ordered online via the Kit Management system (https://ricapps.nationwidechildrens.org/KitManagement).

Sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Each user may order two kit per kit type day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. Two kit types will be provided for this protocol: a single chamber for the submission of tissue from Pre-treatment or Off Study and an ambient shipper for the submission of blood in a cfDNA Streck tube. A complete list of kit contents for each kit type is located on the Kit Management system website and in the instructions included with the kits.

9.2.2 Scheduling of Specimen Collections

Tumor tissue cores collected during biopsy procedures that are fixed must be shipped on the same day as collection. Tissue can be collected Monday through Wednesday, and shipped overnight (FedEx Priority Overnight strongly preferred to avoid potential delays, which will negatively impact specimen quality) for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.

Fresh blood specimens may be collected and shipped Monday through Friday. Saturday delivery is only available for shipments of fresh blood.

9.3 Specimen Tracking System Instructions

9.3.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name

  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section **Error! Reference source not found.**.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.
A shipping manifest **must** be included with all sample submissions.

9.3.2 Specimen Labeling

9.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood)
- Collection date (to be added by hand)

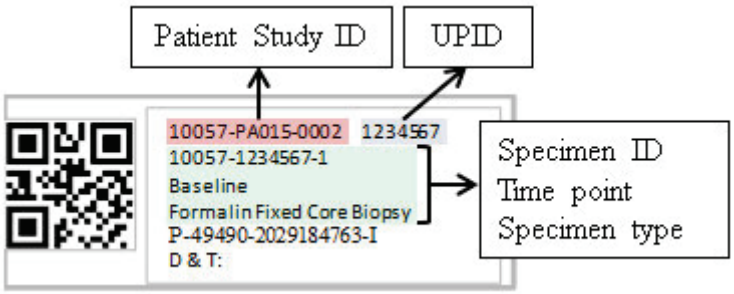
9.3.2.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, Formalin Fixed Tissue)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID – if applicable) number
- Collection date (to be added by hand)

9.3.2.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

9.3.3 Overview of Process at Treating Site

9.3.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

9.3.3.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, labeled specimens can be kept at room temperature until ready for shipment.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Tissue Biopsy Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number or relevant dates (such as collection date), and include the UPID and patient study ID on each document

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form**:** Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF**:** Enter tracking number, your contact information, recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF**:** Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

9.4 Specimen Collection

9.4.1 Formalin-fixed Tumor Biopsies

Biopsies will be performed by an interventional radiologist or other appropriate radiologist under CT guidance (ultrasound guidance is allowed if preferred by the radiologist.) Blood samples will be drawn within 28 days of the biopsy to document an acceptable coagulation profile (INR < 1.5, PTT < 45, platelets >50,000). Aspirin and/or Plavix should be discontinued 5 days prior to the biopsy. On the day of the biopsy, a short physical exam will be performed by the radiologist including assessing the patient's general ASA score and airway rating. Informed written consent will be obtained following discussion of the risks (bleeding, infection, adjacent tissue injury, and pain) and benefits of the procedure. Biopsies will be performed using standard coaxial techniques under CT (or ultrasound) guidance without the administration of intravenous contrast. Conscious sedation will be administered by a trained radiology nurse using small doses of Versed and fentanyl titrated to the patient's level of discomfort. Following the biopsy, patients will be observed for 2 hours following their last dose of conscious sedation for any complications (severe pain, hematoma, neurologic deficit) prior to departing with a chaperone.

The study investigator and interventional radiologist or other appropriate radiologist will decide on appropriate biopsy site likely to yield tissue amenable to NGS analysis[51] while exposing the patient to acceptable risk (see Appendix E). If such a site cannot be identified, the patient will be excluded from this study. Large bore core biopsies will be performed per institutional standards.

9.4.2 Handling of Specimens(s)

1. Label formalin-filled containers according to instructions in Section 9.3.1.2.
2. Obtain biopsy specimens and place one core in each cassette.
3. Snap the cassette lids closed and place cassettes into a formalin-filled pre-labeled

container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.
4. Secure the container lids and package containers into the shipping kit according to instructions in Section 5.6. Keep tissue in formalin jars at room temperature until shipment to the EET Biobank

Specimen size requirement is as follows:
• Surface area of 25mm^2 is optimal. Minimum is 5mm^2.
• Volume: 1mm^3 optimal. Minimum volume is 0.2mm^3
however the success of DNA extraction decreases at suboptimal tissue volume.

At least 4 biopsy cores should be obtained and placed in formalin: one for submission to the Pathology department at each institution, at least 3 for submission to the EET Biobank to distribute to the MoCha laboratory for Whole Exome Sequencing and to Dana-Farber Cancer Institute for RAD51 Focus Formation Assay per section 9.2.2. Cores submitted to the EET Biobank will be prioritized for whole exome sequencing first and RAD51 focus formation second.

9.4.2.1 Collection of Blood
Collect 10 mL of blood in cfDNA Streck tube at the following time points:

- Pre-treatment (for genomic DNA)
- For Arm B: Every third cycle on study (i.e. C1D1, C4D1, C7D1, etc.)
- For Arm A: C1D1, C4D1, C7D1, etc., then C1D1[crossover], C4D1[crossover] etc.
- Off study.

9.4.2.2 Handling of Blood in cfDNA Streck Tube(s)

1) Label one 10 mL cfDNA Streck tube per section 9.3.1.1.
2) Collect 10 mL blood into the pre-labeled tube and invert to mix. **Note: blood must be thoroughly mixed to ensure preservation of specimen.**
3) After collection, blood in cfDNA Streck tubes **should never be refrigerated**, as this may compromise the specimen**.** Blood collected in cfDNA Streck tubes is stable at room temperature.

9.5 Shipping Specimens from Clinical Site to the EET Biobank

9.5.1.1 General Shipping Information:
Core biopsies that are fixed in formalin and fresh blood should be shipped as one shipment at ambient temperature, whenever possible. The shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For formalin-fixed biopsies, if the corresponding anatomical pathology report is not available at the time of shipment, then the surgical and/or radiology reports from the tissue removal procedure and the diagnostic anatomic pathology report must be included in the package, or the specimen will not be processed. Once completed, upload the corresponding pathology report to the ETCTN specimen tracking system and send a copy to the EET Biobank.

9.5.1.2 Specimen Shipping Instructions:

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.

Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

9.5.1.3 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. Note: If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. Do not refrigerate, freeze, or microwave.
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. Note: The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

9.5.1.4 Shipping Ambient Tissue and Blood in a Single-Chamber Kit [used when tissue in formalin is included]

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed. The lids of formalin jars should be wrapped in parafilm. Absorbent material must be placed around each primary container that holds liquid.
2. Place the specimens in zip-lock bags. Use a separate bag for each specimen type.
3. Place specimens into the secondary pressure vessel surrounded by bubble wrap. Place the lid on the secondary pressure vessel and set it inside the kit chamber.
4. Place a copy of the shipping manifest and corresponding reports such as pathology, surgical, or radiology reports into the insulated shipping container.
5. Set the lid on top of the container. Close the outer flaps and tape shut.
6. Attach a shipping label to the top of the shipping container.
7. Attach an Exempt Human Specimen sticker to the side of the container.
8. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

9.5.1.5 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org
FedEx Priority Overnight service is very strongly preferred.
NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

9.5.1.6 Contact Information for Assistance
For all queries, please use the contact information below:
EET Biobank
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

9.6 Integrated Correlative Study – Whole Exome Sequencing

Whole exome sequencing will be performed through Molecular Characterization (MoCha) laboratory at the Frederick National Laboratory for Cancer Research. Patients will be considered to have homologous recombination deficiency (HRD) from this assay if a *bona fide* mutation, deletion, or truncation predicted to be functionally deleterious in a gene involved in homologous recombination repair. Statistical analysis comparing response rates to M6620 (VX-970, berzosertib)+carboplatin and docetaxel+carboplatin in patients found to have HRD as compared to those who do not is described in section 13.6.2.

In patients who elect for optional post-treatment biopsy, whole exome sequencing will also be performed on this tissue to assess for genomic correlates of resistance to therapy.

9.6.1 Specimens and Processing at the EET Biobank
Formalin-fixed tissue at pre-treatment (mandatory) and Off Study (optional, if available) time points will be used for this assay. Tumor tissue will be processed and embedded upon receipt at the EET Biobank. Slides will be cut from 1 – 2 cores, and the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and then DNA and RNA will be co-extracted, aliquoted, and stored in a -80°C freezer until distribution for testing.

9.6.2 Site(s) Performing Correlative Study:
Whole exome sequencing will be performed through Molecular Characterization (MoCha) laboratory at the Frederick National Laboratory for Cancer Research.

9.7 Exploratory/Ancillary Correlative Studies

9.7.1 **RNA Sequencing for RB loss of function**

RNA-Seq from tumor biopsies is an exploratory biomarker in this study. Background and Rationale for using RNA-Seq for assessment of RB loss of function are described in section 2.5.5.

9.7.1.1 Specimens and Processing at the EET Biobank
RNA will be co-extracted with DNA from tumor tissue as detailed in section 9.6.1, aliquoted, and stored in a -80°C freezer until distribution for testing.

9.7.1.2 Site(s) Performing Correlative Study:
RNA sequencing will be performed through the NCLN Genomics Laboratory. Data will be analyzed in the laboratory of Dr. Leigh Ellis at Cedars-Sinai Medical Center.

9.7.2 **Ultra low-pass whole genome sequencing, 50 x whole genome sequencing, and prostate cancer-specific targeted sequencing from circulating free DNA**

Genomic analysis from cfDNA is an exploratory biomarker in this study. Background and Rationale for genomic studies from cfDNA are described in section 2.5.2.

9.7.2.1 Specimens and Processing at the EET Biobank
All specimens will be processed to plasma and frozen per ETCTN standard operating procedures. Plasma will be aliquoted and stored in a -80°C freezer until distribution for testing.

9.7.2.2 Site(s) Performing Correlative Study
Genomic DNA extracted from blood collected at the pre-treatment time point, as well as frozen plasma from C1D1, C1D1 [crossover] (for patients randomized to arm A), and Off Study time points will be shipped in batches in by the ECTCN Biorepository to the Genomics Platform at the Broad Institute at the following address:

Broad Institute
Attn: Genomics Platform – Samples Lab
320 Charles St – Lab 181
Cambridge, MA 02141
Phone: (617) 714-8952

Remaining plasma samples (from C4D1, C7D1, C10D1, etc. time points as well as C4D1[crossover], C7D1[crossover], etc. time points) will remain banked in the EET Biobank for future studies.

9.7.3 **RAD51 Focus Formation Assay, ATM/p-KAP1 Immunohistochemistry**

9.7.3.1 Specimens and Processing at the EET Biobank

Formalin-fixed tissue at pre-treatment (mandatory) and end of treatment (optional, if available) time points will be used for this assay. Tumor tissue will be processed and embedded upon receipt at the EET Biobank. One of the embedded biopsies will be banked at room temperature until distribution for the RAD51 Focus Formation Assay, ATM/p-KAP1 Immunohistochemistry.

9.7.3.2 Site performing correlative study

RAD51 Focus Formation Assay and ATM/p-KAP1 Immunohistochemistry will be performed at the Center for DNA Damage and Repair at Dana-Farber Cancer Institute. FFPE biopsy tissue blocks will be shipped in batches by the EET Biobank to the Dana Farber Cancer Institute:

Bose Kochupurakkal, PhD
HIM208, Center for DNA Damage and Repair
Dana-Farber Cancer Institute
77 Avenue Louis Pasteur, Boston, MA 02115

10. STUDY CALENDAR

Pre-study (screening) laboratory testing, imaging studies, and EKG must be done ≤4 weeks prior to the start of therapy. Packed red blood cell (PRBC) transfusions are permitted to meet eligibility criteria prior to screening but platelet transfusions and growth factors are not permitted within 28 days of screening. Pre-treatment assessments (prior to day 1 and day 9 drug dosing for each cycle) should be performed within 72 hours of planned treatment dose. Results from the patient's complete blood counts and serum chemistry[1] must be reviewed prior to drug dosing. The patient's laboratory parameters must meet eligibility criteria (section 3.1.6) to initiate cycle 1 day 1 of trial therapy; eligibility to receive subsequent doses is based on dose delay/modification criteria detailed in Section 6, with platelet count required to be ≥75,000/mcL to initiate a new cycle. The acceptable window for start of day 1 of a cycle is 21 days +/- 3 days in relation to day 1 of the prior cycle. The acceptable window for day 2 is +2 days (i.e. day 2-4); the acceptable window for day 9 is +/- 2 days in reference to day 2 (i.e. day 7-11 if M6620 (VX-970, berzosertib) is administered on day 2 of the cycle, day 9-13 if administered on day 4 of the cycle). Administration outside of these windows may be permitted for weather or other emergencies after discussing with the principal investigator. Note that the study calendar is related to cycle, so assessments (radiologic evaluations, biomarker, etc.) are delayed when cycles are delayed.

	Pre-Study	Cycle 1			Cycle 2			Cycle 3			Subsequent cycles			Off Study[4]
		C1 D1	C1 D2	C1 D9	C2 D1	C2 D2	C2 D9	C3 D1	C3 D2	C3 D9	C_ D1	C_ D2	C_ D9	
Docetaxel		A			A			A			A			
Carboplatin		A,B			A,B			A,B			A,B			
M6620 (VX-970, berzosertib)			B	B		B	B		B	B		B	B	
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X		B	X		B	X		B	X		B	X
Height	X													
Weight	X	X			X			X			X			X
Performance status	X	X			X			X			X			X
CBC w/diff, plts	X	X		B	X		B	X		B	X		B	X
Serum chemistry[1]	X	X		B	X		B	X		B	X		B	X
PSA	X	X			X			X			X			X
Testosterone	X													
EKG (as indicated)	X													

Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated prior to every third cycle (i.e. prior to C4D1, C7D1, etc.). For patients on Arm A who crossover, imaging studies are obtained within 30 days of C1D1[crossover] and then prior to C4D1[crossover], C7D1[crossover], etc. Documentation (radiologic) must be provided for participants removed from study for progressive disease.												X
Radiologic evaluation[2]	X	Radiologic measurements should be performed prior to every third cycle (i.e. prior to C4D1, C7D1, etc.) For patients on Arm A who crossover, imaging studies are obtained within 30 days of C1D1[crossover] and then prior to C4D1[crossover], C7D1[crossover], etc. Imaging is preferred within 7 days of scheduled D1 of the subsequent cycle but a window of up to 14 days prior to scheduled D1 of the subsequent cycle (and up to 30 days prior to C1D1[crossover]) is allowed.												X
Tumor biopsy	X													X[4]
Biomarker (blood in cfDNA Streck)[3]	X	X									X[3]			X
Other correlative studies														

A: Docetaxel 60 mg/m2 day 1 + Carboplatin AUC 4 day 1 (or Carboplatin AUC 5 alone, day 1 if docetaxel-ineligible)
B: M6620 (VX-970, berzosertib) 90 mg/m2 on days 2 and 9 + Carboplatin AUC 5 day 1
1: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
2: Cross-sectional imaging of Chest, Abdomen and Pelvis as well as bone scintigraphy
3: Pre-study biomarker sample is for genomic DNA and can be drawn any time between and including screening and C1D1; remaining biomarker samples are for cfDNA. For patients randomized to Arm B, cfDNA blood draws will be performed C1D1, C4D1, and every 3 cycles thereafter and at end of study. For patients randomized to Arm A and then crossover, cfDNA blood draws will be performed on C1D1, C4D1, and every 3 cycles while on carbo+/-docetaxel, then C1D1 [crossover], C4D1 [crossover], and every 3 cycles thereafter while on carbo+M6620 (VX-970, berzosertib) and at end of study
4: Off-study evaluation. End of study biomarker blood draw is mandatory, but end of study tumor biopsy is optional. Note: for IND/IDE trials, follow up visits or other contact are required in order to identify SAEs during the 30 days following the end of study treatment.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response prior to every third cycle (i.e. prior to C4D1, C7D1, etc.); for patients on Arm A who crossover, imaging studies are obtained within 30 days of C1D1[crossover] and then prior to C4D1[crossover], C7D1[crossover], etc. Imaging is preferred within 7 days of scheduled D1 of the subsequent cycle but a window of up to 14 days prior to scheduled D1 of the subsequent cycle (and up to 30 days prior to C1D1[crossover]) is allowed. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression of non-osseous disease will be evaluated in this study using the new international criteria proposed by the 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. Response and progression of osseous disease by bone scintigraphy will be per Prostate Cancer Working Group 3 criteria.[2]

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with M6620 (VX-970, berzosertib), carboplatin, and/or docetaxel.

Evaluable for PSA response: Only those patients with PSA ≥ 2.0 ng/mL at baseline, have received at least one cycle of therapy, and have had their PSA re-measured will be evaluable for PSA response per section 11.2.

Evaluable for radiographic 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 radiographic 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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan or MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis

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

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

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

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

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

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Only imaging-based evaluation will be performed for this study.

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 (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

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

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

Tumor markers Refer to Section 11.2

Cytology, Histology These techniques can be used to differentiate between partial

responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

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

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

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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 (0.5 cm). (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.

11.1.4.2 Evaluation of Non-Osseous Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

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

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

11.1.4.3 Evaluation of Osseous Disease by Bone scintigraphy per PCWG3 criteria[2]

Osseous disease will be monitored by bone scintigraphy. The bone scan performed at 9 weeks will serve as the baseline for assessment of radiographic progression of osseous disease. Bone scan progression will be defined as the appearance of at least two new lesions relative to the first post-treatment scan, confirmed on a subsequent scan. Date of progression is the date of the scan that first documents the second lesion (and not the date of the confirmatory scan). Changes in intensity of uptake alone do not constitute either progression or regression.

11.1.4.4 Evaluation of Best Overall Response

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

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

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

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

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

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

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

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

11.1.5 Duration of Radiographic Response

Duration of radiographic response: The duration of radiographic response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that radiographic progression is objectively documented (taking as

reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

11.1.6 Time to Event Endpoints

Overall Survival: Overall Survival (OS) is defined as the time from randomization to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization to the earlier of progression by PCWG3 criteria[2] or death due to any cause. PCWG3 progression is defined as when it is felt by the treating physician that the patient is "no longer clinically benefiting" (NLCB) from therapy. Generally, this is understood as radiographic or clinical/symptomatic progression (i.e. not PSA progression alone), but PCWG3 criteria allow treatment beyond radiographic progression if the treating physician feels that the patient is continuing to derive clinical benefit from therapy (compared to other available treatments or no treatment). Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization to progression by PCWG3 criteria[2], or censored at date of last disease evaluation for those without progression reported.

Time to PSA Progression: Time to PSA Progression is defined as the time from randomization to PSA progression by PCWG2 criteria[1], defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later.

Radiographic Progression-Free Survival: rPFS is defined as the time from randomization to the earlier of progression of non-osseous disease by RECIST 1.1 criteria or bone scan progression by PCWG3 criteria[2] or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

11.1.7 Response Review

Responses will be reviewed by an expert independent of the study at the study's completion.

11.2 PSA Response

Only patients with baseline PSA ≥ 2 ng/mL at baseline will be evaluable for PSA response.

Biochemical Response:[52]
The laboratory will utilize a consistent method to check serum PSA at baseline, on treatment as per the study calendar, and at study termination.
A PSA response will be defined as any PSA decline ≥50% from baseline during trial therapy.

Percent change in serum PSA[1]
The percent change (rise or fall) from baseline at 12 weeks, and separately, the maximal change (rise or fall) at any time will be recorded using a waterfall plot.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

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.

The Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance.

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

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

12.2 Data Reporting

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

assignments. To access Rave via iMedidata:

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

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

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

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at:

http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

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

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

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

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

12.3 Data Quality Portal

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

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

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

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

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

12.4 CTEP Multicenter Guidelines

N/A

12.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI

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

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

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

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

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

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

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

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the

NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

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

Email: ncicteppubs@mail.nih.gov

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

12.6 Genomic Data Sharing Plan

De-identified samples and data (clinical as well as genomic or epigenomic) collected under this protocol will be shared with collaborators performing the biomarker studies and stored in the database of Genotypes and Phenotypes (dbGaP). Specimens will be de-identified using a Trial ID # that is different from the patient's medical record number. Language regarding the acquisition and sharing of genomic data is included in the consent form for this trial. Data at both the individual level (de-identified) and aggregate level may be shared in collaboration with other researchers.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a randomized open-label of Phase 2 study of M6620 (VX-970, berzosertib) + carboplatin vs. docetaxel + carboplatin in patients with metastatic castration-resistant prostate cancer. Patients who have been treated with at least one secondary hormonal therapy and taxane-based chemotherapy will be randomized 1:1 to receive Arm A (docetaxel + carboplatin) or Arm B

(M6620 (VX-970, berzosertib) + carboplatin). Patients who are ineligible for docetaxel due to 1. Allergy or intolerance to docetaxel or 2. Gr 2 neuropathy and are randomized to the control arm will be treated with carboplatin as a single agent. Patients will be treated on study until the occurrence of progression by PCWG3 criteria[2], unequivocal clinical progression, unacceptable side effects, withdrawal of consent, or death. Patients will be stratified by 1) whether they received prior PARP inhibitor (yes vs. no) at randomization, 2) whether they have evaluable disease by RECIST criteria at baseline (yes vs. no) at randomization, with a post-hoc analysis by whether or not they have a canonical pathogenic mutation in a gene involved in homologous recombination repair by whole exome sequencing from a mandatory pre-treatment tumor biopsy. Patients on the docetaxel+carboplatin arm will be allowed to crossover to the M6620 (VX-970, berzosertib)+carboplatin arm at the earlier of time of PSA progression (by PCWG2 criteria[1]) or radiographic progression (by RECIST 1.1 criteria for non-osseous disease or PCWG3 criteria[2] for osseous disease) if the patient remains clinically stable and continues to meet the eligibility criteria of the protocol.

The primary objective of this trial is to investigate the response rate (CR+PR as defined by radiographic response by RECIST 1.1 or PSA response defined in Section 11.2) in patients treated with a combination of M6620 (VX-970, berzosertib) and carboplatin as compared to a combination of docetaxel and carboplatin. Patients who are evaluable for both PSA and radiographic response will be considered responders if they experience a response by either criterion.

Secondary objectives include comparison of time to PSA progression by PCWG2 criteria[1] (defined in section 11.1.6) between the 2 arms. Patients who had radiographic progression prior to PSA progression (rare cases) will be counted as failures for time to PSA progression comparisons. Given that the crossover design does not allow for direct comparison of radiologic progression–free survival and progression-free survival by PCWG3 criteria between the arms of this study, these parameters in each arm will be reported separately. We will assess the relationship with homologous recombination deficiency (HRD) detected from baseline tumor biopsy with response to the combination of M6620 (VX-970, berzosertib) and carboplatin and the combination of docetaxel and carboplatin. Other secondary endpoints include safety of carboplatin+M6620 (VX-970, berzosertib) and adverse events in each arm.

13.2 Sample Size/Accrual Rate

For the primary endpoint, we anticipate a response rate of 20% in the docetaxel+carboplatin arm in this cohort of patients who have previously received at least 2 prior therapies[19]. If the response rate of carboplatin+M6620 (VX-970, berzosertib) is 40%, with 65 patients on each treatment arm (total N=130), there will be 80% power to distinguish a response rate of 40% versus 20% using a chi-square test (one sided a=0.05). 142 subjects will be enrolled to account for 10% of patients who never start treatment after randomization.

The study will be monitored for futility with one interim analysis, planned at approximately 50% information (i.e. 65 response evaluable patients). The decision for stopping the trial will be based

on the futility delta boundary (δ=response rate on M6620 (VX-970, berzosertib)/carboplatin arm – response rate on docetaxel/carboplatin arm). If the estimated δ lies below 0 (i.e. the response rate is lower in the experimental treatment arm among the first one-half of the patients), the study will be stopped early for lack of efficacy. The boundary crossing probability is 0.50 under the null hypothesis and is 0.04 under the alternative hypothesis. East version 6 (Cytel Inc.) is used for sample size and interim monitoring considerations.

For a sample size of 142 participants, we expect a total of 30 months to complete the accrual at a rate of 4-5 participants/month.

The total duration of the study is approximately 39 months which includes 30 months of enrollment and 9 months of expected treatment duration.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native					
Asian		15		0	**15**
Native Hawaiian or Other Pacific Islander					
Black or African American		13		1	**14**
White		92		21	**113**
More Than One Race					
Total		**120**		**22**	**142**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

13.3 Analysis of Primary Endpoint

The primary comparison of response rate will be conducted using the Cochran-Mantel-Haenszel(CMH) test, with one-sided p-value of ≤ 0.05 considered significant. The stratification factor at randomization (whether they received prior PARP inhibitor (yes versus no), whether

they have measurable disease per RECIST at baseline (yes versus no)) as well as HRD status from post-hoc analysis of collectively tissue after randomization (HRD(+), HRD(-), or unknown) will be applied to the stratified CMH test.

13.4 Analysis of Secondary/Exploratory/Correlative Endpoints

13.4.1 Analysis of secondary endpoints

Time to event endpoints (PFS, time to PSA progression and rPFS) will be estimated with the Kaplan Meier methodology. Median and event-free rate at selected time points will be provided with 95% confidence interval. Comparison of time to PSA progression between arms will be conducted using the log-rank test. Since patients will be allowed to crossover at the time of PSA progression, PFS and rPFS will not be compared between arms.

Safety analysis will be conducted using the Safety Population defined as any participant receiving one dose of study treatment. All safety endpoints will be summarized according to treatment arm. For toxicity reporting, all adverse events will be graded and analyzed using CTCAE version 5.0. Type of adverse events, intensity (grading), and attribution will be provided in a listing. All adverse events resulting in discontinuation, dose modification, and/or dosing interruption, and/or treatment delay of drug will also be summarized. Laboratory test results will be classified according to the CTCAE version 5.0.

13.4.2 Analysis of exploratory endpoints

OS will be estimated with the Kaplan Meier methodology. Comparison of OS between arms will be conducted using the log-rank test base on the intention-to-treat approach, where two treatment arms will be compared regardless of cross-over or any subsequent therapy.

We anticipate that ~50% of patients who progress on docetaxel+carboplatin will choose to crossover to the M6620 (VX-970, berzosertib)+carboplatin arm of the study, and the response rate, PFS, rPFS, and time to PSA progression after crossover will be descriptively assessed in this population.

13.4.3 Analysis of correlative endpoints

Gene mutation frequencies and mean ± SD of quantitative biomarkers will be summarized by arm and in overall population at baseline and/or at end of study. We anticipate that about 75% of biopsy specimens will be evaluable for homologous recombination deficiency (HRD) status by next generation sequencing. With a total of 98 evaluable samples, the 90% exact binominal CI width is 0.11 and 0.16 with the observed mutation rate of 0.1 and 0.3 respectively. We hypothesize that in both arms of the study, responses to carboplatin will be enriched in patients with HRD as determined by detection of alterations in genes involved in homologous recombination repair from the tumor. If 20% of patients harbor HRD, there is 83% power to detect a 30% difference in response (e.g. for a response rate 20% in HRD(-) versus 50% in HRD(+) patients) using a chi-square test (one sided a=0.05). Assuming 40~60% of patients with paired (pre- and post-treatment) biopsy available, there is 80% power to detect a 0.32~0.40 SD mean change in quantitative biomarkers between time points with n=52~78 using a paired t-test (two-sided α=0.05).

13.5 Reporting and Exclusions

The following Analysis Populations are planned for this study:

Safety Analysis Set: Evaluation of toxicity will be done in the safety population, which will include all patients who received at least one dose of study treatment. Patients will be analyzed in the treatment group according to the study treatment they actually received.

Full Analysis Set (FAS): The FAS will include all randomized patients who are deemed eligible and receive at least one dose of study treatment. FAS will be used for the primary comparison of response rate and other efficacy endpoints (time to PSA progression and OS) in an intent-to-treat analysis. Response unevaluable patients or early death from any causes prior to response evaluation will be included in the main analysis of the response rate as non-responders.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B CTEP MULTICENTER GUIDELINES

N/A

APPENDIX C PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD
Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

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, berzosertib) 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, berzosertib) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.
Protein transporters	The proteins in questions are **OATP1B3 and BCRP**. M6620 (VX-970, berzosertib) is a moderate inhibitor of these proteins and may affect drugs that are moved in and out of cells/organs by these transport proteins.

These are the things that you need to know:
The study drug M6620 (VX-970, berzosertib), 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 and sensitive substrates of CYP3A4, OATP1B3 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.

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**
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, berzosertib) interacts 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:**	Your healthcare providers should be aware of any medicines that are strong inhibitors or inducers of CYP3A4, and sensitive substrates of CYP3A4, OATP1B3, and BCRP. • Strong inhibitors or inducers of CYP3A4 should be avoided. • Sensitive substrates of CYP3A4, OATP1B3,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 Apr/2021	
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 D - BIOASSAY TEMPLATES

WHOLE EXOME SEQUENCING

Whole exome sequencing will be performed through Molecular Characterization (MoCha) laboratory at the Frederick National Laboratory for Cancer Research. At least two research core biopsies placed in formalin are shipped overnight to the EET Biobank for rapid embedding and subsequent nucleic acid extraction. These procedures are summarized in Section 9.4.

Whole Exome Sequencing will be performed at the Molecular Characterization Laboratory on the purified DNA aliquots provided by the Biorepository.

WES DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System, and quantitated via digital droplet PCR (ddPCR). Library samples are denatured, diluted and sequenced on the
Illumina NovaSeq 6000.

RNA SEQ

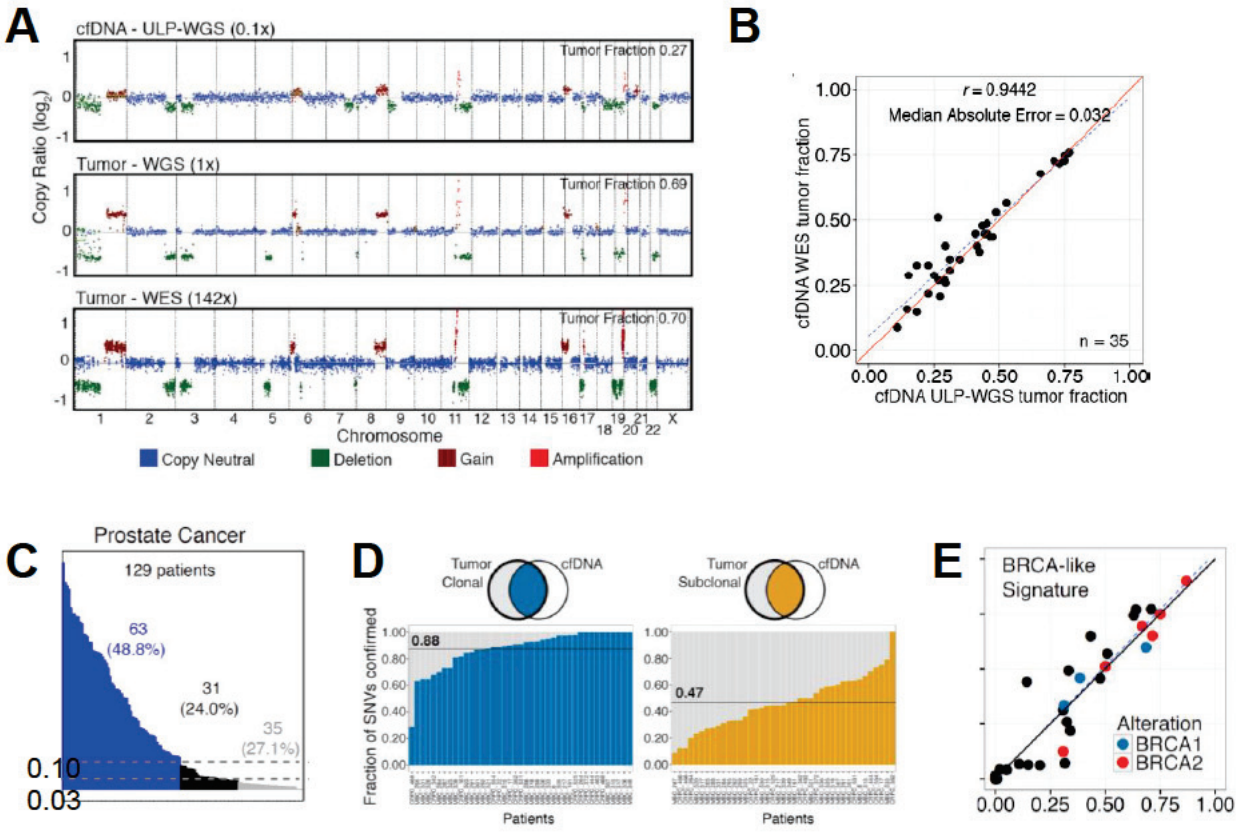
RNA sequencing will be performed through the NCLN Genomics Laboratory. At least two research core biopsies placed in formalin are shipped overnight to the EET Biobank for rapid embedding and subsequent nucleic acid extraction. These procedures are summarized in Section 9.4.

RNA-Seq will be performed at the the NCLN Genomics Laboratory on the purified RNA aliquots provided by the Biobank.

Reverse transcription to cDNA is primed with random hexamers, and the TruSeq RNA Exome kit from Illumina is used to specifically capture the coding regions of the transcriptome for cDNA sequencing.

Ultra low-pass whole genome sequencing (ULP-WGS) and whole exome sequencing (WES) from ctDNA
Adalsteinsson/Broad Institute of Harvard and MIT

Description of these techniques along with extensive technical benchmarking has been previously described.[29]



A. Analysis of whole genome sequencing performed at 0.1 x (termed Ultra-Low Pass Whole Genome Sequencing or ULP-WGS) using a novel software tool called ichorCNA can accurately assess regions of copy number gain and loss in patients with metastatic breast and prostate cancer. Here, a copy number profile from a breast cancer patient from circulating free DNA (cfDNA) is depicted along with copy number profiles generated from whole genome sequencing (WGS) and whole exome sequencing (WES) from a matched metastasis biopsy from the same patient. **B.** This tool can also be used to estimate the fraction of DNA in a patient's bloodstream derived from tumor (rather than normal tissue). Estimates of tumor purity from ULP-WGS of circulating free DNA using ichorCNA has high concordance with tumor purity estimates from WES using an orthogonal method called ABSOLUTE. **C.** In the first 129 patients with metastatic prostate cancer analyzed by this method, almost 73% of patients had detectable tumor DNA (threshold >3%) from at least one time point, and almost 49% of patients had DNA adequate for WES (threshold >10%) from at least one time point. **D.** Fraction of clonal (≥ 0.9 cancer cell fraction, CCF) and subclonal (< 0.9 CCF) somatic single nucleotide variants detected by MuTect

in WES of tumor biopsies and confirmed (i.e. supported by ≥ 3 variant reads) in WES of cfDNA. This demonstrates that the vast majority of clonal events detected in a metastasis biopsy are detectable in cfDNA, suggesting cfDNA as a reasonable proxy for metastasis biopsy. Subclonal events are less commonly detected in cfDNA, suggesting that cfDNA is composed of DNA derived from multiple metastatic sites. **E.** Mutational signatures in whole-exome sequencing of cfDNA and tumor biopsies were predicted using a Bayesian non-negative matrix factorization (NMF) approach. Samples with predicted homozygous loss of BRCA1/2 through whole exome sequencing are indicated in red and blue. This demonstrates that a BRCA-like signature (compatible with deficiency in homologous recombination repair deficiency) can be detected from cfDNA, and that there are patients with this signature who do not have known loss of BRCA1 and BRCA2.

Assay Details for ultra low pass whole genome sequencing (ULP-WGS): Frozen aliquots of plasma are thawed at room temperature. Cell-free DNA is extracted from 2 mL of plasma and eluted into 60 uL of resuspension buffer using the Qiagen Circulating DNA kit on the QIAsymphony liquid handling system. Extracted cell-free DNA is frozen at -20 C until ready for further processing. Quantification of extracted cfDNA and gDNA is performed using the PicoGreen (Life Technologies) assay on a Hamilton STAR-line liquid handling system. Library construction of cell-free DNA is performed using the Kapa HyperPrep kit with custom adapters (IDT). Generally, 5 ng of cfDNA input is used for ultra low-pass whole-genome sequencing (ULP-WGS). A Hamilton STAR-line liquid handling system is used to automate and perform this method. Constructed sequencing libraries are pooled (2 uL of each x 96 per pool) and sequenced using 100bp paired-end runs over 1 x lane on a HiSeq2500 (Illumina) for ULP-WGS.

The genome is divided into T non-overlapping windows, or bins, of 1Mb. Aligned reads are counted based on overlap within each bin using the tools in HMMcopy Suite (http://compbio.bccrc.ca/software/hmmcopy/). The read counts are then normalized to correct for GC-content and mappability biases using HMMcopy R package. This data is used to generate a Hidden Markov Model to derive copy number alterations and Tumor DNA purity using TitanCNA R package v1.9.0 (https://github.com/gavinha/TitanCNA) 8. Samples must pass a quality threshold (median absolute deviation score < 0.115) for accurate purity estimate.

Assay details for whole exome sequencing: When possible, 20ng of cfDNA input is used to construct another cfDNA library for WES, which affords greater library complexity and reduced the depth of sequencing required to achieve the desired mean target coverage. Library construction was performed using the Kapa HyperPrep kit with custom adapters (IDT) on a Hamilton STAR-line liquid handling system. Libraries are then quantified using the PicoGreen (Life Technologies) assay on a Hamilton STAR-line liquid handling system and pooled up to 12-plex. Hybrid selection of cfDNA libraries is performed using the Nextera Rapid Capture Exome kit (Illumina) with custom blocking oligos (IDT and Broad Institute). Sequencing to generate 100bp paired-end reads is performed on the Illumina HiSeq2500 in high-output mode with 2-4 libraries per lane. Single nucleotide variants are identified using MuTect and cancer cell fractions of these variants are derived using ABSOLUTE.

RAD51 Focus Formation Assay
Kochupurakkal/D'Andrea/Shapiro/Dana-Farber Cancer Institute

RAD51 staining pattern correlates with HR repair status and PARP--inhibitor response in breast cancer cell line models. We screened commercially available RAD51 antibodies by (1) detection of a single band on a western blot of whole cell extract in either non--irradiated or irradiated cells; (2) determination that only nuclear staining was present, without cytoplasmic staining, even at high concentrations of antibody, since RAD51 is a nuclear protein; and (3) detection of Rad51 foci in normal fibroblasts and lack of foci--like structures in BRCA2--/-- fibroblasts following irradiation. This screen identified a monoclonal rabbit antibody that recognizes RAD51 with high specificity.

We next tested RAD51 staining patterns in non--irradiated and irradiated FFPE sections of breast cancer cell lines. The BRCA--deficient cells lines used were MDA--MB--436 and HCC1395;; BRCA--proficient cell lines included BT20, HCC1569 and MDA--MB--468. MDA--MB436 and HCC1395 are highly sensitive to the PARP inhibitor olaparib compared to the BRCA--proficient cell lines. Immunohistochemical (IHC) staining conditions were optimized using paraffin sections containing these cell lines. Analysis of RAD51 staining pattern revealed three features: (1) RAD51 levels were high in BRCA--deficient lines in comparison to cell lines with wild--type BRCA; (2) Foci were observed in cell lines with wild--type BRCA and the number of cells with foci and the number of foci/cell increased with irradiation; in contrast, foci were absent in BRCA-- deficient cell lines irrespective of irradiation; and (3) only a fraction of cells stained for RAD51 irrespective of irradiation **(Figure 1)**.

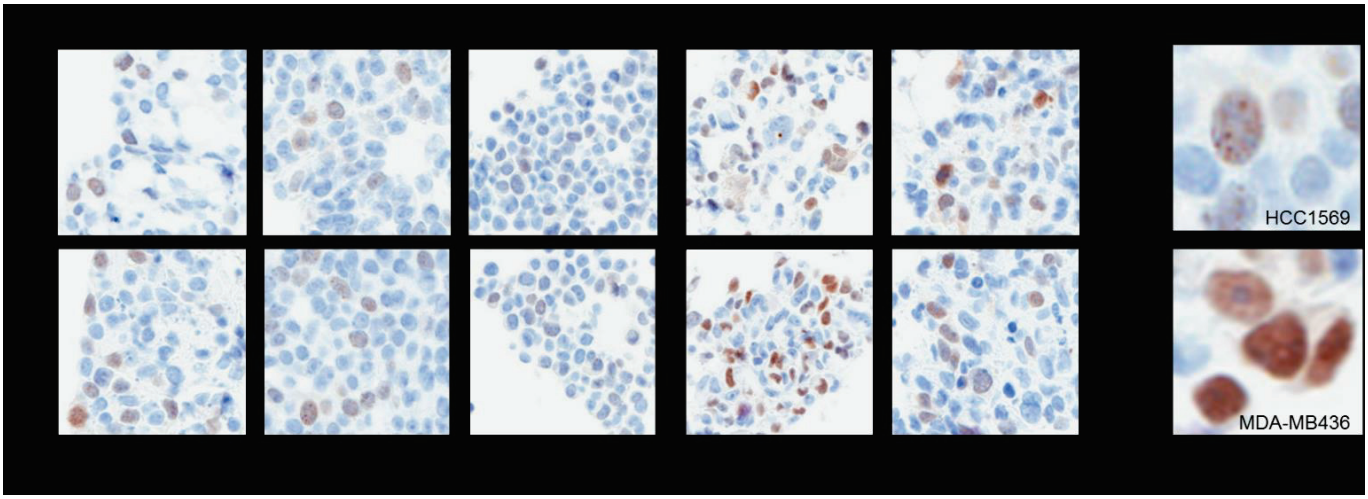


Figure 1. RAD51 staining pattern correlates with HR repair status. FFPE blocks were prepared of the indicated cell lines grown as spheroids embedded in a collagen--laminin matrix that were either un--irradiated or exposed to 10 Gy g□-- irradiation. Sections from these blocks were stained for RAD51 using a standardized protocol. RAD51 staining was observed in a fraction of the cells. **(A)** BRCA wild--type cell lines have low levels of RAD51, with foci evident in both unirradiated and irradiated cells, whereas, BRCA--mutant cell lines have high levels of diffuse nuclear RAD51 without evidence of foci. **(B)** Example of nuclei at higher

magnification from indicated cells lines with either RAD51 foci (HCC1569, BRCA wild--type), or diffuse high levels of RAD51 without foci (MDA--MB--436, BRCA1 mutant). Based on these results, it is possible to construct a matrix for evaluation of HR repair proficiency and deficiency, as shown below.

Analytical characteristics of the assay

Accuracy. We believe our screening conditions and criteria for selecting the best RAD51 antibody were appropriate. The staining patterns we observe using the selected antibody are consistent with current knowledge about the HR repair pathway. Therefore, the results obtained using the antibody are expected to have a high degree of accuracy. The staining conditions were standardized using the Leica auto--staining platform, which minimizes human error in performing the stains. The Aperio Scanscope image acquisition and analysis platform offers the ability to generate analysis--specific standardized macros that can be used consistently across samples and minimize human error/estimation discordance. This platform has proved successful in analyzing clinical samples. Accurate estimation of the functional HR repair score will require further validation.

Precision. The stains were done on the Leica auto--stainer platform and the stains of different batches of control samples were consistent. Staining using the standardized protocol, using Aperio ScanScope for image acquisition and analysis using standardized macros is expected to ensure a high degree of precision and minimize batch--to--batch variation. Precision in estimating the functional HR repair score will require further validation in expanded cohorts of samples.

Analytical Sensitivity. Since the RAD51 nucleofilament (foci) contains multiple molecules of RAD51 concentrated at a specific sub--nuclear location, we diluted the antibody such that only foci are visible in HR repair--proficient samples. At this dilution, HR repair--deficient cells have strong diffuse nuclear RAD51 staining. Testing larger cohorts of samples will help establish the exact dilution of the antibody for the staining. Although RAD51 nucleofilament (focus) formation is an essential step in HR repair, other steps downstream of RAD51 loading are necessary to complete HR. At this point, we are unsure if high RAD51 levels and presence of RAD51 foci indicate disruption of HR events downstream of RAD51 loading. The functional HR repair score is expected to identify tumors with disruption in HR repair upstream of RAD51 loading. The sensitivity of HR repair--deficient calls requires further validation.

Analytical specificity. This monoclonal antibody was generated in rabbits using recombinant full length RAD51. Western blot containing whole cell lysates of multiple cell lines detected a single ~37kDa band. Moreover, the staining pattrn observed in immunofluorescence--based and IHC-- based assays are consistent with high--specificity of the antibody to detect RAD51. The antibody is commercially available from Cell Signaling Technology, Danvers, MA. Cell Signaling Technology has procedures in place to provide Good Manufacturing Practice (GMP) certified antibody. Currently, the antibody is used at a dilution of 1:75. Our plan is to procure a GMP certified custom batch of the antibody and establish multiple parameters, including storage stability, assay sensitivity, and precision. Since Rad51 loading is an intermediate step in HR

repair, it is possible that presence of RAD51 foci may not indicate HR repair competence when genes encoding proteins downstream from RAD51 loading are altered. For example, cell lines in which RAD52 is disrupted fail to remove RAD51 nucleofilaments and complete HR repair (unpublished results). In such cases, the functional HR repair score may not correlate with HR repair proficiency, leading to a false--positive result.

Reportable range of results for the test system. A low functional HR repair score indicates HR repair deficiency, whereas a high score indicates proficiency. The percentage of foci--positive nuclei is the major component of the functional HR repair score. However, in HR repair--proficient tumors, cells with high levels of RAD51 are rare and this may inflate the functional HR repair score depending on the number of nuclei analyzed. Nevertheless, the functional HR repair scores observed in the five cell lines (un--irradiated and irradiated) range from 0.07 to 28.87 with scores ≤ 1.06 indicative of HR repair deficiency.

Controls for assay harmonization at multiple locations, quality controls and other performance characteristics. A paraffin block containing irradiated and un--irradiated cell lines described earlier in a Tissue MicroArray (TMA) format will be used as the control for staining and analysis using Aperio ScanScope. A section from this block will be included with all batches of samples that are stained and analyzed. Since the cell lines are an unlimited resource, duplicate blocks can be prepared, certified and shared with all locations where the staining will be performed. The macro used to analyze images of stains will also be shared. Alternatively, the stains can be performed at a centralized location.

APPENDIX E PROCEDURE FOR COLLECTION OF BIOPSY TISSUE

Introduction

The majority of the tissue/tumor collections for this project will occur via an image-guided (CT scan or US-guided) needle biopsy of a soft tissue or bone lesion. Biopsy of soft tissue is preferred when possible. Excisional biopsy of a lymph node or tissue from a surgical procedure (e.g. repair of a pathological fracture, liver nodule resection samples, cord compression samples, brain metastasis, etc. that are usually large samples) could be allowed as the pre-treatment tissue specimen if performed within the screening window and tissue specimens are preserved with formalin for biomarker analysis as described in the protocol.

Blood samples will be drawn within 4 weeks of the biopsy to document an acceptable coagulation profile (INR < 1.5, PTT < 45, platelets > 50,000). Aspirin and/or Plavix should be discontinued 5 days prior to the biopsy (continuation of aspirin 81 mg may be permitted based on institutional guidelines). On the day of the biopsy, a short physical exam will be performed by the radiologist including assessing the participant's general ASA score and airway rating.

Bone Biopsies:

Bone biopsies will be performed using standard coaxial techniques under CT guidance without the administration of intravenous contrast. Bone biopsies should not be performed on irradiated lesions. Bone sites include lumbar vertebrae, pelvic bones and long bones. Excluded sites are thoracic, cervical vertebrae, skull and rib lesions. 11G needle is preferred to be used for bone biopsies. Given lower yield on bone biopsy special attention should be given to the following parameters which may correlate with tumor yield on bone biopsy[51]:

· Size (larger size correlated with greater yield)

· Degree of sclerosis (more sclerosis correlating with more difficulty with biopsy and nucleic acid extraction)

· Distance from the skin to the lesion (lower yield for lesions farther from the skin)

· Distance from the cortex to the lesion (lower yield for lesions farther from the cortex)

· Presence of a bone scan correlate (greater yield with positive bone scan correlate)

· Area to target for biopsy (potentially greater yield at the periphery vs. center of the lesion)

Soft Tissue Biopsies:

Soft tissue biopsies will be performed using standard coaxial techniques under CT guidance without the administration of intravenous contrast or US-guidance. Soft tissue biopsy sites include: lymph node or visceral metastases. 18G or larger is preferred to be used for soft tissue biopsies. Fine Needle Aspirate (FNA) samples are not acceptable. Same radiological parameters above will be noted.

Cores and Core Size:

For each tissue collection procedure, the intent is to acquire 4 needle cores for formalin fixation. Size of these biopsy cores can be variable (0.1-1.0 cm). Good quality cores are usually at least 0.3- 0.4 cm in size. While larger cores are preferable to optimize tumor capture, cores of any size should be processed.

Pre-Biopsy Labeling of Tubes and Cryomolds

Following information must be included:

· Biopsy date

· Specimen ID

· Biopsy type

· Clinical protocol number

· Sample #, 1, 2, 3, 4, 5, 6

Attach the labels to the mega-cassettes and formalin container. You can always remove them later for future use if not used this time.

Biopsy Notice

Research staff should communicate with Interventional Radiology team in advance of the biopsy to ensure that specimens are collected according to the laboratory manual.

Tumor Needle Biopsy Collection

Research staff should arrive at the biopsy site at least 15 minutes ahead of the scheduled time to allow sufficient time to set up laboratory supplies.

APPENDIX F -TISSUE BIOPSY VERIFICATION

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the EET Biobank.

If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.

Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Metastatic

Time point (circle one): Pre-Treatment Off-Study

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

_____ _____

Clinician Signature Date

_____

Clinician Printed Name

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist (or other appropriate radiologist), Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.

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