SUMMARY OF CHANGES – Protocol

For Protocol Amendment # 15

NCI Protocol #: 10313
Local Protocol #: 20-134

NCI Version Date: 11/05/2024
Protocol Date: 11/05/2024

I. Comments requiring a response – Major Issues (submitted 11/05/24):

#	Section	Change
1.	**10.1.2**	Please remove the SPEER column for pembrolizumab as it is commercially supplied and the following related language: 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). 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. **PI Response: Updated**
2.	**4.1**	As previously requested, please replace the first paragraph with the updated language below: Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr. **PI Response: Updated**

#	Section	Change
3.	**8.1.1**	As previously requested, for M6620, please update the storage conditions to: Storage: Store intact vials protected from light inside cardboard boxes at room temperature, below 25°C (77°F), do not freeze ~~with excursions allowed between 15 and 30°C (59 and 86°F)~~. If a storage temperature excursion is identified, promptly return M6620 to ~~between 15 and 30°C~~ below 25°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. **PI Response: Updated**
4.	**ICD**	As previously requested, please update the gemcitabine and carboplatin side effects lists to the latest version available on the CTEP website: Tables of Possible Side Effects for Commonly-Used Oncology Drugs **PI Response: Updated**

II. II. Response to RRA (submitted 10/30/24):

#	Section	Change
5.	**Cover Page**	**Added: Amendment 15 / October 30, 2024 -** Response to an RRA from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov).
6.	**10.3.3**	**Revision of the AE Reporting Table** - to version 08/30/2024

#	Section	Change
7.	**10.1.2**	Added New Risk: • Rare but Serious: Enterocolitis; Gastrointestinal disorders - Other (exocrine pancreatic insufficiency); Lipase increased; Myasthenia gravis; Myelitis; Nervous system disorders - Other (autoimmune neuropathy); Nervous system disorders - Other (demyelination); Nervous system disorders - Other (nerve paresis); Skin and subcutaneous tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms [DRESS]) Increase in Risk Attribution: • Changed to Less Likely from Rare but Serious: Infusion related reaction • Changed to Rare but Serious from Also Reported on Pembrolizumab MK-3475 Trials But With Insufficient Evidence for Attribution: Acute kidney injury; Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia); Gastritis Decrease in Risk Attribution: • Changed to Rare but Serious from Less Likely: Pneumonitis • Changed to Also Reported on Pembrolizumab MK-3475 Trials But With Insufficient Evidence for Attribution from Less Likely: Cough Provided Further Clarification: • Hemolysis (under Also Reported on Pembrolizumab MK-3475 Trials But With Insufficient Evidence for Attribution) is now reported as Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia) (under Rare but Serious).
8.	**ICD**	Added New Risk: • Rare and Serious: Inability to digest food which may cause bloating; Swelling of the bowels; Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure Decrease in Risk Attribution: • Changed to Rare and Serious from Occasional: Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath. • Changed to Also Reported on Pembrolizumab MK-3475 Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from Risk Profile): Cough Provided Further Clarification: • Reaction during or following a drug infusion which may cause fever, chills, rash (under Rare) is now reported as Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure (under Occasional)

#	Section	Change
9.	**5.6.3**	EET Biobank Shipping Address updated to new address: EET Biobank 2200 International Street Columbus, OH 43228 PH: (614) 722-2865 FAX: (614) 722-2897 E-mail: BPCBank@nationwidechildrens.org
10.	**5.6.4**	EET Biobank Contact Information for Assistance updated EET Biobank ~~Toll-free Phone: (800) 347-2486~~ PH: (614) 722-2865 E-mail: BPCBank@nationwidechildrens.org

NCI Protocol #: 10313

Local Protocol #: 20-134

ClinicalTrials.gov Identifier: NCT04216316

TITLE: A phase IB and randomized open-label phase II study of Berzosertib (M6620, VX-970) in combination with carboplatin/gemcitabine/ pembrolizumab in patients with chemotherapy-naïve advanced non-small cell lung cancer of squamous cell histology

Corresponding Organization: **LAO-PA015** / UPMC Hillman Cancer Center LAO

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LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / UPMC Hillman Cancer Center LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

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NCI-Supplied Agents: Berzosertib (M6620, VX-970) (NSC #780162)

Other Agent(s): Gemcitabine hydrochloride (NSC #613327, Commercial), Carboplatin (NSC #241240, Commercial), Pembrolizumab (NSC #776864, Commercial)

IND #: 129800

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:
Original / August 2, 2019
Revision 1 / October 3, 2019
Revision 2 / November 7, 2019
Revision 3a / January 3, 2020
Revision 4 / January 31, 2020
Revision 5 / February 19, 2020
Amendment 1 / July 08, 2020 Response to CTEP and ETCTN Biorespository comments; response to a CTEP Amendment Request from Gary L. Smith, M.G.A; University of Pittsburgh changes
Amendment 2 / September 04, 2020 (Changes made in response to an RA from CTEP)
Amendment 3 / October 23, 2020 Changes made in response to CTEP recommendations, and to add windows and clarify response assessments
Amendment 4 / December 18, 2020 Changes made in response to NCI CIRB comments.
Amendment 5 / January 19, 2021 Changes made in response to CTEP comments dated 01/14/2021
Amendment 6 / January 27, 2021 change made in response to CTEP comments dated 01/26/2021
Amendment 7 / March 09, 2021 changes made in

response to CTEP and FDA comments
Amendment 8 / May 14, 2021 changes made in response to a CTEP Notice dated 04/22/2021; changes to treatment administration
Amendment 9 / June 24, 2021 changes made in response to CIRB stipulations; additional University of Pittsburgh Changes
Amendment 10 / July 16, 2021 changes made in response to CTEP recommendations, received 07/12/2021
Amendment 11 / October 20, 2021 Changes in response to an RRA from Dr. Elad Sharon (sharone@mail.nih.gov)
Amendment 12 / August 29, 2022 Response to an RRA from Dr. Stevenson Gore
Amendment 13 / October 21, 2022 changes made in response to CTEP Request for Amendment dated 10/06/2022
Amendment 14 / February 23, 2023 Response to an RRA from Dr. Elad Sharon
Amendment 15 / November 5, 2024 Response to an RRA from Dr. Howard Streicher and additional administrative updates

SCHEMA

The projected study duration is 30 months from first to last enrolled evaluable patient, with an expected additional 12 months of follow-up from the last patient enrollment to ascertain 85 PFS events.

Phase 1B Safety Lead-In (n = 6-18)

Dose De-Escalation Schema

	Berzosertib (M6620, VX-970) (mg/m^2)	**Gemcitabine (mg/m^2)**	**Carboplatin (AUC)**	**Pembrolizumab (mg)**
Schedule				
Cycles 1-4 (every 3 weeks)	Days 2 and 9 *	Days 1 and 8	Day 1	Day 1
Cycles 5-16 (every 3 weeks)	Day 1	-	-	Day 1
Cycles 17-26 (every 6 weeks)	-	-	-	Day 1**
Dose Level (Cycles 1-16)				
1	135 mg/m^2	800 mg/m^2	5	200
-1	135 mg/m^2	800 mg/m^2	4	200
-2	90 mg/m^2	600 mg/m^2	3	200

We will start at dose level 1, as our patient population is chemotherapy-naïve, and would be expected to tolerate higher doses of platinum chemotherapy.

The following treatment schedule will be used for a total of two years of treatment. Pembrolizumab administration should not exceed 2 years.

- Cycles 1 to 4 (first 3 months of the first year): gemcitabine on D1 and D8, carboplatin and pembrolizumab on D1, and +/- berzosertib (M6620, VX-970) on D2 and D9, every three weeks
- Cycles 5 to 16 (last 9 months of the first year): pembrolizumab +/- berzosertib (M6620, VX-970) on D1, every 3 weeks
- Cycles 17 to 26 (second year): pembrolizumab on D1, every 6 weeks

* Beyond 4 cycles (*i.e.*, 3 months), when berzosertib (M6620, VX-970) and pembrolizumab administration continues without gemcitabine or carboplatin, the berzosertib (M6620, VX-970) and pembrolizumab may be dosed on the same day for patient convenience, where pembrolizumab is administered before berzosertib (M6620, VX-970).

** Pembrolizumab will be administered as 200mg for Cycles 1-16 and 400mg for Cycles 17-26 and should not exceed 2 years of treatment.

DLTs will be defined as grade 4 absolute neutrophil count for ≥ 7 days, grade 4 anemia, platelet count < 25,000, or other non-hematologic events ≥ grade 3 as per NCI Common Terminology Criteria for Adverse

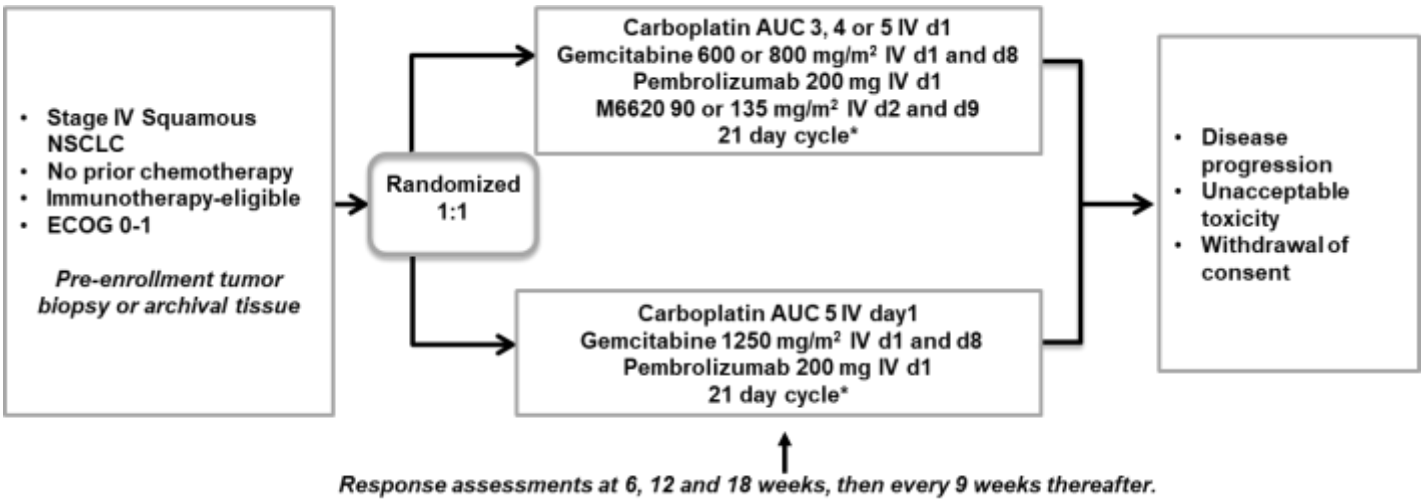
Events Version 5.0 (except fatigue, alopecia, anorexia, nausea, and emesis occurring despite optimal antiemetic therapy). Patients are allocated to doses by the following algorithm:

Three patients will be treated at Level 1.

1. If # DLT≤1/3, treat 3 more patients at Level 1, otherwise, go to step 2, below.
   a. If # DLT≤1/6, proceed to Phase 2 at Level 1,
   b. Else if # DLT=2/6 or 3/6, go to step 2, below,
   c. Else if # DLT>3/6, do not proceed to Phase 2.
2. If # DLT≤1/3, treat 3 more patients at Level -1, otherwise, go to step 3, below.
   a. If # DLT≤1/6, proceed to Phase 2 at Level -1,
   b. Else if # DLT=2/6 or 3/6, go to step 3, below,
   c. Else if # DLT>3/6, do not proceed to Phase 2.
3. Treat 3 patients at Level -2.
   a. If # DLT≤1/3, treat 3 more patients at Level -2,
      i. If #DLT≤1/6, proceed to Phase 2 at Level -2,
      ii. Else if #DLT≥2/6, do not proceed to Phase 2.
   b. If # DLT≥2/3, do not proceed to Phase 2.

If the trial does not proceed to Phase 2, an internal DSMB consisting of the study investigators and medical monitor will meet to discuss potential protocol amendments. DLTs will be determined in cycle 1 of therapy, though accrual will not be halted for DLT evaluation.

Schema - Phase 2 (n = 88)



** The following treatment schedule will be used for a total of two years of treatment. Pembrolizumab administration should not exceed 2 years.

- Cycles 1 to 4 (first 3 months of the first year): gemcitabine on D1 and D8, carboplatin and pembrolizumab on D1, and +/- berzosertib (M6620, VX-970) on D2 and D9, every three weeks
- Cycles 5 to 16 (last 9 months of the first year): pembrolizumab +/- berzosertib (M6620, VX-970) on D1, every 3 weeks
- Cycles 17 to 26 (second year): pembrolizumab on D1, every 6 weeks

Beyond 4 cycles (*i.e.*, 3 months), when berzosertib (M6620, VX-970) and pembrolizumab administration continues on D1 only without gemcitabine or carboplatin, the berzosertib (M6620, VX-970) and pembrolizumab may be dosed on the same day (D1) for patient convenience, where pembrolizumab is administered before berzosertib (M6620, VX-970).

Dose De-Escalation Schema

Phase 2, Arm A (n = 44)				
	Berzosertib (M6620, VX-970) (mg/m^2)	**Gemcitabine (mg/m^2)**	**Carboplatin (AUC)**	**Pembrolizumab (mg)**
Schedule				
Cycles 1-4 (every 3 weeks)	Days 2 and 9	Days 1 and 8	Day 1	Day 1
Cycles 5-16 (every 3 weeks)	Day 1	-	-	Day 1
Cycles 17-26 (every 6 weeks)	-	-	-	Day 1*
Dose Level (Cycles 1-16)				
1	135	800	5 (or 4)	200
-1	135	800	4 (or 3)	200
-2	90	600	3	200

Modifications are by dose level.

*Pembrolizumab will be administered as 200mg for Cycles 1-16 and 400mg for Cycles 17-26 and should not exceed 2 years of treatment.

Phase 2, Arm B (n = 44)			
	Gemcitabine (mg/m^2)	**Carboplatin (AUC)**	**Pembrolizumab (mg)**
Schedule			
Cycles 1-4 (every 3 weeks)	Days 1 and 8	Day 1	Days 1
Cycles 5-16 (every 3 weeks)	-	-	Day 1
Cycles 17-26 (every 6 weeks)	-	-	Day 1*
Dose Level (Cycles 1-16)			
1	1250	5	200
-1	1000	4	200
-2	750	3	200
Modifications are by individual agent.			

* Pembrolizumab will be administered as 200mg for Cycles 1-16 and 400mg for Cycles 17-26 and should not exceed 2 years of treatment.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Lead-in phase 1B only: To determine the recommended phase 2 dose (RP2D) of carboplatin in combination with berzosertib (M6620, VX-970) and gemcitabine/pembrolizumab, in patients with squamous cell non-small cell lung cancer (Sq-NSCLC).

1.1.2 Phase 2 only: To compare progression-free survival (PFS) of carboplatin/gemcitabine/pembrolizumab with and without berzosertib (M6620, VX-970) in patients with Sq-NSCLC, as measured by a hazard ratio in an intent-to-treat analysis.

1.2 Secondary Objectives

1.2.1 To compare progression-free survival (PFS) of carboplatin/gemcitabine/pembrolizumab with and without berzosertib (M6620, VX-970) in patients with Sq-NSCLC, as measured by a hazard ratio in an as-treated analysis.

1.2.2 To compare PFS of carboplatin/gemcitabine/pembrolizumab with and without berzosertib (M6620, VX-970) in patients with ataxia telangiectasia mutated (ATM)-deficient Sq-NSCLC, as measured by a hazard ratio.

1.2.3 To compare overall survival (OS) and overall response rate (ORR) of carboplatin/gemcitabine/pembrolizumab with and without berzosertib (M6620, VX-970), in patients with chemotherapy-naïve Sq-NSCLC.

1.2.4 To determine the systemic drug exposure of berzosertib (M6620, VX-970) and gemcitabine, as correlates of efficacy and toxicity.

1.2.5 To determine the safety and tolerability of berzosertib (M6620, VX-970) in combination with carboplatin/gemcitabine/pembrolizumab.

1.2.6 To observe and record anti-tumor activity. Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.3 Exploratory Objectives

1.3.1 To identify molecular subpopulations of patients who have increased sensitivity to the berzosertib (M6620, VX-970)/carboplatin/gemcitabine/pembrolizumab combination.

1.3.2 To explore the prognostic and predictive qualities of the ATM immunohistochemistry (IHC) assay for clinical response and PFS.

1.3.3 To explore inflammation-associated gene signatures and clinical response.

2. BACKGROUND

2.1 Study Disease

Squamous cell non-small cell lung cancer (NSCLC) accounts for approximately 30% of all NSCLCs worldwide (Perez-Moreno *et al*., 2012). While significant therapeutic advances in non-squamous NSCLCs have been driven by the discovery of targetable oncogenic drivers, therapeutic advances in NSCLC of squamous histology have lagged behind. This therapeutic divide has been narrowed in recent years with the development of monoclonal antibodies targeting the Programmed Cell Death Protein 1/Programmed Death Ligand-1 (PD1/PD-L1) pathway, which have been associated with significant survival advantages in the previously treated metastatic non-squamous and squamous NSCLC settings compared with single-agent chemotherapy (Borghaei *et al*., 2015; Brahmer *et al*., 2015; Herbst *et al.*, 2016; Rittmeyer *et al.*, 2017). In patients whose tumors express 50% or more PD-L1 (tumor proportion score; TPS ≥50^%), which is observed in about 30% of newly diagnosed NSCLC patients, the immune checkpoint inhibitor pembrolizumab is associated with a significant improvement in progression-free survival (PFS) and overall survival (OS) compared with platinum-based chemotherapy in the 1st-line setting (Reck *et al.*, 2016). While these findings have shifted the therapeutic landscape of squamous NSCLCs with high PD-L1 expression, the standard of care in the majority of patients with newly diagnosed advanced squamous NSCLC remains platinum-based chemotherapy. In this patient population, carboplatin-based doublet regimens are widely accepted as the standard of care in the US. A randomized phase 3 clinical trial identified the histology-specific benefit of gemcitabine-based doublet therapy when compared with pemetrexed-based doublet therapy in patients with squamous NSCLC (Scagliotti *et al.*, 2008). Studies comparing cisplatin- and carboplatin-based doublets suggest comparable clinical efficacy with improved tolerability with carboplatin-based therapy in the advanced NSCLC setting (Schiller *et al.*, 2002). More recently, two randomized phase 3 clinical trials demonstrated significant overall survival gains with the addition of pembrolizumab to carboplatin/pemetrexed and carboplatin/taxane in newly diagnosed non-squamous and squamous NSCLC, respectively (Gandhi *et al.*, 2018; Paz-Ares *et al.*, 2018). The survival benefit of a combined platinum doublet-immunotherapy approach was demonstrated across PD-L1 expression levels and in patients with a PD-L1 TPS <1%. An ongoing phase II is evaluating the combination of cisplatin, gemcitabine, cetuximab and avelumab in patients with squamous NSCLC (NCT03717155).

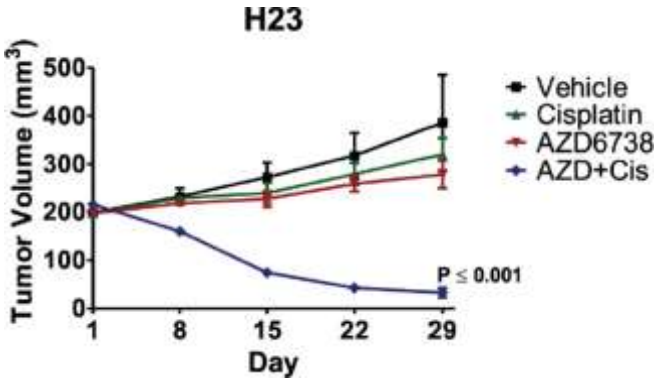


Figure 1: ATR inhibition with AZD6738 in combination with cisplatin results in near complete response in ATM-deficient H23 NSCLC xenografts models

Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia Rad3-related (ATR) protein kinases are the primary sensors of DNA damage and regulators of the DNA damage response (DDR). These DNA repair enzymes contribute to maintaining genomic integrity in response to cytotoxic chemotherapy, ultraviolet light, ionizing radiation (IR), or hypoxia (Fokas *et al.*, 2014; Pitts *et al.*, 2014; Yan *et al.*, 2014). Vendetti et al. at the UPMC Hillman Cancer Center (HCC) have demonstrated that inhibition of ATR with the small molecule AZD6738 potentiates the cytotoxicity of cisplatin and gemcitabine in human NSCLC cell lines with intact ATM kinase signaling (Vendetti *et al.*, 2015). In ATM-deficient NSCLC cell lines, AZD6738 potently synergizes with cisplatin (Vendetti *et al.*, 2015). In NSCLC xenograft models, the combination of AZD6738 and cisplatin results in near complete response of ATM-deficient NSCLC tumors, suggesting ATM-deficient tumors are particularly sensitized to ATR inhibition in combination with platinum (Figure 1) (Vendetti *et al.*, 2015).

Berzosertib (M6620, VX-970) is a highly potent and selective ATP-competitive inhibitor of ATR, and it has been shown to potentiate the antitumor effects of cisplatin, gemcitabine, irinotecan, and IR in several mouse xenograft models derived from human lung cancer cell lines and primary human tumor cells in a dose- and schedule-dependent manner (Fokas *et al.*, 2012; Jossé *et al.*, 2014; Hall *et al.*, 2014). Our lung cancer research group here in Pittsburgh has reported on the validation of a commercial antibody (ab32420) for the identification of ATM by immunohistochemistry and have shown that 41% (61 of 147; 95% CI 34%-50%) of lung adenocarcinomas are negative for ATM protein expression, identifying a significant proportion of lung cancer patients whose tumors may be exquisitely sensitized to ATR kinase inhibition (Villaruz *et al.*, 2016). Further unpublished preliminary data found a similarly high rate (39%) of squamous cell carcinomas to be negative for ATM protein expression (36 of 93; 95% CI 29%-49%) (Figure 2). Our clinical research team has been working closely with NCI-CTEP on the clinical development of berzosertib (M6620, VX-970); Dr. Villaruz is currently the study chair of NCI P9938, a UM1-sponsored phase I study of M6620 and irinotecan in patients with solid tumors, which was developed as part of the NCI-CTEP M6620 Drug Project Team.

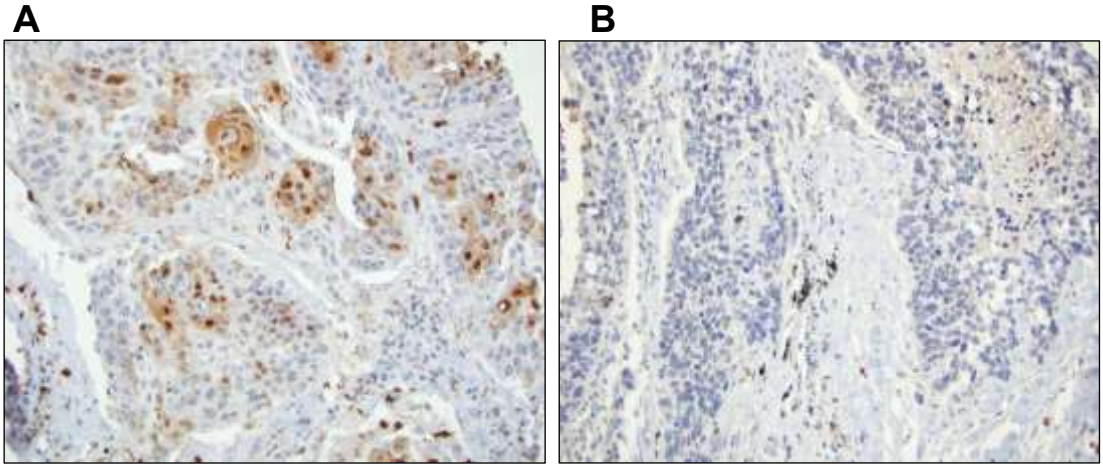


Figure 2: ATM loss is identified in squamous cell carcinoma of the lung with the rabbit monoclonal anti-ATM antibody ab32420 (AstraZeneca, 20X).
A. ATM positive squamous cell carcinoma of the lung, and **B.** ATM loss in squamous cell carcinoma of the lung.

2.2 CTEP IND Agents

2.2.1 Berzosertib (M6620, VX-970)

2.2.1.1 Berzosertib (M6620, VX-970) Mechanism of Action

Berzosertib (M6620, VX-970) (formerly VX-970) is a potent and selective ATP-competitive inhibitor of ataxia telangiectasia and Rad3-related protein (ATR) kinase, with an inhibition constant (K_i) <0.3 nM (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). In comparison, berzosertib (M6620, VX-970) was a >100-fold weaker inhibitor of ataxia-telangiectasia mutated (ATM) kinase (K_i=34 nM) and >1000-fold less effective against other closely related kinases, such as DNA-PK (K_i>4 mcM), mTOR (K_i>1 mcM), and PI3K-gamma (K_i=0.22 mcM) (Fokas *et al.,* 2012). Overall, berzosertib (M6620, VX-970) was >50-fold more selective for ATR than for 290 of 291 kinases tested (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). Cellular 50% inhibitory concentration (IC_{50}) of ATR was 0.019 mcM, demonstrating good selectivity over ATM (IC_{50}=2.1 mcM) and DNA-PK (IC_{50}=18.1 mcM) (Fokas *et al.*, 2012).

Berzosertib (M6620, VX-970) potentiates activity of multiple DNA-damaging agents in numerous cancer cell lines (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). In contrast, normal cells treated with DNA-damaging agents tolerated ATR inhibition with just a reversible increase in growth arrest. Treatment of cancer cell lines with berzosertib (M6620, VX-970) and various DNA-damaging agents led to sustained berzosertib (M6620, VX-970)-dose-dependent decreases in the levels of CHK1pS^{345} induced by chemotherapy; CHK1pS^{345} is the main substrate of ATR (Fokas *et al*., 2012; Hall *et al*., 2014). Radiosensitization of pancreatic ductal adenocarcinoma cells by berzosertib (M6620, VX-970) was associated with inhibition of homologous recombination (HR) repair (Fokas *et al*., 2012). Berzosertib (M6620, VX-970) caused persistent increase in γH2AX levels both *in vitro* and *in vivo*. Adding berzosertib (M6620, VX-970) to gemcitabine-based chemoradiation dramatically enhanced antitumor effects, resulting in early and late apoptosis and abrogation of radiation-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 HR repair of double-strand breaks (DSBs) and for survival.

2.2.1.2 Berzosertib (M6620, VX-970) Nonclinical Data

In tumor cell line and patient-derived tumor xenograft mouse models, berzosertib (M6620, VX-970) dose-dependently enhanced antitumor effects of multiple DNA-damaging drugs and radiation (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). Dose-schedule optimization studies in xenograft models demonstrated that timing of berzosertib (M6620, VX-970) administration was critical for maximum activity in combination with a DNA-damaging agent. In combination with cisplatin or gemcitabine, maximum activity was observed when berzosertib (M6620, VX-970) was given 12 to 24 hours after the DNA-damaging agent. In contrast, when combined with irinotecan, concurrent treatment was the most effective while delayed administration of berzosertib (M6620, VX-970) was completely ineffective.

Non-clinical Pharmacology: In non-clinical species, berzosertib (M6620, VX-970) had a high volume of distribution; tissue exposure, including tumor, was high (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). The blood to plasma concentration ratios ranged from 1.6 to 1.79 in nonclinical species and was 1.36 in human blood. berzosertib (M6620, VX-970) had high plasma protein binding (mainly to albumin), and the free fraction in human blood was 3.29%. In the whole blood, berzosertib (M6620, VX-970) half-life was 11.6 and 9.8 hours in rats and dogs, respectively. Berzosertib (M6620, VX-970) is primarily metabolized through cytochrome P450 (CYP) isoform 3A4 and thus strong inducers or inhibitors of CYP3A4 may alter berzosertib (M6620, VX-970) kinetics and blood levels. Berzosertib (M6620, VX-970) is a weak inhibitor of UDP-glucuronosyltransferases (UGTs) with IC_{50}s >10 mcM, and a weak to moderate inhibitor of transporters such as P-glycoprotein (P-gp; IC_{50}=14 mcM) and breast cancer resistance protein (BCRP; IC_{50}=3.4 mcM).

Non-clinical Toxicology: Berzosertib (M6620, VX-970) toxicology studies in rats and dogs identified the liver, testes, and peripheral blood cell populations as target organs following oral or IV administration (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). Liver and peripheral blood toxicities were reversed within 4 weeks of discontinuation of berzosertib (M6620, VX-970). Berzosertib (M6620, VX-970) had no hemolytic potential in human blood or compatibility issues in human plasma as a clinical IV formulation at 20 mg/mL. Berzosertib (M6620, VX-970) was not genotoxic in the *in vitro* Ames assay, but was genotoxic in an *in vitro* micronucleus screening test. Testicular degenerative changes were observed in rats and dogs. Based on these genotoxicity studies, a potential risk that berzosertib (M6620, VX-970) can affect maturing germ cells in humans cannot be excluded. No reproductive toxicity tests have been performed, but because of its inhibition of DNA-damage repair and *in vitro* genotoxicity, the potential for teratogenicity should be considered high. Berzosertib (M6620, VX-970) absorbs light in UV-visible spectrum and phototoxic effects on mouse fibroblasts were observed.

Recently, the addition of berzosertib (M6620, VX-970) and avelumab to a carboplatin or cisplatin regimen was tested in MC38 murine colorectal tumor model (Alimzhanov *et al.*, 2019). The triplet combination demonstrated a statistically significant improvement in the control of tumor growth, more frequent tumor regressions, and increased overall survival, relative to the doublet combination (berzosertib (M6620, VX-970) and avelumab only). Animals with complete tumor responses were re-challenged with MC38 tumor cells, and subsequently found to be refractory to the second tumor inoculation, suggesting the durability of the anti-tumor immunity in complete responders. Further, the triplet combination was found to be well-tolerated, as assessed by body weight and clinical signs.

2.2.1.3 Berzosertib (M6620, VX-970) Clinical Data

Clinical Pharmacokinetics: Berzosertib (M6620, VX-970) systemic exposures expressed as either maximum concentration (C_{max}) or area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) tended to increase proportionally with increasing dose after IV administration of berzosertib (M6620, VX-970) as a single agent at the doses tested (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). The mean terminal elimination half-life was approximately 17 hours across all dose groups. Mean berzosertib (M6620, VX-970) plasma exposures, when berzosertib (M6620, VX-970) was given 1 day after administration of

gemcitabine, cisplatin, or carboplatin, were largely similar to exposures observed for berzosertib (M6620, VX-970) administered alone at equivalent doses.

Clinical Safety: Berzosertib (M6620, VX-970) appeared to be well-tolerated when administered as either single-agent therapy or in combination with 1 or 2 chemotherapeutic agents to subjects with solid tumors (berzosertib (M6620, VX-970) Investigator's Brochure, 2018). No dose-limiting toxicities (DLTs) were observed when berzosertib (M6620, VX-970) was administered as single-agent therapy at doses from 18 mg/m^2 to 480 mg/m^2. Almost all patients who received berzosertib (M6620, VX-970) in combination with chemotherapy experienced at least one treatment-emergent adverse events (AEs). Frequency of grade ≥3 AEs, serious AEs (SAEs), and AEs leading to study drug discontinuation notably varied across different combinations. Fatal AEs were infrequent.

Infusion-related reactions (local or systemic), nausea, and vomiting are considered adverse drug reactions (ADRs) for berzosertib (M6620, VX-970), and myelosuppression events are considered ADRs for berzosertib (M6620, VX-970) in combination with carboplatin (berzosertib (M6620, VX-970) Investigator's Brochure, 2018).

- Infusion-related reactions (local or systemic) for berzosertib (M6620, VX-970) are the following:
    - Systemic infusion-related reactions to berzosertib (M6620, VX-970) 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 berzosertib (M6620, VX-970) have been serious, including those described as acute hypersensitivity reactions. In almost all cases, these reactions occurred within minutes of the second exposure to berzosertib (M6620, VX-970) and they included hypotension and mental status changes. All subjects fully recovered with standard care procedures.
    - Local infusion-related reactions to berzosertib (M6620, VX-970), sometimes described as infusion site reactions, may include signs or symptoms such as infusion site erythema, swelling, or pain. The IV catheter through which berzosertib (M6620, VX-970) is infused should be monitored for evidence of erythema, tenderness, or induration. To minimize the possibility of phlebitis, berzosertib (M6620, VX-970) should be administered through a large-bore catheter into a large-caliber peripheral vein.
- Nausea and vomiting have occurred commonly in patients receiving berzosertib (M6620, VX-970) monotherapy. Many of the affected subjects experienced these events on the same day as berzosertib (M6620, VX-970) was administered, and there was some suggestion of a dose response.

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

2.3 Commercial Agents

2.3.1 Pembrolizumab

Pembrolizumab (Keytruda®), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co. for the treatment of cancer. Pembrolizumab is approved for treatment of melanoma in several countries; in the United States (US) and European Union it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by a Food and Drug Administration (FDA)-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. Pembrolizumab is approved in the US for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

Pembrolizumab has demonstrated initial clinical efficacy in single-arm monotherapy trials in patients with NSCLC, HNSCC, urothelial cancer, gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure (2017).

2.3.2 Gemcitabine

Gemcitabine is a deoxycytidine chain-terminating nucleoside analogue that kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary (Gemcitabine FDA Package Insert, revised 5/2019). It is metabolized to the diphosphate and triphosphate metabolite forms. Gemcitabine diphosphate inhibits the enzymatic generation of deoxynucleoside triphosphates (dNTPs) for DNA synthesis, resulting in reductions in dNTP concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. Together, these activities enhance the incorporation of gemcitabine triphosphate into DNA, blocking further DNA synthesis and resulting in apoptosis. Gemcitabine as a single agent or combined with other chemotherapies is FDA-approved for the treatment of relapsed ovarian cancer, metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer. Gemcitabine combinations are also commonly used in the treatment of relapsed or refractory non-Hodgkins and Hodgkins lymphomas and are supported by the guidelines of the National Comprehensive Cancer Network.

2.3.3 Carboplatin

The standard of care in the majority of patients with newly diagnosed advanced squamous NSCLC remains platinum-based chemotherapy. In this patient population, carboplatin-based doublet regimens are widely accepted as the standard of care in the US. A randomized phase 3 clinical trial identified the histology-specific benefit of gemcitabine-based doublet therapy when compared with pemetrexed-based doublet therapy in patients with squamous NSCLC (Scagliotti *et al.*, 2008).

Studies comparing cisplatin- and carboplatin-based doublets suggest comparable clinical efficacy with improved tolerability with carboplatin-based therapy in the advanced NSCLC setting (Schiller *et al.*, 2002). More recently, two randomized phase 3 clinical trials demonstrated significant overall survival gains with the addition of pembrolizumab to carboplatin/pemetrexed and carboplatin/taxane in newly diagnosed non-squamous and squamous NSCLC, respectively (Gandhi *et al.*, 2018; Paz-Ares *et al.*, 2018). The survival benefit of a combined platinum doublet-immunotherapy approach was demonstrated across PD-L1 expression levels and in patients with a PD-L1 TPS <1%. Ongoing clinical trials are exploring the safety and efficacy of the PD-L1 inhibitor, avelumab, alone and in combination with platinum-based chemotherapy in multiple tumor types, including newly diagnosed NSCLC (NCT02576574, NCT03317496). An ongoing phase II is evaluating the combination of cisplatin, gemcitabine, cetuximab and avelumab in patients with squamous NSCLC in study disease background (NCT03717155).

Carboplatin use has previously been described in patients with “anaplastic” or “aggressive variant” prostate cancer (Aparicio *et al.*, 2013). 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 (Cheng *et al.*, 2016; Pomerantz *et al.*, 2017). 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 (Bunting *et al.*, 2012); BRCA1 mutations that lead to defects in alternate DNA repair pathways such as nucleotide excision repair but retain proficiency in homologous recombination repair (Johnson *et al.*, 2016); and mutation of other genes involved in nucleotide excision repair such as ERCC6 and ERCC4 (Ceccaldi *et al.*, 2015). 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

In this protocol, we propose a phase 2 clinical trial aimed at the evaluation of berzosertib (M6620, VX-970) in combination with carboplatin and gemcitabine and pembrolizumab in patients with non-small cell lung cancer (NSCLC) of squamous cell histology (Sq).

NCI P9948, investigating this same triplet combination in an ovarian cancer population, has identified the MTD to be berzosertib (M6620, VX-970) 90 mg/m^2 in combination with gemcitabine 800 mg/m^2 and carboplatin AUC 5 in patients previously treated with platinum-based chemotherapy. In this study, the target population will be platinum-naïve (or +1 year out from platinum-based treatment) Sq-NSCLC patients. In general, these patients are expected to tolerate higher doses of berzosertib (M6620, VX-970) than ovarian cancer patients who have progressed after cytotoxic chemotherapy. A lead-in phase 1B study will, therefore, be first conducted to assess the safety and tolerability of the established triplet RP2Ds of gemcitabine (800 mg/m^2) and carboplatin (AUC 5) in combination with a higher dose of berzosertib (M6620, VX-970) (135 mg/m^2).

Although most of the berzosertib (M6620, VX-970) (ATRi) combination data has been generated with cisplatin, clinical responses have been observed with gemcitabine alone (3/18 partial responses in NSCLC, including 1 squamous NSCLC, 15 stable disease) and with carboplatin alone (1/21 PR, 14 SD). Moreover, carboplatin shows similar synergistic effects with berzosertib (M6620, VX-970) when tested in a panel of human NSCLC cell lines (see berzosertib (M6620, VX-970) Investigator's Brochure, 2018). Taken together, these findings suggest that similar synergistic effects would be observed between berzosertib (M6620, VX-970) and carboplatin in the clinical setting.

2.5 Correlative Studies Background

2.5.1 ATM expression

Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia Rad3-related (ATR) protein kinases are the primary sensors of DNA damage and regulators of the DNA damage response (DDR). These DNA repair enzymes contribute to maintaining genomic integrity in response to cytotoxic chemotherapy, ultraviolet light, ionizing radiation (IR), or hypoxia (Fokas *et al.*, 2014; Pitts *et al.*, 2014; Yan *et al*., 2014). Investigators at the UPMC Hillman Cancer Center (HCC) have demonstrated that inhibition of ATR with the small molecule AZD6738 potentiates the cytotoxicity of cisplatin and gemcitabine in human NSCLC cell lines with intact ATM kinase signaling (Vendetti *et al.*, 2015). In ATM-deficient NSCLC cell lines, AZD6738 potently synergizes with cisplatin (Vendetti *et al.*, 2015). In NSCLC xenograft models, the combination of AZD6738 and cisplatin results in near complete response of ATM-deficient NSCLC tumors, suggesting ATM-deficient tumors are particularly sensitized to ATR inhibition in combination with platinum (Vendetti *et al.*, 2015).

berzosertib (M6620, VX-970) is a highly potent and selective ATP-competitive inhibitor of ATR, and it has been shown to potentiate the antitumor effects of cisplatin, gemcitabine, irinotecan, and IR in several mouse xenograft models derived from human lung cancer cell lines

and primary human tumor cells in a dose- and schedule-dependent manner (Josse *et al.*, 2014; Hall *et al.*, 2014). Our lung cancer research group here in Pittsburgh has reported on the validation of a commercial antibody (ab32420) for the identification of ATM by immunohistochemistry and have shown that 41% (61 of 147; 95% CI 34%-50%) of lung adenocarcinomas are negative for ATM protein expression, identifying a significant proportion of lung cancer patients whose tumors may be exquisitely sensitized to ATR kinase inhibition (Villaruz *et al.*, 2016). Further unpublished preliminary data found a similarly high rate (39%) of squamous cell carcinomas to be negative for ATM protein expression (36 of 93; 95% CI 29%-49%).

We will test the hypothesis that berzosertib (M6620, VX-970) in combination with carboplatin/gemcitabine/pembrolizumab is associated with superior progression-free survival (PFS) when compared with carboplatin/gemcitabine/pembrolizumab alone in patients with chemotherapy-naïve ATM-deficient Sq-NSCLC.

2.5.2 Whole Exome Sequencing

Tumors harboring pre-existing defects in the DNA damage response (mutations in p53, ATM, FANCA, FANCC, and FANCG, or BRCA) may demonstrate enhanced sensitivity to the combination of ATR inhibition with berzosertib (M6620, VX-970) and carboplatin/gemcitabine/pembrolizumab.

We will test the hypothesis that molecularly defined subpopulations may be particularly sensitive to the addition of berzosertib (M6620, VX-970) to chemo-immunotherapy.

2.5.3 RNASeq

Expression of inflammation-associated gene signatures in tumor infiltrating lymphocytes may be useful indicators of response to immune checkpoint inhibition. We will test the hypothesis that inflammation-associated gene expression may correlate with response to berzosertib (M6620, VX-970) and carboplatin/gemcitabine/pembrolizumab.

2.5.4 PK of Gemcitabine and berzosertib (M6620, VX-970)

Berzosertib (M6620, VX-970) is a novel agent, and the proposed PK studies will further define the properties in a homogeneous population. Gemcitabine PK, though more established, has been proposed for therapeutic drug monitoring (Kozo *et al.*, 2017), and after defining the PK in this trial, we will explore correlations with toxicity and response. Cytidine deaminase (CDA) is the main enzyme responsible for gemcitabine and cytarabine degradation. CDA serum activity has been reported as a predictive marker for gemcitabine related toxicity (Ciccolini *et al.*, 2010; Peters *et al.*, 2014).

3. PATIENT SELECTION

All eligibility and exclusion criteria apply to Phase 1B and Phase 2 patients.

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed NSCLC of predominantly squamous cell histology, Stage IV (AJCC 8th edition).

3.1.2 Patients must have measurable disease, as defined by RECIST v1.1 (See Section 12.1).

3.1.3 Patients must have tumor tissue available at time of enrollment or be willing to undergo a biopsy for integrated biomarker studies.

3.1.4 Patients with a history of prior platinum-based systemic chemotherapy given as neoadjuvant, adjuvant, or consolidation therapy for early stage or loco-regionally advanced NSCLC are eligible, if therapy is completed one year prior to initiation of treatment. Patients must not have had prior systemic chemotherapy or immunotherapy for metastatic disease.

3.1.5 Patients with prior immunotherapy given as neoadjuvant, adjuvant, or consolidation therapy for early stage or loco-regionally advanced disease are eligible, if treatment is completed one year prior to initiation of treatment.

3.1.6 Patients must have ECOG performance status of 0-1 (Karnofsky >60%, see Appendix A).

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

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	> lower limit of normal (LLN)
– platelets	> LLN
– total bilirubin	≤ institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN
– creatinine	≤ institutional ULN OR
– glomerular filtration rate (GFR)	≥60 mL/min/1.73 m^2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73 m^2 (see Appendix B)

3.1.9 Patients with human immunodeficiency virus (HIV) infection are eligible if they are on effective anti-retroviral therapy with undetectable viral load within 6 months, provided there is no expected drug-drug interaction.

3.1.10 Patients with evidence of chronic hepatitis B virus (HBV) infection are eligible if the HBV viral load is undetectable on suppressive therapy (if indicated), provided there is no

expected drug-drug interaction.

3.1.11 Patients with a history of hepatitis C virus (HCV) infection are eligible if they have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.12 Patients with treated brain metastases are eligible if clinically stable, *i.e.*, on stable doses of anti-convulsant therapy and/or stable doses of corticosteroids which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

3.1.13 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.14 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.15 Patients must be willing to comply with birth control requirements: The effects of the agents in this study (or similar agents) on the developing human fetus are either unknown, or known to be teratogenic, embryotoxic, and fetotoxic in mice and rabbits. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months after completing treatment administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to avoid donating sperm for during the study period, and to use adequate contraception prior to the study, for the duration of study participation, and for 6 months after completion completing treatment administration. Acceptable contraceptives are further described in Appendix C.

3.1.16 Patients must have the ability to understand and willingness to sign a written informed consent document. Participants with impaired decision-making capacity who have a legally-authorized representative and/or family member available will also be eligible.

3.2 Exclusion Criteria

3.2.1 Patients with severe intercurrent illness or comorbidity are not eligible.

3.2.2 Patients with contraindications to immunotherapy (*e.g.*, solid organ transplant or active autoimmune disease requiring immunosuppressant therapy within 2 years of enrollment) are not eligible.

3.2.3 Patients with prior systemic chemotherapy for metastatic disease are not eligible.

3.2.4 Patients who are receiving any other investigational agents are not eligible.

3.2.5 Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to berzosertib (M6620, VX-970), pembrolizumab, gemcitabine, carboplatin, or other agents used in study are not eligible.

3.2.6 Patients with severe bone marrow depression or significant bleeding are not eligible.

3.2.7 Patients with psychiatric illness/social situations that would limit compliance with study requirements are not eligible.

3.2.8 Berzosertib (M6620, VX-970) is primarily metabolized by CYP3A4; therefore, concomitant administration with strong inhibitors of CYP3A4 (*e.g*. clarithromycin, itraconazole, ketoconazole, HCV and HIV protease inhibitors, nefazodone, posaconazole, telithromycin, voriconazole) or strong inducers of CYP3A4 (*e.g*. carbamazepine, rifampin, phenobarbital, phenytoin, St. John's Wort) should be avoided. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. 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. Appendix D should be provided to patients.

3.2.9 Pregnant women are excluded from this study because the agents in this study may have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the study agents, breastfeeding should be discontinued if the mother is treated with the study agents berzosertib (M6620, VX-970), pembrolizumab, gemcitabine, or carboplatin.

3.2.10 Berzosertib (M6620, VX-970) should be used with caution in patients with clinical evidence of germline defects in their DNA damage repair pathway (for example, patients with Li-Fraumeni syndrome or ataxia telangiectasia) due to a possible increase in the toxicity of DNA-damaging agents when paired with berzosertib (M6620, VX-970).

3.2.11 Patients must not have received or be scheduled to receive radiation therapy within 7 days or less from gemcitabine administration.

3.2.12 Current or prior use of immunosuppressive medication within 28 days before the first dose of pembrolizumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

3.2.13 Patients must not have received an allogeneic stem cell transplant.

3.2.14 Patients must not have active, uncontrolled infections or recently received active vaccinations.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

4.2 Site Registration

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

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 IRB Manager 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).

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

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

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

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

4.2.1 Downloading Regulatory Documents

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

- 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-PA015**, and protocol number 10313,
- 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.)

4.2.2 Protocol Specific Requirements For 10313 Site Registration

- A Study Initiation Visit (SIV) or Site Initiation Teleconference (SIT) is required for each

participating site prior to activation. The local site PI must participate on the call. To schedule a SIV or SIT, please email the study coordinator listed on the front pages of the protocol.

- 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 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 using 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.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

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

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

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

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 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: Must be on an LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

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

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

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

applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may 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.

Patient enrollment for this study will be facilitated using the Slot Reservation System (Phase 1B only) in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

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 in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **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 5.4.

To register a patient, the following documents must be submitted to the Coordinating Center at least 48 hours prior to planned start of protocol therapy:

• Completed Eligibility Checklist
• Copy of required laboratory tests
• Copy of signed and dated Informed Consent Form (ICF)
• Copy of signed and dated HIPAA Authorization form (if separate from ICF)
• Copy of all required scan reports
• Copy of pathology report(s)
• Copy of History and Physical and or Progress Notes (including oncologic treatment history, vital signs, height, weight, performance status, concurrent medications)

• Copy of EKG

All registration source documents should be properly de-identified prior to submitting to the Coordinating Center. Registration documents may be submitted to the Coordinating Center via fax (412-647-0949) or e-mail (phase1@upmc.edu). Upon receipt of the required source documentation, authorized staff at the Coordinating Center will confirm all eligibility requirements.

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.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 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. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival		
	• 4 slides (charged unstained slides with 5-micron thick sections), freshly cut[1] (mandatory)	Sanja Dacic UPMC Pathology dacics@upmc.edu
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)[1] (mandatory) If a block is not available, then submit:	EET Biobank

	• 1 H&E stained slide (3-5 µm) • 20 unstained, uncharged, air-dried slides (10 µm)	
Baseline (specimens to be collected **only** if archival tissue is insufficient or unavailable)		
	• 4 slides (charged unstained slides with 5-micron thick sections), freshly cut[2] (mandatory)	Sanja Dacic UPMC Pathology dacics@upmc.edu
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)[2] (mandatory) If a block is not available, then submit: • 1 H&E stained slide (3-5 µm) • 20 unstained, uncharged, air-dried slides (10 µm)	EET Biobank
Baseline		
	• 10 mL blood in EDTA Tube (mandatory)	EET Biobank
	• Peripheral blood serum (red top tube, 3-4 mL) (mandatory)	Jan Beumer Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC beumerjh@upmc.edu
Cycle 1, Day 1		
• pre-dose • 25 minutes (-5 min) post start of gemcitabine (~5 min before end of infusion)	• 1 x 4 mL blood in purple top EDTA tube spiked with THU for each PK time point (mandatory)	Jan Beumer Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC beumerjh@upmc.edu
Cycle 1, Day 2		
• pre-dose • 30 minutes (+/-5 min) post start of berzosertib (M6620, VX-970) • 55 minutes (+/-5 min) post start of berzosertib (M6620, VX-970) (~5	• 1 x 4 mL blood in purple top EDTA tube spiked with THU for each PK time point (mandatory for patients receiving M6620)	Jan Beumer Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC beumerjh@upmc.edu

min before end of infusion) • 15 min (+/-5 min) post end of berzosertib (M6620, VX-970) • 30 min (+/-5 min) post end of berzosertib (M6620, VX-970) • 1h (+/-5 min) post end of berzosertib (M6620, VX-970)		
[1]For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51). [2]For new biopsies, a completed copy of the Tissue Biopsy Verification Form (Appendix G), a copy of the radiology report or operative report from the biopsy procedure *and,* if available, the diagnostic pathology report must be sent to the EET Biobank. If the corresponding pathology report becomes available, then it should be uploaded to RAVE and a copy should be provided to the EET Biobank.		

5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies

Biopsy #: 1				
Trial Time Point: Baseline (To be conducted only if no archival tissue is available).				
IR Biopsy Definition: Research – No Clinical Impact				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	ATM expression	>50%	• FFPE. • 4 slides needed for the ATM IHC assay (four charged unstained slides with 5-micron thick sections), freshly cut
2	Integrated	WES	>50%	• FFPE. • tumor tissue block (preferred) or: • 1 H&E stained slide, and • 20 unstained, uncharged, air-dried slides (10 μm)
3	Exploratory	RNAseq	*(to be conducted using tissue from WES assay)*	

Note: Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system.

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

Kits are not provided for this protocol. Sites will use institutional supplies for specimen collection and shipment.

5.3.2 Scheduling of Specimen Collections (for specimens being sent to the EET Biobank)

Please adhere to the following guidelines when scheduling procedures to collect tissue:

- FFPE tissue may collected any day.
- Fresh blood specimens may be collected and shipped Monday through Friday.

5.3.3 Scheduling of Specimen Collections (for specimens being sent to the University of Pittsburgh)

Beumer Laboratory: Blood samples will be collected at the timepoints specified in Section 5.1. Frozen plasma/serum will be shipped overnight on either Monday, Tuesday, or Wednesday (and not before a federal or university holiday) to the Beumer Laboratory at the University of Pittsburgh.

UPMC Pathology: Tumor tissue specimens collected during biopsy procedures and fixed in formalin, after sectioning, must be shipped within 1 business day of completion of fixation. Slides may be shipped overnight Monday through Thursday for arrival on Tuesday through Friday at UPMC Pathology.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System (STS) 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 3.
- 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 or any other 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, date of birth, 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.

The Shipping List report **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 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, serum)
- Collection date and time (to be added by hand)

5.4.2.2 Tissue Specimen Labels (for WES/RNAseq samples going to the Biorepository)

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 paraffin-embedded [FFPE] Block,

Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report
- Collection date (to be added by hand)
- Slide section number (only if archival or baseline tissue is submitted as slides) (to be added by hand)

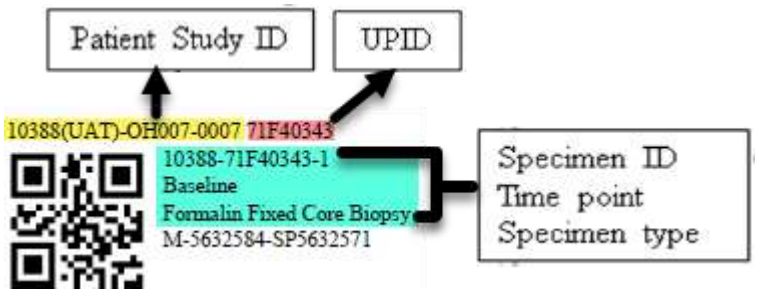
5.4.2.3 Tissue Specimen Labels (for ATM expression samples going to UPMC Pathology)

Include the following on all tissue specimens:
- Patient Study ID
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Fixation Time
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date
- Date slides were cut

5.4.2.4 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5” high and 1.28” wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers:

https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following 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. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 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.

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.

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

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, and number of

labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 5.4.2. 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. 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) and/or the Tissue Biopsy Verification form (when applicable, Appendix G). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. **Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document** (either by adding a label or hand writing).

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 sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status**.

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

- Shipping List report is available at the site level.
- 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).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Specimen Collection

See Section 5.4.2 for labeling instructions.

5.5.1 Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen for WES and RNAseq

If archival FFPE tissue will be submitted, then the following criteria must be met:

- Tissue must have been collected within 3 months prior to registration
- FFPE tumor tissue block(s) must be submitted. The optimal block is at least >50% tumor. Specimen size requirements are as follows:
    - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
    - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available:

- One (1) H&E slide, (3-5 μm)
- Twenty (20) (10 μm) unstained air-dried uncharged slides.
    - Process and number slides sequentially (e.g., H&E stained slide should be created first and labeled with "1," and additional unstained slides should be processed next and be labeled 2 – n.

5.5.2 Archival Tumor Specimen for ATM Expression

- Four freshly-cut charged, unstained slides from FFPE tissue, 5 microns (mcm) thick.
- Fixation time should be between 6-12 hours (Lindeman *et al.*, 2013).

5.5.3 Collection of Blood in EDTA Tube for WES/RNAseq Germline Control

1. Label EDTA tubes according to the instructions in Section 5.4.2.
2. Collect 10 mL of blood in EDTA tube(s) and gently invert tube to mix.
3. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
4. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.5.4 Collection of Blood in Red Top Tube for Serum Processing for PK Studies

Document exact start and stop times of each infusion and exact times of blood draws per Appendix F.

1. Label one 3-4 mL red-top tube according to the instructions in Section 5.4.2.1. (*e.g.* BD vacutainer 367812 plastic 13 x 75 4 mL tube), note that no tetrahydrouridine (NO THU) shall be added to this tube.
2. Collect 3-4 mL of whole blood in red-top tube.
3. Allow blood to clot upright at room temperature for at least 30 minutes (maximum 60 minutes) prior to processing. If the blood is not immediately processed after the clotting period, then tubes should be stored (after the 30-60 minutes of clotting time) at 4°C for no longer than 4 hours. Process serum from red top tubes by centrifuging for 10 minutes at 1,200 × g at room temperature.
4. **Using a clean transfer pipette,** aliquot serum into the labeled (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.4.2) cryovials at an aliquot volume of 1 mL per tube. Avoid picking up red blood cells when aliquoting by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube. Tightly secure the cap of the vials before storage. Aliquoting and freezing of serum specimens should be completed within 1 hour of centrifugation.
5. Store serum cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to delivering to laboratory. Do not allow specimens to thaw after freezing.

5.5.5 Collection of Blood in EDTA Tubes for Plasma Processing for PK Studies

General Considerations

Blood samples to be obtained through a peripheral or central line blood draw. Samples should be drawn from the opposite arm if infusion is a peripheral infusion. Samples should NOT be drawn from the infusion line. EDTA Vacutainer tubes shall be prepared by addition of THU solution to prevent *ex vivo* degradation of gemcitabine.

Preparation of Tubes with THU

Prepare an aqueous stock solution of tetrahydrouridine (THU) at 10 mg/mL. THU can be added to Vacutainer tubes up to several days in advance without causing significant loss of vacuum (keep in fridge, no more than 1-2 weeks).

1. Using a 3/10 cc insulin syringe or other similar sized syringe with a fine needle, draw up 10 mcL of the THU solution for each 1 mL of blood to be drawn and transfer it to a Vacutainer tube by piercing the stopper.
2. Do not draw up THU solution for more than one tube at a time. You will not be able to control the volume of THU solution that leaves the needle, as it is sucked out by the vacuum.

3. Because of the fine needle, you will not lose the vacuum (apart from the volume added) in the collection tube.

Drawing and Processing

1. Label EDTA tube(s) (*e.g.*, BD vacutainer 367861 plastic 13 x 75 4 mL tube) according to the instructions in Section 5.4.2.
2. Collect 3-4 mL of whole blood in EDTA (purple top) tube(s).
3. Process plasma by centrifuging for 10 minutes at approximately 1,200 × g at room temperature.
4. Using a clean transfer pipette, transfer 1 mL of plasma into each of the labeled cryovials (using the label printed from the ETCTN Specimen Tracking System or following the instructions in Section 5.4.2.1). Avoid picking up the blood cells when aliquoting by keeping the pipet above the cell layers and leaving a small amount of plasma in the tube. Tightly secure the cap of the vials before storage. Aliquoting and freezing of plasma specimens should be completed within 1 hour of centrifugation.
5. Store plasma cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to delivering to laboratory. Do not allow specimens to thaw after freezing.

5.6 Shipping Specimens to the EET Biobank from the Clinical Site

5.6.1 General Shipping Information

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must sent to the EET Biobank as soon as possible and be uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

For new biopsies, include a completed copy of the Tissue Verification Form (Appendix G), and a copy of the radiology or operative report, *and,* if available, the diagnostic pathology report with the shipment.

5.6.1.1 Required Forms for Specimen Submissions

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	Required Forms
Archival	1. Shipping List 2. Corresponding Pathology Report

Tissue	Required Forms
New Biopsy	1. Shipping List 2. Tissue Biopsy Verification Form 3. Diagnostic Pathology Report 4. Surgical and/or Radiology Report
Blood	1. Shipping List

5.6.2 Specimen Shipping Instructions

Archival or Baseline (FFPE) tissue may be shipped on Monday through Thursday.

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

5.6.2.1 Shipping of FFPE Blocks or Glass Slides

1. Before packaging blocks or slides, verify that each specimen is labeled according to Section 5.4.2.2.
2. Blocks should be placed in a special block holder, if possible. Glass slides are to be placed in plastic slide holders. Place tissue paper on top of the separated slides prior to closing the slide holder to reduce slide movement during shipment.
3. Place the blocks or slides in a reinforced cardboard shipping box with appropriate packaging filler to minimize movement of specimens within the shipping box.
4. Include a copy of the corresponding pathology report, if available, and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.
6. Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2.2 Shipping Blood in Your Own Container

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in section 5.4.2.
2. Place the blood collection tube(s) in a zip-lock bag.
3. Place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System into a sturdy shipping container. In winter months, please use an insulated container and include extra insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
6. Close the container and tape shut.

7. Attach a shipping label to the top of the shipping container.
8. Attach an Exempt Human Specimen sticker to the side of the container.
9. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.3 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
2200 International Street
Columbus, OH 43228
PH: (614) 722-2865
FAX: (614) 722-2897
E-mail: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

5.6.4 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
PH: (614) 722-2865
E-mail: BPCBank@nationwidechildrens.org

5.7 Shipping Specimens to Other Laboratories from the Clinical Site

5.7.1 Shipping of Specimens to UPMC Pathology

5.7.1.1 Specimen Shipping Instructions

Samples should be labeled according to Section 5.4.2.3.

For all archival tissue, the corresponding anatomical clinical pathology report is required in the package. If this is not available at the time of shipment, then it must be sent to the address below when it becomes available. The pathology report must state the disease diagnosis made by the reviewing pathologist.

For formalin-fixed biopsies, if the corresponding anatomical pathology report is not

available at the time of shipment, then it must be sent to the address below if it becomes available. The pathology report, if available, must state the disease diagnosis made by the reviewing pathologist.

Unstained slides should be placed into an appropriately labeled transport container. Ship using 4°C cool packs. Do not freeze the specimen. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.7.1.2 Shipping Address

Sanja Dacic, M.D., Ph.D.
Professor of Pathology
Rm. PUH C608
UPMC-PUH
200 Lothrop St.
Pittsburgh, PA 15213

5.7.1.3 Contact Information for Assistance

Office Telephone: 412-647-8694
Email Laboratory Director: dacics@upmc.edu

5.7.2 Shipping of Specimens to Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC (Beumer PK Laboratory)

5.7.2.1 Specimen Shipping Instructions

Preparing the shipment:

1. Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", L x W x H).

2. Organize the samples by Patient and Time point in the box.

3. Do not store in plastic bags (they break on dry-ice and labels will detach).

4. A copy of each of the pharmacokinetic sample collection forms for the respective patients should be included with each shipment (see Appendix F). To prevent problems with illegible writing on tubes, consider numbering them and numbering samples on the sample sheet.

- Note the study number, PI, and the drugs used/to be measured.
- A name, phone number, and email address should be included with the samples so that receipt can be acknowledged.

5. Please notify the lab by email (pitt-pk@upmc.edu), telephone (412-623-3248), or fax (412-623-1212) at least 24 hours prior to shipment.

Regulations: Shipment of samples must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture-resistant (*e.g*. cardboard mailing tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

Shipping Restrictions: All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state. All specimens are to be shipped on either Monday, Tuesday, or Wednesday, and not before federal or university holidays.

5.7.2.2 Shipping Address

Jan Beumer, University of Pittsburgh
Cancer Pharmacokinetics and Pharmacodynamics Facility
UPMC Hillman Cancer Center
Room G27 Hillman Research Laboratories
5117 Centre Avenue
Pittsburgh, PA 15213

5.7.2.3 Contact Information for Assistance

Lab phone: 412-623-3248
Lab fax: 412-623-1212
PK Lab email: PITT-PK@upmc.edu
PK director email: beumerjh@upmc.edu

5.8 Biomarker Plan

List of Biomarker Assays in Order of Priority
Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing

Priority	Biomarker Name	Assay CLIA: Y/N	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	M/O	Assay Laboratory and Lab PI
		Tissue-based Biomarkers					
1	ATM expression	Chromogenic IHC CLIA: Y	Integrated Correlate with PFS	FFPE Tumor	Archival, within 3 months prior to treatment (or baseline if archival tissue is insufficient or unavailable)	M	UPMC Pathology Sanja Dacic dacics@upmc.edu
2	Whole Exome Sequencing	NGS CLIA: N	Integrated Correlate with Response	DNA from FFPE Tumor	Archival, within 3 months prior to treatment (or baseline if archival tissue is insufficient or unavailable)	M	NCLN Genomics Laboratory Mickey Williams, Ph.D. mickey.williams@nih.gov
3	RNAseq	NGS CLIA: N	Exploratory To identify TIL signatures and correlate response	RNA from FFPE Tumor	Archival, within 3 months prior to treatment (or baseline if archival tissue is insufficient or unavailable)	O	NCLN Genomics Laboratory Mickey Williams, Ph.D. mickey.williams@nih.gov
		Blood-based Biomarkers					

Priority	Biomarker Name	Assay CLIA: Y/N	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	M/O	Assay Laboratory and Lab PI
		Tissue-based Biomarkers					
1	PK of gemcitabine and Berzosertib (M6620, VX-970)	LC/MS CLIA: N	Integrated Correlate drug levels with toxicity and efficacy	Blood	All: Cycle 1, Day 1: pre-dose and 25 min (-5 min) post start of gemcitabine (~ 5 min before end of infusion) Patients receiving M6620 only: Cycle 1, Day 2: pre-dose, 30 min (+/-5 min) post start of berzosertib (M6620, VX-970), 55 min (+/-5 min) post start of berzosertib (M6620, VX-970) (~ 5 min before end of infusion), 15 min (+/-5 min) post end of berzosertib (M6620, VX-970), 30 min (+/-5 min) post end of berzosertib (M6620, VX-970), 1 hr (+/-5 min) post end of berzosertib (M6620, VX-970).	M	Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Jan Beumer beumerjh@upmc.edu
2	Whole Exome Sequencing	NGS CLIA: N	Integrated Correlate with Response	DNA from Blood in EDTA (Germline Control)	Baseline	M	NCLN Genomics Laboratory Mickey Williams, Ph.D. mickey.williams@nih.gov

5.9 Integrated Correlative Studies

5.9.1 ATM Expression

5.9.1.1 Specimen Receipt and Processing at UPMC Pathology

Each case upon receipt in the pathology laboratory at UPMC Pathology will be assigned a unique accession number (PHR) in the pathology electronic records. Cases will be sent for staining with 1 business day of receipt. ATM IHC as developed and validated by the UPMC Hillman Cancer Center and UPMC Pathology will be performed as previously reported (Villaruz *et al*., 2016).

5.9.1.2 Site Performing Correlative Study

Sanja Dacic, M.D., Ph.D.
Professor of Pathology
Rm. PUH C608
UPMC-PUH
200 Lothrop St.
Pittsburgh, PA 15213

Office Telephone: 412-647-8694
Email Laboratory Director: dacics@upmc.edu

5.9.2 PK of Gemcitabine and Berzosertib (M6620, VX-970)

5.9.2.1 Specimen Receipt and Processing at UMPC Cancer Pharmacokinetics and Pharmacodynamics Facility

Frozen Plasma aliquots will be received at the Beumer laboratory for processing and storage.

The LC-MS/MS assay for berzosertib (M6620, VX-970) was developed and validated at the UPMC Hillman Cancer Center, Cancer Pharmacokinetics and Pharmacodynamics Facility (Kiesel *et al.*, 2017). An LC-MS/MS assay to quantitate gemcitabine and metabolite dFdU and CDA activity (Stoller *et al.*, 2017) is currently available in the UPMC Hillman Cancer Center, Cancer Pharmacokinetics and Pharmacodynamics Facility. The study team will use accepted assay characteristics for each test.

5.9.2.2 Site Performing Correlative Study

Jan Beumer, University of Pittsburgh
Cancer Pharmacokinetics and Pharmacodynamics Facility
UPMC Hillman Cancer Center
Room G27 Hillman Research Laboratories

5117 Centre Avenue
Pittsburgh, PA 15213

Lab phone: 412-623-3248
Lab fax: 412-623-1212

5.9.3 Whole Exome Sequencing

5.9.3.1 Specimen Receipt and Processing at the EET Biobank

- Tumor tissue received in formalin will be paraffin-embedded. All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide for pathology QA assessment, and unstained slides for macrodissection (if needed) for nucleic acid extractions.
- DNA and RNA will be co-extracted from tumor tissue. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA will be shipped to the central sequencing laboratory for analysis.
- DNA will be extracted from the whole blood collected in EDTA tube(s)

5.9.3.2 Site Performing Correlative Study

NCLN Genomics Laboratory
Dr. Mickey Williams
mickey.williams@nih.gov

5.9.3.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

NCLN Genomics Laboratory at The University of Texas MD Anderson Cancer Center
Attn: Jincy Veliyathu or Khushali Rajendra Patel
Zayed Building
CTLU Z3.4020
6565 MD Anderson Blvd
Houston, TX 77030

5.9.3.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (NCLNGenomicsReceiving@nih.gov)

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 RNA Sequencing

5.10.1.1 Specimen Receipt and Processing at the EET Biobank

- **Tumor tissue** received in formalin will be paraffin-embedded. All FFPE blocks will be sectioned to generate an initial hematoxylin and eosin (H&E)-stained slide for pathology QA assessment and unstained slides for nucleic acid extractions
- DNA and RNA will be co-extracted from tumor tissue. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of RNA will be shipped to the central sequencing laboratory for analysis.

5.10.1.2 Site Performing Correlative Study

NCLN Genomics Laboratory
Dr. Mickey Williams
mickey.williams@nih.gov

5.10.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

NCLN Genomics Laboratory at The University of Texas MD Anderson Cancer Center
Attn: Jincy Veliyathu or Khushali Rajendra Patel
Zayed Building
CTLU Z3.4020
6565 MD Anderson Blvd
Houston, TX 77030

5.10.1.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (NCLNGenomicsReceiving@nih.gov)

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description (Phase 1B and Phase 2)

Agent*	Order of Admin-istration	Pre-medications & Precautions**	Route	Schedule Cycles 1-4 (every 3 weeks)	Schedule Cycles 5-16 (every 3 weeks)	Schedule Cycles 17-26 (every 6 weeks)	Cycle Length
Pembrolizumab	1	Pre-medications should be administered per institutional guidelines.	IV over 30 min (± 10 minutes)	D1	D1	D1	Cycles 1-16: 21 days (3 weeks) Cycles 17-26: 42 days (6 weeks)
Gemcitabine	2	Antiemetics should be administered per institutional guidelines.	IV over 30 min (± 10 minutes)	D1 and D8	-	-	
Carboplatin	3	Antiemetics should be administered per institutional guidelines.	IV over 30 min (± 10 minutes)	D1	-	-	
Berzosertib (M6620, VX-970)	--	No pre-medications required unless clinically indicated.	IV over 60 min (± 10 minutes)	D2 and D9	D1	-	
*Doses as appropriate for assigned dose level. **All pre-medications will be given prior to starting infusions.							

Phase 1B Safety Lead-In (n = 6-18) **Dose De-Escalation Schema**				
	Berzosertib (M6620, VX-970) (mg/m^2)	**Gemcitabine (mg/m^2)**	**Carboplatin (AUC)**	**Pembrolizumab (mg)**
Schedule				
Cycles 1-4 (every 3 weeks)	Days 2 and 9	Days 1 and 8	Day 1	Day 1
Cycles 5-16 (every 3 weeks)	Day 1	-	-	Day 1
Cycles 17-26 (every 6 weeks)	-	-	-	Day 1*
Dose Level (Cycles 1-16)				
1	135 mg/m^2	800 mg/m^2	5	200
-1	135 mg/m^2	800 mg/m^2	4	200
-2	90 mg/m^2	600 mg/m^2	3	200
• All study drugs will be administered IV. • Dosing will begin at DL 1. • Plans for dose de-escalation to DL -1 are described in Section 7.				

*Pembrolizumab will be administered as 200mg for Cycles 1-16 and 400mg for Cycles 17-26 and should not exceed 2 years of treatment.

Phase 2 Expansion, Arm A (n = 44) **Treatment Schema**				
	Berzosertib (M6620, VX-970) 135 or 90 mg/m^2	**Gemcitabine** 800 or 600 mg/m^2	**Carboplatin** AUC 3, 4 or 5	**Pembrolizumab** 200 mg*
Cycles 1-4 (every 3 weeks)	Days 2 and 9	Days 1 and 8	Day 1	Days 1
Cycles 5-16 (every 3 weeks)	Day 1	-	-	Day 1
Cycles 17-26 (every 6 weeks)	-	-	-	Day1
• All study drugs will be administered IV. • Arms will be randomized 1:1.				

*Pembrolizumab will be administered as 200mg for Cycles 1-16 and 400mg for Cycles 17-26 and should not exceed 2 years of treatment.

Phase 2 Expansion, Arm B (n = 44) Treatment Schema			
	Gemcitabine 1250 mg/m^2	**Carboplatin** AUC 5	**Pembrolizumab** 200 mg*
Cycles 1-4 (every 3 weeks)	Days 1 and 8	Day 1	Days 1
Cycles 5-16 (every 3 weeks)			Day 1
Cycles 17-26 (every 6 weeks)			Day1
• All study drugs will be administered IV. • Arms will be randomized 1:1.			

* Pembrolizumab will be administered as 200mg for Cycles 1-16 and 400mg for Cycles 17-26 and should not exceed 2 years of treatment.

The following treatment schedule will be used for a total of two years of treatment. Pembrolizumab administration should not exceed 2 years.

- Cycles 1 to 4 (first 3 months of the first year): gemcitabine on D1 and D8, carboplatin and pembrolizumab on D1, and +/- berzosertib (M6620, VX-970) on D2 and D9, every three weeks
- Cycles 5 to 16 (last 9 months of the first year): pembrolizumab +/- berzosertib (M6620, VX-970) on D1, every 3 weeks
- Cycles 17 to 26 (second year): pembrolizumab on D1, every 6 weeks

Beyond 4 cycles (i.e., 3 months), when berzosertib (M6620, VX-970) and pembrolizumab administration continues on D1 only without gemcitabine or carboplatin, the berzosertib (M6620, VX-970) and pembrolizumab may be dosed on the same day (D1) for patient convenience, where pembrolizumab is administered before berzosertib (M6620, VX-970).

6.1.1 CTEP IND Agents

6.1.1.1 Berzosertib (M6620, VX-970)

Berzosertib (M6620, VX-970) will be supplied as a 20 mg/mL solution provided in 20% betadex sulfobutyl ether sodium (w/v) and 86 mM acetate buffer. Berzosertib (M6620, VX-970) must be diluted with 5% dextrose in water solution before intravenous infusion as detailed in Section 8.1.1.

An appropriate volume of concentrated drug product solution is diluted before use, according to the dose indicated in the dose administration table in Section 6.1. The total dose of berzosertib (M6620, VX-970) is not to exceed 800 mg/dose. The dose of berzosertib (M6620, VX-970) in dextrose in water solution will be infused IV over 60 minutes (± 10 minutes).

Infuse using an infusion set containing low-sorption or non-PVC, DEHP-free tubing and bags

and an in-line 0.2-micron filter. 5% dextrose in water solution must be used for IV line priming and flushing. Berzosertib (M6620, VX-970) should not come in contact with 0.9% Sodium Chloride due to incompatibility.

6.1.2 Commercial Agents

For General Concomitant Medication Guidelines for commercial agents, please refer to the FDA package inserts for gemcitabine, carboplatin, and pembrolizumab.

6.1.2.1 Pembrolizumab

Trial treatment of pembrolizumab will be administered on Day 1 of each 3-week treatment cycle after all procedures/assessments have been completed. Pembrolizumab will be administered using a 30-minute IV infusion for all cycles, and the dose will be 200 mg for Cycles 1-16 and 400 mg for Cycles 17-26. Pembrolizumab administration should not exceed 2 years. Infusion timing should be as close to 30 minutes as possible; however, a window of ±10 minutes is permitted.

6.1.2.2 Gemcitabine

Gemcitabine is administered intravenously over 30 minutes (± 10 minutes) on Days 1 and 8 of each 21-day cycle.

Infusion time should not exceed 60 minutes. In clinical trials evaluating the maximum tolerated dose of gemcitabine, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia.

Prior to each dose of gemcitabine, obtain a complete blood count (CBC) with a differential and a platelet count. Modify the dosage as recommended. Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent, and the risks are increased when gemcitabine is combined with other cytotoxic drugs.

Gemcitabine is a hazardous agent, and double gloving, a gown, and (if dosage form allows) Closed System Drug-Transfer Devices (CSTDs) should be used during administration (NIOSH 2016).

6.1.2.3 Carboplatin

Carboplatin, as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m^2 IV on day 1 every 4 weeks. In general, however, single intermittent courses of carboplatin should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Carboplatin is administered intravenously (IV) as a diluted solution over 30 minutes (± 10

minutes) through an IV line. Do not co-administer other drugs in the same IV line.

The subject-specific dose should be calculated using the Calvert formula per institutional policy for AUC calculation. Carboplatin should be administered per institutional standards.

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. If a participant has an infusion reaction to carboplatin, standard of care for re-challenge should be followed.

6.2 Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the NCI Common Toxicity Criteria for Adverse Events version 5.0 (CTCAE version 5.0). DLT is defined as the occurrence of any of the treatment-related events listed below during the first cycle (21 days) of study treatment and is felt to be possibly, probably, or definitely related to the study drug. Approaches for dose modification are presented Section 7.

Patients who fail to complete cycle 1 of therapy (*i.e.*, fail to receive carboplatin, pembrolizumab, and two full doses of gemcitabine and berzosertib (M6620, VX-970)) for reasons unrelated to treatment (*e.g.*, rapid disease progression) will be deemed to be non-evaluable for DLT and be replaced. Patients who fail to complete cycle 1 at the prescribed dose level due to treatment related adverse side effects (*i.e.,* dose modification per Section 7.2.1 are required) will be classified as having a DLT.

DLTs will be defined as grade 4 absolute neutrophil count for ≥7 days, grade 4 anemia, platelet count <25,000, or other non-hematologic events ≥grade 3 as per NCI Common Terminology Criteria for Adverse Events Version 5.0 (except fatigue, alopecia, anorexia, nausea and emesis occurring despite optimal antiemetic therapy).

Patients are allocated to doses by the following algorithm:

Three patients will be treated at Level 1.

1. If # DLT≤1/3, treat 3 more patients at Level 1, otherwise, go to step 2, below.
    a. If # DLT≤1/6, proceed to Phase 2 at Level 1,
    b. Else if # DLT=2/6 or 3/6, go to step 2, below,
    c. Else if # DLT>3/6, do not proceed to Phase 2.
2. If # DLT≤1/3, treat 3 more patients at Level -1, otherwise, go to step 3, below.
    a. If # DLT≤1/6, proceed to Phase 2 at Level -1,
    b. Else if # DLT=2/6 or 3/6, go to step 3, below,
    c. Else if # DLT>3/6, do not proceed to Phase 2.
3. Treat 3 patients at Level -2.
    a. If # DLT≤1/3, treat 3 more patients at Level -2,
        i. If #DLT≤1/6, proceed to Phase 2 at Level -2,
        ii. Else if #DLT≥2/6, do not proceed to Phase 2.

b. If # DLT≥2/3, do not proceed to Phase 2

6.3 General Concomitant Medication and Supportive Care Guidelines

6.3.1 Berzosertib (M6620, VX-970) is primarily metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4); exposure of berzosertib (M6620, VX-970) may be affected by concomitant administration of drugs that are strong inhibitors or inducers of CYP3A4. Concomitant administration with potent inhibitors or inducers of CYP3A4 is prohibited in this study. Berzosertib is a weak inhibitor of CYP3A4. Based on in vitro data, berzosertib has the potential to be an inhibitor of BCRP and OATP1B3 at clinically relevant concentrations and may increase exposure of BCRP and OATP1B3 substrates. Concomitant administration with sensitive CYP3A4 substrates with a narrow therapeutic index, and substrates of BCRP and OATP1B3 with berzosertib (M6620, VX-970) should be considered with caution and careful monitoring for safety.

6.3.2 While taking berzosertib (M6620, VX-970), if any patient develops phlebitis or signs of inflammation which 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. If any patient develops pruritus or evidence of an allergic reaction, standard measures may be employed to ameliorate these symptoms or prevent recurrence (*e.g.,* premedication with acetaminophen 325 mg, PO approximately 30 minutes before the infusion, 200 mg hydrocortisone IV approximately 60 minutes before infusion, and 25 mg diphenhydramine IV approximately 30 minutes before infusion). Alternative antihistamine and steroid combinations may be considered, as long as they are not prohibited by protocol. If standard procedures to limit symptoms of injection site reaction or pruritus are insufficient, the infusion time may be extended beyond 60 minutes, but no more than 90 minutes.

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

6.3.4 Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

6.3.5 Current or prior use of immunosuppressive medication within 28 days before the first dose of pembrolizumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Higher doses of steroids given as

premedications on day 1 and 8 of therapy are permitted.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will continue according to the following schedule for a total of 2 years of therapy. Pembrolizumab administration should not exceed 2 years.

- Cycles 1 to 4 (first 3 months of the first year): gemcitabine on D1 and D8, carboplatin and pembrolizumab on D1, and +/- berzosertib (M6620, VX-970) on D2 and D9, every three weeks
- Cycles 5 to 16 (last 9 months of the first year): pembrolizumab +/- berzosertib (M6620, VX-970) on D1, every 3 weeks
- Cycles 17 to 26 (second year): pembrolizumab on D1, every 6 weeks

Or treatment will continue until one of the following criteria applies:

- Disease progression. In patients with disease progression, treatment may continue if there is clear ongoing clinical benefit, after discussion with the PI.
- 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
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.5 Duration of Follow-Up

Patient follow-up will occur via standard of care or a phone call every 3 months +/- (2 weeks) for 12 months following removal from study. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dosing Levels

Dose Levels for Carboplatin, Gemcitabine, and Berzosertib (M6620, VX-970) (Phase 1B and Phase 2, Arm A)*			
Dose Level	**Carboplatin** (AUC)	**Gemcitabine**	**Berzosertib (M6620, VX-970)**
1	5 (or 4)	800 mg/m^2	135 mg/m^2
-1	4 (or 3)	800 mg/m^2	135 mg/m^2
-2	3	600 mg/m^2	90 mg/m^2

***Modifications are by dose level and not by individual agent.**

Dose Levels for Carboplatin and Gemcitabine (Phase 2, Arm B)*		
Dose Level	**Carboplatin** (AUC)	**Gemcitabine**
1	5	1250 mg/m^2
-1	4	1000 mg/m^2
-2	3	750 mg/m^2

***Modifications are by individual agent.**

7.2 Dosing Modifications

7.2.1 **Gemcitabine** should be permanently discontinued in patients who experience or develop the following:

- Unexplained dyspnea, with or without bronchospasm, or severe pulmonary toxicity
- Hemolytic uremic syndrome (HUS) or severe renal impairment
- Severe hepatic toxicity
- Capillary leak syndrome (CLS)
- Posterior reversible encephalopathy (PRES)

7.2.2 Dose Modification Tables for Phase 1B and Phase 2, Arm A

7.2.2.1 Dose Modifications for Neutropenia on Day 1 at Time of Treatment of Any Cycle

Modifications are by dose level and not by individual agent.

Neutropenia	**Management/Next Dose for Berzosertib (M6620, VX-970)***, Gemcitabine and Carboplatin**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower. Second recurrence, reduce by one dose level, if indicated**
Grade 4	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
*Patients with a grade 3 toxicity requiring a delay of >2 weeks should be discussed with the PI. Patients may continue therapy if receiving benefit. In patients with a grade 4 toxicity requiring a delay of >2 weeks, study should be discontinued. ** Patients requiring > two dose reductions should be discussed with PI. Patients may continue therapy if receiving benefit. *** Berzosertib (M6620, VX-970) dose is given on day 2; however, the CBC from day 1 will be used to determine the day 2 dose	

7.2.2.2 Dose Modifications for Neutropenia at Time of Treatment on Day 8 and Day 9 of Any Cycle

Neutropenia	**Management/ Next Dose for Berzosertib (M6620, VX-970)***	**Management/ Next Dose for Gemcitabine**	**Management/ Next Dose for Carboplatin****
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose	No change in dose
Grade 3	Omit current cycle day 9 dose	Omit current cycle day 8 dose	No change in dose
Grade 4	Omit current cycle day 9 dose	Omit current cycle day 8 dose	No change in dose
* Berzosertib (M6620, VX-970) dose is given on day 9; however, the CBC from day 8 will be used to determine the day 9 dose **Carboplatin is not given on day 8 or day 9 of the cycle.			

7.2.2.3 Dose Modifications for Thrombocytopenia at Time of Treatment on Day 1 of Any Cycle

Modifications are by dose level and not by individual agent.

Thrombocytopenia	**Management/Next Dose for Berzosertib (M6620, VX-970)***,**

	Gemcitabine, and Carboplatin
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at one dose level lower. Second recurrence, reduce by one dose level, if indicated**
Grade 4	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
*Patients with a grade 3 toxicity requiring a delay of >2 weeks should be discussed with the PI. Patients may continue therapy if receiving benefit. In patients with a grade 4 toxicity requiring a delay of >2 weeks, study should be discontinued. ** Patients requiring > two dose reductions should be discussed with PI. Patients may continue therapy if receiving benefit. *** Berzosertib (M6620, VX-970) dose is given on day 2; however, the CBC from day 1 will be used to determine the day 2 dose	

7.2.2.4 Dose Modifications for Thrombocytopenia at Time of Treatment on Day 8 and 9 of Any Cycle

Thrombocytopenia	**Management/ Next Dose for Berzosertib (M6620, VX-970)***	**Management/ Next Dose for Gemcitabine**	**Management/ Next Dose for Carboplatin****
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose	No change in dose
Grade 3	Omit current cycle day 9 dose	Omit current cycle day 8 dose	No change in dose
Grade 4	Omit current cycle day 9 dose	Omit current cycle day 8 dose	No change in dose
* Berzosertib (M6620, VX-970) dose is given on day 9; however, the CBC from day 8 will be used to determine the day 9 dose **Carboplatin is not given on day 8 or day 9 of the cycle.			

7.2.2.5 Dose Modifications for Other Non-Hematological Toxicities at Time of Treatment on Days 1, 2, 8 or 9*

On days 1 and 2, modifications are by dose level and not by individual agent.

Event	**Management/ Next Dose for Berzosertib (M6620, VX-970) (VX-970)******	**Management/ Next Dose for Gemcitabine**	**Management/ Next Dose for Carboplatin**
≤ Grade 1	No change in dose	No change in dose	No change in dose

Grade 2	No change in dose	No change in dose	No change in dose
Grade 3	Day 2: Hold** until ≤ Grade 2 Resume at one dose lower*** Day 9: Omit current cycle dose	Day 1: Hold** until ≤ Grade 2 Resume at one dose lower*** Day 8: Omit current cycle dose	Day 1: Hold** until ≤ Grade 2 Resume at same dose
Grade 4	Day 2: Hold** until ≤ Grade 2 Resume at one dose lower*** Day 9: Omit current cycle dose	Day 1: Hold** until ≤ Grade 2 Resume at one dose lower*** Day 8: Omit current cycle dose	Day 1: Hold** until ≤ Grade 2 Resume at same dose
* Does not include alopecia and fatigue ** Patients with a grade 3 toxicity requiring a delay of >2 weeks should be discussed with the PI. Patients may continue therapy if receiving benefit. In patients with a grade 4 toxicity requiring a delay of >2 weeks, study should be discontinued. *** Patients requiring > two dose reductions should be discussed with PI. Patients may continue therapy if receiving benefit. **** Berzosertib (M6620, VX-970) dose is on day 2, 9, but dose can be determined based on toxicity assessment performed on day 1 and 8 as well as on days 2 and 9.			

7.2.3 Dose Modification Tables for Phase 2, Arm B

7.2.3.1 Dose Modifications for Neutropenia on Day 1 at Time of Treatment of Any Cycle

Modifications are by individual agent.

Neutropenia	Management/Next Dose for Carboplatin	Management/Next Dose for Gemcitabine
≤ 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 1. First recurrence, resume at same dose level. Second recurrence, reduce by one dose level, if indicated**	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated. **
Grade 4	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 1. Resume at one dose level lower if indicated.**
* Patients with a grade 3 toxicity requiring a delay of >2 weeks should be discussed with PI. Patients may continue therapy if receiving benefit. In patients with a grade 4 toxicity requiring a delay of >2 weeks, study should be discontinued. ** Patients requiring > two dose reductions should be discussed with PI. Patients may continue therapy if receiving benefit.		

7.2.3.2 Dose Modifications for Neutropenia on Day 8 at Time of Treatment of Any Cycle

Neutropenia	Management/ Next Dose for Gemcitabine
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Administer one dose level lower than administered on day 1 of that cycle. Resume next cycle based on the day 1 dose of gemcitabine.
Grade 4	Omit current cycle day 8 dose

7.2.3.3 Dose Modifications for Thrombocytopenia on Day 1 at Time of Treatment of Any Cycle

Modifications are by individual agent.

Thrombocytopenia	Management/Next Dose for Carboplatin	Management/Next Dose for Gemcitabine
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold* until ≤ Grade 2. Resume at same dose at first recurrence. Second recurrence, resume at one dose lower, if indicated.**	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**
* Patients with a grade 3 toxicity requiring a delay of >2 weeks should be discussed with the PI. Patients may continue therapy if receiving benefit. In patients with a grade 4 toxicity requiring a delay of >2 weeks, study should be discontinued. ** Patients requiring > two dose reductions should be discussed with PI. Patients may continue therapy if receiving benefit.		

7.2.3.4 Dose Modifications for Thrombocytopenia on Day 8 at Time of Treatment of Any Cycle

Thrombocytopenia	Management/Next Dose for Gemcitabine
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Administer one dose level lower than the dose administered on day 1 of the cycle. Resume next cycle based on the day 1 dose of gemcitabine.
Grade 4	Administer one dose level lower than the dose administered on day 1 of the cycle.

7.2.3.5 Dose Modifications for Other Non-hematological Toxicities at Time of Treatment*

Modifications are by individual agent.

Event	Management/Next Dose for Carboplatin	Management/Next Dose for Gemcitabine
Grade 1 or 2	No change in dose	No change in dose
Grade 3	Day 1: Hold** until ≤ Grade 2 Resume at same dose	Day 1: Hold** until ≤ Grade 2 Resume at one dose lower*** Day 8: Omit current cycle dose
Grade 4	Day 1: Hold** until ≤ Grade 2 Resume at same dose	Day 1: Hold** until ≤ Grade 2 Resume at one dose lower*** Day 8: Omit current cycle dose
*Excluding alopecia and fatigue **Patients with a grade 3 toxicity requiring a delay of >2 weeks should be discussed with the PI. Patients may continue therapy if receiving benefit. In patients with a grade 4 toxicity requiring a delay of >2 weeks, study should be discontinued. ***Patients requiring > two dose reductions should be discussed with PI. Patients may continue therapy if receiving benefit.		

7.2.4 Pembrolizumab Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events (revised 1-10-2023)

7.2.4.1 Dose Modifications

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as described in Section 7.2.4.3.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (*e.g.*, elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

7.2.4.2 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 7.2.4.3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to

be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

7.2.4.3 Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines for irAEs and infusion reactions associated with pembrolizumab are provided in the table below.

Note that non-irAEs will be managed as appropriate, following clinical practice recommendations

Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone.
2. For non-endocrine-related toxicities, pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. Generally, when corticosteroids are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to ≤Grade 1 after a corticosteroid taper.

irAEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (*i.e.*, diarrhea, abdominal pain, blood or mucus in stool

	Recurrent Grade 3 or Grade 4	Permanently discontinue	Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	with or without fever) and of bowel perforation (*i.e.* peritoneal signs and ileus) Specifically assess for celiac disease serologically, and exclude *Clostridium difficile* infection Participants with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose control.

	New onset T1DM (evidence of β-cell failure) or Grade 3 or 4 hyperglycemia	Withhold [d] Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc*.) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		

Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (*e.g.*, propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (*e.g.*, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		

Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month

	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Exfoliative Dermatologic	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE	Ensure adequate evaluation to

Conditions	Confirmed SJS, TEN, or DRESS	Permanently discontinue	administer corticosteroids	confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Infusion-Related Reactions

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Mild reaction; infusion interruption not indicated; intervention not indicated	Grade 1	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Grade 2	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.* from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Prolonged (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (*e.g.* methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing.

Infusion Reactions	**NCI CTCAE Grade**	**Treatment**	**Premedication at subsequent dosing**
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (*e.g.* vasculitis and sclerosing cholangitis).

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue pembrolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold pembrolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  o If event resolves to Grade 1 or better, resume pembrolizumab. [b]
	  o If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]
	• For facial paresis:
	  o If event resolves fully, resume pembrolizumab. [b]
	  o If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.
[c] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis,	• Continue pembrolizumab unless symptoms worsen or

Event	Management
Grade 1	do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue pembrolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue pembrolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue pembrolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

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 10.1.

8.1 CTEP IND Agents

8.1.1 M6620 (NSC # 780162)

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

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

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

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

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

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

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

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

Storage: Store intact vials protected from light inside cardboard boxes at room temperature, below 25°C (77°F), do not freeze.

> If a storage temperature excursion is identified, promptly return berzosertib (M6620, VX-970) to below 25°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

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

Route of Administration: Intravenous (IV) infusion.

Method of Administration: Prior to administration the solution should be given one hour at ambient temperature to warm up if stored refrigerated following preparation. Infuse over 60 minutes using an infusion set containing low-sorption or non-PVC, DEHP-free tubing and an in-line 0.2 micron filter. 5% dextrose in water solution must be used for IV line priming and flushing. Berzosertib (M6620,

VX-970) should not come in contact with 0.9% Sodium Chloride due to incompatibility. The infusion time may be extended beyond 60 minutes (as tolerated) but no more than 90 minutes if standard procedures to limit symptoms of an infusion reaction are insufficient or if the total volume of the infusion exceeds 600 mL. To minimize the possibility of phlebitis, berzosertib (M6620, VX-970) should be administered through a large bore catheter into a large caliber peripheral vein or central venous access.

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

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

Potential Drug Interactions: Berzosertib (M6620, VX-970) is primarily metabolized by CYP3A4. Berzosertib (M6620, VX-970) 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 berzosertib (M6620, VX-970) 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.

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

Berzosertib (M6620, VX-970) 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 transporters.

8.1.2 CTEP IND Agent Ordering, Accountability, Further Information, and Contacts

8.1.2.1 Agent Ordering

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.

Sites can place orders for PMB-supplied agents only after enrollment onto the study. Please provide the patient ID# in the comment box when placing orders.

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.

8.1.2.2 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.

8.1.2.3 Investigator Brochure Availability

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

8.1.2.4 Useful Links and Contacts

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

8.2 Commercial Agents

8.2.1 Pembrolizumab (NSC 776864)

Product Description: Pembrolizumab is a humanized MAb of the IgG4/kappa isotype.

Solution Preparation: Pembrolizumab solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of pembrolizumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between 1 mg/mL to 10 mg/mL.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Route of Administration: IV infusion only. Do not administer as an IV push or bolus injection. Infuse over approximately 30 minutes (±10 minutes) using an infusion set containing a low-protein binding 0.2 to 5 μm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

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

8.2.2 Gemcitabine (NSC 613327)

Product description: Gemcitabine (gemcitabine for injection, USP) is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer). The empirical formula for gemcitabine HCl is C9H11F2N3O4 • HCl. It has a molecular weight of 299.66.

Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemcitabine is supplied in a sterile form for intravenous use only. Vials of gemcitabine contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F).

Exercise caution and wear gloves when preparing gemcitabine solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if gemcitabine contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption.

Solution preparation: Reconstitute the vials with 0.9% Sodium Chloride Injection without preservatives.

Add 5 mL to the 200-mg vial or 25 mL to the 1-g vial. These dilutions each yield a Gemcitabine concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. Inspect visually prior to administration and discard for particulate matter or discoloration. Gemcitabine solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F). Do not refrigerate as crystallization can occur. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Route of administration: Gemcitabine is supplied in a sterile form for intravenous use only.

Agent ordering: Commercially available from various manufacturers. See package insert for further information.

8.2.3 Carboplatin (NSC #241240)

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

Solution preparation: Refer to package insert for complete preparation and dispensing

instructions.

Storage requirements: Store intact vials at room temperature and protect from light.

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.

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.

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

9. STATISTICAL CONSIDERATIONS

9.1 Study Design

9.1.1 Overview of the Design

A phase 1B lead-in study will be conducted to establish the safety and tolerability of the combination RP2Ds of gemcitabine and berzosertib (M6620, VX-970) with carboplatin at a dose of AUC 5 and pembrolizumab. A randomized phase 2 clinical trial aimed at the evaluation of berzosertib (M6620, VX-970) in combination with carboplatin/gemcitabine/pembrolizumab, compared with carboplatin/gemcitabine/pembrolizumab alone in patients with chemotherapy-naïve Sq-NSCLC will then be conducted. Eligible patients will be randomized to carboplatin/gemcitabine/pembrolizumab with or without berzosertib (M6620, VX-970). Patients will adhere to the following treatment schedule for a total of 2 years of treatment or until disease progression, unacceptable treatment-related toxicity, or withdrawal of consent. Pembrolizumab administration should not exceed 2 years.

- Cycles 1 to 4 (first 3 months of the first year): gemcitabine on D1 and D8, carboplatin and pembrolizumab on D1, and +/- berzosertib (M6620, VX-970) on D2 and D9, every three weeks
- Cycles 5 to 16 (last 9 months of the first year): pembrolizumab +/- berzosertib (M6620, VX-970) on D1, every 3 weeks
- Cycles 17 to 26 (second year): pembrolizumab on D1, every 6 weeks

The primary endpoint of this clinical trial is PFS. Patients will be required to have tumor tissue at the time of enrollment in order to conduct a secondary analysis of ATM-deficiency and PFS with carboplatin/gemcitabine/pembrolizumab with and without berzosertib (M6620, VX-970) and exploratory analyses of other mediators of the DNA damage response and inflammation-

associated gene expression that may be associated with response to berzosertib (M6620, VX-970) and carboplatin/gemcitabine/pembrolizumab.

9.1.2 Phase 1B Safety Lead-In

We will start at dose level 1, as our patient population is chemotherapy-naïve, and would be expected to tolerate higher doses of platinum chemotherapy. Patients who fail to complete cycle 1 (*i.e.*, fail to receive carboplatin, pembrolizumab, and two full doses of gemcitabine and berzosertib (M6620, VX-970) of therapy for reasons unrelated to toxicities or treatment side effects) will be non-evaluable for DLT and will be replaced. Patients who fail to complete cycle 1 for reasons of toxicities or treatment side effects will be classified as having a DLT.

Patients who fail to complete cycle 1 of therapy (*i.e.*, fail to receive carboplatin, pembrolizumab, and two full doses of gemcitabine and berzosertib (M6620, VX-970)) for reasons unrelated to treatment (*e.g.*, rapid disease progression) will be deemed to be non-evaluable for DLT and be replaced. Patients who fail to complete cycle 1 at the prescribed dose level due to treatment related adverse side effects (*i.e.*, dose modification per Section 7.2.1 are required) will be classified as having a DLT.

DLTs will be defined as grade 4 absolute neutrophil count for ≥ 5 days, grade 4 anemia, platelet count < 25,000, or other non-hematologic events ≥ grade 3 as per NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (except fatigue, alopecia, and anorexia). Patients are allocated to doses by the following algorithm (Dixon and Mood, 1948):

Three patients will be treated at Level 1.

1. If # DLT≤1/3, treat 3 more patients at Level 1, otherwise, go to step 2, below.
    a. If # DLT≤1/6, proceed to Phase 2 at Level 1,
    b. Else if # DLT=2/6 or 3/6, go to step 2, below,
    c. Else if # DLT>3/6, do not proceed to Phase 2.
2. If # DLT≤1/3, treat 3 more patients at Level -1, otherwise, go to step 3, below.
    a. If # DLT≤1/6, proceed to Phase 2 at Level -1,
    b. Else if # DLT=2/6 or 3/6, go to step 3, below,
    c. Else if # DLT>3/6, do not proceed to Phase 2.
3. Treat 3 patients at Level -2.
    a. If # DLT≤1/3, treat 3 more patients at Level -2,
        i. If #DLT≤1/6, proceed to Phase 2 at Level -2,
        ii. Else if #DLT≥2/6, do not proceed to Phase 2.
    b. If # DLT≥2/3, do not proceed to Phase 2.

If the trial does not proceed to Phase 2, an internal DSMB consisting of the study investigators and medical monitor will meet to discuss potential protocol amendments. DLTs will be determined in cycle 1 of therapy, though accrual will not be halted for DLT evaluation.

The operating characteristics for the run-in study are shown in the table below ("Probabilities of Dose Selection"), using the algorithm stated above and assuming the true probabilities of DLT stated in the first two rows.

Probabilities of Dose Selection							
True P(DLT) at Level 1	**0.050**	**0.100**	**0.150**	**0.200**	**0.250**	**0.300**	**0.400**
True P(DLT) at Level -1	**0.025**	**0.050**	**0.075**	**0.100**	**0.125**	**0.150**	**0.200**
P(Select Level 1)	0.968	0.895	0.794	0.670	0.525	0.413	0.226
P(Select Level -1)	0.029	0.091	0.167	0.265	0.329	0.376	0.397
P(Do Not Proceed to Phase 2)	0.003	0.041	0.035	0.065	0.146	0.211	0.377

9.1.3 Phase 2

The goal of the phase 2 study is to detect improvement in PFS with the addition of berzosertib (M6620, VX-970) to carboplatin/gemcitabine/pembrolizumab. A secondary analysis will examine the potential association between ATM deficiency and benefit of berzosertib (M6620, VX-970) in combination with carboplatin/gemcitabine/pembrolizumab. Patients will not be stratified by or selected based on ATM mutation status, as efficacy of berzosertib (M6620, VX-970) in the ATM-deficient population is a secondary endpoint and is not being used to power the primary endpoint. In order to control for drifts in patient selection and treatment outcomes and to prepare for assessment of ATM as a predictive biomarker, a randomized phase 2 trial is the selected design (Gan *et al.*, 2010). The median PFS for patients with chemotherapy-naïve advanced NSCLC of squamous cell histology (unselected by ATM status) is expected to be about 6 months in the control (carboplatin/gemcitabine/pembrolizumab) arm (Scagliotti *et al.*, 2008; Thatcher *et al.*, 2015; Sederholm *et al.*, 2005). A promising hazard ratio for PFS would be 0.75 (approximate observed median PFS of 10 months in the +berzosertib (M6620, VX-970) arm).

The sample size is justified in terms of the primary endpoint: progression-free survival. It is assumed that: the median PFS is 6 months in the control arm and 10 months in the experimental arm, resulting in a hazard ratio of 0.6 (assuming exponentially-distributed survival times); 88 participants will be randomized 1:1 over 30 months; the futility analysis will be performed when 40 events have been observed; the final analysis will be performed when 85 events have been observed. According to Monte Carlo simulation, it is anticipated that the futility analysis will take place 24 months after accrual starts and the final analysis will take place 38 months after accrual begins, and there is a 0.056 probability that the trial will be stopped at the futility analysis. The one-sided hypothesis test at α=0.1 has 82.4% power; this calculation includes the probability that the trial will be halted at the futility analysis. Phase 1B participants will not be included in the Phase 2 analysis.

9.1.4 Safety and Tolerability

The NCI CTCAE 5.0 will be used to evaluate toxicity, and we will consider a toxicity to be an adverse event that is possibly, probably, or definitely related to treatment. The maximum grade of toxicity for each category of interest will be recorded for each patient, and the summary

results will be tabulated by category, grade, and dose level. Serious (≥ Grade 3) toxicities will be described on a per patient basis and will include any relevant baseline data.

9.2 Analyses of Endpoints and Objectives

For purposes of analysis, PFS is defined as the duration of time from the date of randomization to time of progression or death, whichever occurs first.

9.2.1 Primary Endpoints

1. Phase 1B: The RP2D will be the dose selected as described in the description of the dose de-escalation schema.
2. Phase 2: Proportional hazards (Cox) regression will be used to estimate the hazard ratio and the primary null hypothesis, that PFS is identical between arms, will be tested by a one-sided likelihood ratio test at α=0.10. The hazard ratio will be estimated with a 95% confidence interval. The assumption of proportionality of hazards will be checked graphically and by the method of Therneau and Grambsch. If it is found that the assumption is violated, the log-rank test will be used to compare the product-limit estimates of the survival functions. The analysis will take place when 85 events have been observed. This analysis will be on an intent-to-treat basis, that is, participants will be analyzed as they were randomized.

9.2.2 Secondary Objectives in Phase 2

1. The Phase 2 primary objective analysis will be repeated on an as-treated basis, that is, participants will be analyzed as they were actually treated.
2. PFS will be analyzed as in the Primary Phase 2 Objective in the subset of patients with ATM-deficient Sq-NSCLC.
3. Overall survival will be analyzed in the same fashion as PFS. Overall response will be analyzed by means of Fisher's exact test. The odds ratio will be estimated with a 95% confidence interval.
4. Objective response, overall survival, progression-free survival, and worst grade of adverse event experienced of the participants in the berzosertib (M6620, VX-970) arm will be modeled as a function of total berzosertib (M6620, VX-970) exposure using logistic regression, proportional hazards (Cox) regression and cumulative logit models, as appropriate.
5. Adverse events will be tabulated according to CTCAE v5.0 type, grade and relation to treatment. The worst grade of adverse event will be determined for each participant, and the distributions of worst grades will be compared between arms using a cumulative logit model.

9.2.3 Exploratory Objectives in Phase 2

1. Sparse modeling (*e.g.*, the lasso) will be used to determine if any features of whole exome and RNA sequencing are predictive of OR, OS or PFS.
2. Proportional hazards (Cox) regression will be used to assess the relationship between the ATM assay and OS and PFS.
3. Logistic regression and proportional hazards (Cox) regression will be used to explore the relationship between inflammation-associated gene signatures and OR, OS and PFS.

9.2.4 Futility Analysis: A futility analysis will be conducted after 40 events have been observed. At this time, the hazard ratio will be calculated, and the trial will be closed if the hazard ratio is greater than 1.

9.3 Sample Size and Accrual Rate

This study is projected to last 30 months from first to last enrolled evaluable patient, with an expected additional 12 months of follow-up from the last patient enrollment to ascertain 85 PFS events. Monthly accrual is estimated at 3-4 patients per month (range: 94-106 patients). Sample size will be 6-18 patients for Phase 1B, and 88 patients for Phase 2.

The sample size is justified in terms of the primary endpoint, progression-free survival. It is assumed that: the median PFS is 6 months in the control arm and 10 months in the experimental arm, resulting in a hazard ratio of 0.6 (assuming exponentially-distributed survival times); 88 participants will be randomized 1:1 over 30 months; the futility analysis will be performed when 40 events have been observed. At this time, the hazard ratio will be calculated, and the trial will be closed if the hazard ratio is greater than 1. The final analysis will be performed when 85 events have been observed. According to Monte Carlo simulation, it is anticipated that the futility analysis will take place 24 months after accrual starts and the final analysis will take place 38 months after accrual begins, and there is a 0.056 probability that the trial will be stopped at the futility analysis if the hazard ratio is 0.6 with a median PFS of 6 months in the control arm and 10 months in the experimental arm, per the primary hypothesis. The one-sided hypothesis test at α=0.1 has 82.4% power; this calculation includes the probability that the trial will be halted at the futility analysis. Phase 1B participants will not be included in the Phase 2 analysis.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Asian	0	1	0	0	**1**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	1	0	0	**1**
White	52	49	1	1	**103**
More Than One Race	1	0	0	0	**1**
Total	**53**	**51**	**1**	**1**	**106**

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9.4 Monitoring Rule for Toxicity

Toxicity will be monitored after every 10 participants have been treated. For the purpose of monitoring, a participant experiences toxicity if he or she experiences an adverse event of Grade ≥3 at least probably related to treated. If π_X and π_C are the probabilities a participant experiences toxicity in the experimental and control arms, then the trial will be paused for toxicity if $P(\pi_X - \pi_C > 0.1) > 0.75$. A Beta(1,1) (uninformative) prior distribution is assigned to both π_X and π_C. This stopping rule is expressed in the following table, where it is assumed the numbers of participants in both arms are equal, n_X is the number of participants experiencing toxicity in the experimental arm and n_C is the number of participants experiencing toxicity in the control arm

Total # Participants	Stop if n_X-$n_C \geq$
10	2
20	3
30	4
40	5
50	5
60	6
70	6
80	7
90	7

9.5 Reporting and Exclusions

9.5.1 Evaluation of Toxicity

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

9.5.2 Evaluation of Response

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

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

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

9.6 Data Safety Monitoring Board

The conduct of this study will be overseen by the ETCTN DSMB. The DSMB will be responsible for recommendations to the Principal Investigator and NCI regarding possible trial closure and/or early reporting of the study. The study team (with the exception of the study statistician) will not have access to the summary outcome data until released by the DSMB.

10. 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 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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.

10.1.1 CAEPRs for CTEP IND Agents

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

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

Version 2.0, July 13, 2022[1]

Adverse Events with Possible Relationship to M6620 (VX-970, berzosertib) (CTCAE 5.0 Term) [n= 323]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
	Flu like symptoms		
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)***

Adverse Events with Possible Relationship to M6620 (VX-970, berzosertib) (CTCAE 5.0 Term) [n= 323]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
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) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that M6620 (VX-970, berzosertib) caused the adverse event:

CARDIAC DISORDERS - Cardiac arrest; Palpitations
EAR AND LABYRINTH DISORDERS - Tinnitus
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Colonic obstruction; Dyspepsia; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (lower respiratory tract infection); Otitis externa; Sepsis; Soft tissue infection; Urinary tract infection
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Creatinine increased; GGT increased; Hemoglobin increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypokalemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Generalized muscle weakness; Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression); Tumor pain
NERVOUS SYSTEM DISORDERS - Lethargy; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Atelectasis; Cough; Dyspnea; Respiratory, thoracic and mediastinal disorders - Other (hemotypsis)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (hypovolemic shock)

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.

10.1.2 Adverse Event Lists for Commercial Agents

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

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pembrolizumab (MK-3475, NSC 776864)

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. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for Pembrolizumab (MK-3475).

Version 2.8, August 14, 2024[1]

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia[2]	
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]
		Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia)[2]
	Lymph node pain[2]	
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2]	
		Endocrine disorders - Other (hypoparathyroidism)[2]
	Endocrine disorders - Other (thyroiditis)[2]	
	Hyperthyroidism[2]	
	Hypophysitis[2]	
	Hypopituitarism[2]	
	Hypothyroidism[2]	
EYE DISORDERS		
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)
		Uveitis[2]
GASTROINTESTINAL DISORDERS		

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
	Abdominal pain	
	Colitis[2]	
	Diarrhea[2]	
		Enterocolitis[2]
		Gastritis[2]
		Gastrointestinal disorders - Other (exocrine pancreatic insufficiency)
	Mucositis oral[2]	
	Nausea	
	Pancreatitis[2]	
	Small intestinal mucositis[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
	Fever[2]	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
		Hepatobiliary disorders - Other (sclerosing cholangitis)
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis[2]
		Cytokine release syndrome[2]
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]
	Immune system disorders - Other (sarcoidosis)[2]	
		Serum sickness[2]
INFECTIONS AND INFESTATIONS		
		Myelitis[2]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased[2]	
	Blood bilirubin increased	
		GGT increased
		Lipase increased
		Serum amylase increased
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
	Hyponatremia	
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	
	Arthritis[2]	
	Back pain	
	Joint range of motion decreased	
	Myalgia[2]	
	Myositis[2]	
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2]
		Myasthenia gravis
		Nervous system disorders - Other (autoimmune neuropathy)[2]
		Nervous system disorders - Other (demyelination)[2]
		Nervous system disorders - Other (myasthenic syndrome)[2]
		Nervous system disorders - Other (nerve paresis)[2]
		Nervous system disorders - Other (neuromyopathy)[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]
		Nervous system disorders - Other (non-infectious myelitis)
		Nervous system disorders - Other (optic neuritis)
		Nervous system disorders - Other (polyneuropathy)[2]
		Paresthesia
		Peripheral motor neuropathy[2]
RENAL AND URINARY DISORDERS		
		Acute kidney injury
		Renal and urinary disorders - Other (autoimmune nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Pneumonitis[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Bullous dermatitis[2]	

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
		Erythema multiforme[2]
	Erythroderma	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus[2]	
	Rash acneiform[2]	
	Rash maculo-papular[2]	
		Skin and subcutaneous tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms [DRESS])[2]
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]	
	Skin hypopigmentation[2]	
		Stevens-Johnson syndrome[2]
		Toxic epidermal necrolysis[2]
	Urticaria[2]	
VASCULAR DISORDERS		
		Vasculitis[2]

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

[2]Immune-mediated adverse reactions have been reported in patients receiving Pembrolizumab (MK-3475). Adverse events potentially related to Pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with Pembrolizumab (MK-3475) who received hematopoeitic stem cell transplants.

Adverse events reported on Pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pembrolizumab (MK-3475) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastrointestinal disorders - Other (intussusception); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general

physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - CPK increased; Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Joint effusion[2]; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pleuritic pain[2]; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: Pembrolizumab (MK-3475) 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.

10.1.2.1 Gemcitabine

The most common adverse reactions for gemcitabine (≥20%) are nausea/vomiting, anemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

10.1.2.2 Carboplatin

The following adverse events have been associated with 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).

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found

in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website 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 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **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.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave 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 is used to collect AEs that start during the period or persist from the previous reporting period. 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.

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 direct 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 & Help Topics.

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.

10.3.2 Distribution of Adverse Event Reports

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

10.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

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

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse

Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** 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 1-2 Timeframes	Grade 3-5 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 3-5 SAEs
- Within 10 calendar days for Grade 1-2 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

10.4 Routine Adverse Event Reporting

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

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

10.5 Pregnancy

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

10.6 Secondary Malignancy

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

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

10.7 Second Malignancy

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

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. A window of -1 week is allowed for scans and x-rays. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. A window of ±48 hours is allowed for all assessments in the Study Calendar.

Study Calendar

	Baseline	Cycles 1-4 (1 Cycle = 21 days)				Cycles 5-16 (1 Cycle = 21 days)				Cycles 17-26 (1 Cycle = 42 days)				Disease Progression or End of Treatment	Follow Up[j]
		Day 1	Day 2	Day 8	Day 9	Day 1	Day 2	Day 8	Day 9	Day 1	Day 2	Day 8	Day 9		Every 3 months
Berzosertib (M6620, VX-970) [a]			X		X	X [a*]									
Pembrolizumab [a]		X				X				X					
Gemcitabine [a]		X		X											
Carboplatin [a]		X													
Archival Tumor Collection [b]	X														
Blood Collection for WES [c]	X														
Blood Collection for PK [c]		X	X												
Response Assessments [d]	X	*Tumor measurements and radiologic evaluation to occur at 6, 12, and 18 weeks, then every 9 weeks thereafter.*												X	
Comprehensive Chemistry Panel & CBC [e]	X	X		X		X				X					
Thyroid Function Test [f]	X	X				X				X					
General Health Exam [g]	X	X				X				X					
EKG [h]	X														
Adverse Event Evaluation		X -- X												X	
Concurrent Medications	X	X -- X												X	
Informed Consent, Demographics, and Medical History	X														
Pregnancy Test [i]	X														

[a] Dose as assigned. The following treatment schedule will be used for a total of 2 years of treatment. Pembrolizumab administration should not exceed 2 years:

- Cycles 1 to 4 (first 3 months of the first year): gemcitabine on D1 and D8, carboplatin and pembrolizumab on D1, and +/- berzosertib (M6620, VX-970) on D2 and D9, every three weeks
- Cycles 5 to 16 (last 9 months of the first year): pembrolizumab +/- berzosertib (M6620, VX-970) on D1, every 3 weeks
- Cycles 17 to 26 (second year): pembrolizumab on D1, every 6 weeks

[a*] Beyond 4 cycles (i.e., 3 months), when berzosertib (M6620, VX-970) and pembrolizumab administration continues on D1 only

	Baseline	Cycles 1-4 *(1 Cycle = 21 days)*				Cycles 5-16 *(1 Cycle = 21 days)*				Cycles 17-26 *(1 Cycle = 42 days)*				Disease Progression or End of Treatment	Follow Up[j]
		Day 1	Day 2	Day 8	Day 9	Day 1	Day 2	Day 8	Day 9	Day 1	Day 2	Day 8	Day 9		Every 3 months

without gemcitabine or carboplatin, the berzosertib (M6620, VX-970) and pembrolizumab may be dosed on the same day (D1) for patient convenience, where pembrolizumab is administered before berzosertib (M6620, VX-970).

[b] Archival Tumor Collection: The use of archival tumor tissue for ATM Expression and Whole Exome Sequencing is mandatory. The use of archival tissue for RNA Sequencing is optional. Tissue must be collected within 3 months prior to beginning treatment.

[c] Blood Collection for Studies: All study blood samples are mandatory and will be taken at the following times:

- Baseline (for germline control for WES)
- Cycle 1, Day 1: pre-dose and 25 min post start of gemcitabine (~ 5 min before end of infusion).
- Cycle 1, Day 2: pre-dose, 30 min (+/-5 min) post start of berzosertib (M6620, VX-970), 55 min (+/-5 min) post start of berzosertib (M6620, VX-970) (~ 5 min before end of infusion), 15 min (+/-5 min) post end of berzosertib (M6620, VX-970), 30 min (+/-5 min) post end of berzosertib (M6620, VX-970), 1 hr (+/-5 min) post end of berzosertib (M6620, VX-970).

[d] Response Assessments: Response to treatment will be assessed by tumor measurement and radiologic evaluation at 6, 12, and 18 weeks, then every 9 weeks thereafter. Radiologic documentation must be provided for patients to be removed from study for progressive disease. The same modality for all known sites of disease should be used throughout the study. This includes a CT scan of the chest, abdomen ± pelvis (as clinically indicated) or an MRI of the brain (as clinically indicated).

[e] Comprehensive Chemistry Panel & CBC: Assessments to be conducted twice during each cycle (Weeks 1 and 2) or as medically indicated. Assessment to include CBC with a differential and platelet count. Serum Chemistry to include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

[f] Thyroid Function Test: Assessment to be conducted baseline, then at the start of every cycle, or as medically indicated . To include TSH and Free T4.

[g] General Health Exam: To consist of a physical exam and evaluation of vital signs, weight, and performance status. To be evaluated at the beginning of each cycle, or as medically indicated.

[h] EKG: To be conducted at baseline, then as clinically indicated.

[l] Pregnancy Test: Women of childbearing potential will also receive a pregnancy test within 7 days prior to registration.

[j] Follow Up: Patient follow-up will occur via standard of care or a phone call every 3 months +/- (2 weeks) for 12 months following removal from study.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients will be re-evaluated at 6, 12, and 18 weeks, then every 9 weeks thereafter. In addition to a baseline scan, confirmatory scans will also be obtained ≥ 4 weeks following initial documentation of an objective response.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will be re-evaluated at 6, 12, and 18 weeks, then every 9 weeks thereafter. 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 will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

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

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

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

12.1.2 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, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might be considered measurable, if biopsy-proven progression within the radiation field.

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.

12.1.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (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. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

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

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

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

12.1.4 Response Criteria

12.1.4.1 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.

12.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

12.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-	No	PR	

	PD/not evaluated			
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.
** 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

12.1.5 Duration of Response

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

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

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

12.1.6 Progression-Free Survival

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

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 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.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

For a Phase 1/2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

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.

13.2 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.

Requirements to access Rave via iMedidata:

- A valid account, and

- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:

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

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

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

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

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

13.2.1 Method

***CTMS Comprehensive** Monitoring:*

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For

CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 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).

13.3 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.

13.4 Collaborative Agreements Language

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

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

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

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

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

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

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

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

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

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

releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13.5 Genomic Data Sharing Plan

The investigators and statistician and/or bioinformaticians for a study will have access to all data on mutations and variants stored in the Theradex Data Base and the GDC. This information will be sequestered from access throughout the study until it is analyzed for purposes of reporting and publishing of the study results. As specified in the CRADA for the agents used in the clinical study, the pharmaceutical collaborator will have at least 6 months, longer if needed for a regulatory filing, to review the data and or receive copies of the data once the study is completed and analyzed, or sooner, if specified for purposes of generating Intellectual Property. Once these timeframes have been exceeded, the data will be available through a Data Access Committee (DAC) in the GDC following NCI and Collaborator review of the proposals.

13.6 Incidental/Secondary Findings Disclosure Procedure

Given the potential clinical implications conferred by detecting a germline and/or somatic mutation in one of the proven cancer susceptibility genes, this protocol will use the following disclosure procedure, consistent with the recommendations of the American College of Medical and Genomics (ACMG) (Green *et al*., 2013 and Kalia *et al*., 2016):

The NCI Molecular Characterization Laboratory will review the mutations/variants once at the time of initial specimen evaluation according to the most recent version of the ACMG guidance on variants. The NCI Molecular Characterization Laboratory will not re-review all specimens received if a new version of the ACMG guidance is published after the initial review.

For each participant with a pathogenic or likely pathogenic germline and/or somatic variant detected in the WES of blood (as defined in the ACMG guidance), the NCI Molecular Characterization Laboratory will report to the Program Director or Scientific Officer the UPID and variant(s) identified. The Program Director or Scientific Officer will contact Theradex to obtain the name of the protocol, investigator treating the patient, and the Principal Investigator of the grant. The treating physician will be contacted by phone and in writing to ask the patient whether he or she is interested in learning more about the finding.

If the patient wants to know more, the physician should contact the Program Director for more information about the mutation/variant. The treating physician and a medical genetics counselor should meet with the patient to discuss the importance and meaning of the finding, but not the finding itself, and notify the patient that this research finding must be confirmed by Sanger sequencing at the patient's/patient insurer's expense in a Clinical Laboratory Improvement

Amendments (CLIA)-approved laboratory. The treating physician and genetic counselor should inform the patient of the confirmed result and its meaning and significance to the patient. If desired, the patient may elect to undergo genetic counseling and confirmatory CLIA-approved clinical testing on his or her own. Neither the research laboratory nor the National Cancer Institute will be responsible for the costs incurred for any confirmatory genetic testing or counseling.

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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 FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

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APPENDIX C ACCEPTABLE BIRTH CONTROL METHODS

Patients of child-bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study, and for 6 months after completing treatment administration. Acceptable birth control methods are listed below. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to avoid donating sperm for during the study period, and to use adequate contraception prior to the study, for the duration of study participation, and for 6 months after completion completing treatment administration.

Acceptable combinations of birth control methods include:

Condom with spermicide and one of the following:

- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom+spermicide. Provided coils are copper-banded

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon, Norplan)+male condom with spermicide
- Normal and low dose combined oral pills+male condom with spermicide

- Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
- ntravaginal device+male condom with spermicide (eg, EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

APPENDIX D PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

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

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

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

Explanation

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

These are the things that you need to know:
The study drug berzosertib (M6620, VX-970), 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.

Version *Apr2021*

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**	NIH NATIONAL CANCER INSTITUTE
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Berzosertib (M6620, VX-970) 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 E PRE-BIOPSY ASSESSMENT

A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system. Additional information can be found in the Investigational Radiology SOP available at:
https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_IR_Research_Biopsy_SOP.pdf.

Individual Patient Pre-Biopsy Assessment. IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

- IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics.

    1. Biopsy should not be done
        A. Due to safety concerns
        B. Due to lack of suitable lesion for biopsy

    2. Uncertainty about success
        A. Due to access path to lesion
        B. Due to lesion characteristics

    3. Likely successful

- Lesion characteristics to be considered
    - Size (small) (<2 cm)
    - Location/path to lesion
    - Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
    - PET (+/-), avidity
    - Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

APPENDIX F PHARMACOKINETICS (PK) SHEET DAY 1 AND 2

NCI 10313 (M6620, gemcitabine in Plasma): A phase IB and randomized open-label phase II study of M6620 in combination with carboplatin/gemcitabine/pembrolizumab in patients with chemotherapy-naïve advanced non-small cell lung cancer of squamous cell histology

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~4-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA)**, mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also.*

Note the start and stop times of infusions in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

M6620, gemcitabine (GEM)

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 1 Gemcitabine infusion (nominal 30 min) GEM Dose (mg/m2):_____			
pre sample			Also draw the serum sample without THU at this time
GEM infusion **start**			
25 min post GEM start (~5 min prior to EOI)			
GEM infusion **end**			

NCI 10313 (M6620, gemcitabine in Plasma): A phase IB and randomized open-label phase II study of M6620 in combination with carboplatin/gemcitabine/pembrolizumab in patients with chemotherapy-naïve advanced non-small cell lung cancer of squamous cell histology

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each time point, **~4-5 mL** of peripheral blood will be collected in a **purple-topped (EDTA)**, mix by inversion, and place sample immediately on ice after collection; samples must be processed within 30 minutes. After sample processing, store plasma samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, the dosing information must be transferred also.*

Note the start and stop times of infusions in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

M6620, gemcitabine (GEM)

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments**
Cycle 1 Day 2 M6620 infusion (nominal 60 min) M6620 Dose (mg/m2):_____			
pre sample			
M6620 infusion **start**			
30 min post M6620 start			
55 min post M6620 start (~5 min prior to EOI)			
M6620 infusion **end**			
15 min post end M6620			
30 min post end M6620			
60 min post end M6620			

APPENDIX G - 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, if available, 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

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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): Primary Metastatic

Time point (circle one): Baseline

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, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.