SUMMARY OF CHANGES

Date:	August 25, 2020
Document:	NCI Protocol #9947, PhII-135: "A Randomized Phase 2 Trial of Cisplatin/Gemcitabine with or without M6620 (VX-970) in Metastatic Urothelial Carcinoma."
Note:	The following is a Summary of Changes between the 6.4.19 and 8.25.20 versions of protocol

Section	**Description of Change (v. 6.4.19 and v. 8.25.20)**
Face Page	Changed protocol version and headers to August 25, 2020. Updated participating sites to include CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations.

NCI Protocol #: 9947

Local Protocol #: PhII-135

ClinicalTrials.gov Identifier: NCT02567409

TITLE: A Randomized Phase 2 Trial of Cisplatin/Gemcitabine with or without M6620 (VX-970) in Metastatic Urothelial Carcinoma

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CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

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NCI-Supplied Agent: M6620 (VX-970) (NSC 780162)

Other Agent(s): Cisplatin (Platinol) (NSC# 119875) – commercial supply
Gemcitabine (Gemzar) (NSC# 613327) – commercial supply

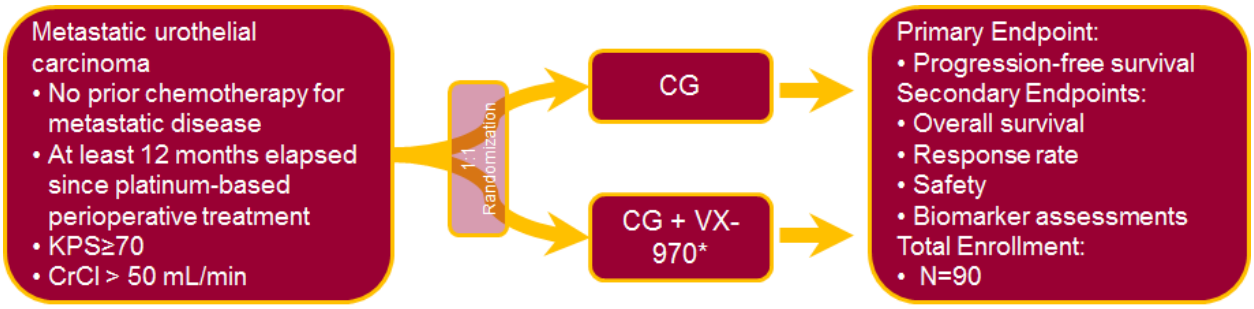
IND #:

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

August 24, 2015	Initial Protocol
October 19, 2015	Consensus Review
November 9, 2015	Follow Up Review
December 9, 2015	Amendment
April 14, 2016	Amendment (FDA)
April 28, 2016	Follow Up Review
July 7, 2016	CIRB Stipulations
August 22, 2016	Amendment
September 28, 2016	Amendment (RRA)
February 28, 2017	Amendment
March 9, 2018	Amendment
June 19, 2018	Amendment
June 4, 2019	Amendment (RA)
August 25, 2020	Amendment

SCHEMA



* Using dosing established from an ongoing phase I trial (NCT02157792). Dosing of cisplatin and gemcitabine are 60 mg/m^2 and 875 mg/m^2 on day 1 and days 1/8, respectively, of a 21 day cycle. Dosing reflects other RP2 studies employing a CG backbone (e.g., NCT01524991). M6620 (VX-970) at 90 mg/m^2 will be administered on days 2 and 9 of a 21 day cycle.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine if the addition of M6620 (VX-970) to cisplatin/gemcitabine improves PFS relative to cisplatin/gemcitabine alone.

1.2 Secondary Objectives

1.2.1 To compare OS with the addition of M6620 (VX-970) to cisplatin/gemcitabine relative to cisplatin/gemcitabine alone

1.2.2 To compare tumor response rate with the addition of M6620 (VX-970) to cisplatin/gemcitabine relative to cisplatin/gemcitabine alone

1.2.3 To compare safety with the addition of M6620 (VX-970) to cisplatin/gemcitabine relative to cisplatin/gemcitabine alone

1.2.4 To assess the role of p53 status in predicting response to M6620 (VX-970)-based therapy

2. BACKGROUND

2.1 Bladder Cancer

Metastatic urothelial carcinoma (MUC) patients have a median overall survival of approximately 15 months, and accounted for an estimated 15,580 deaths in the United States in 2014 (Abida *et al* , 2015). The use of platinating agents in treating urothelial carcinomas has been well-documented in the literature for over 30 years (Yagoda *et al* 1976). Previously, the combination methotrexate, vinblastine (Adriamycin) and cisplatin (MVAC) was the standard first-line treatment for MUC. More recently, combination gemcitabine and cisplatin (GC) has become a standard first-line treatment for MUC, because it appears to have similar efficacy as MVAC and may be less myelosuppressive (Roberts *et al* 2006). Some efforts have been made to build on GC through the addition of targeted agents (e.g., cetuximab or bevacizumab) (Grivas *et al* 2012; Hahn *et al* 2011), but prospective evaluations have shown little benefit with those novel combinations. For patients "unfit" for cisplatin, there are data to support carboplatin-based regimens as a first-line approach. In all others, cisplatin with gemcitabine remains a mainstay of treatment (Roberts *et al* 2006).

ATR and DNA Damage response

The DNA-damage response (DDR) is a multicomplex network of signaling pathways involved in surveillance and repair of DNA damage and transient cell cycle arrest to ensure genomic stability and cell viability (Fokas *et al.*, 2014; Weber and Ryan, 2015; Zeman and Cimprich, 2014). Deficiencies in DDR mechanisms have been shown to contribute to tumor development. The primary sensors of DNA damage and regulators of DDR are ataxia telangiectasia mutated (ATM) and ataxia telangiectasia Rad3-related (ATR) protein kinases. They both contribute to maintaining genome integrity in response to various exogenous and endogenous genotoxic insults, *e.g.*,

cytotoxic chemotherapy, ultraviolet light, ionizing radiation (IR), or hypoxia (Fokas *et al.*, 2014; Pitts *et al.*, 2014; Yan *et al.,* 2014). Although ATR and ATM have broadly overlapping substrate specificities, they have non-redundant functions, which are well coordinated during DDR. ATR appears to be primarily activated by single-strand DNA (ssDNA) breaks (SSB) during replicative stress while ATM is a main sensor of double-strand DNA (dsDNA) breaks (DSB). The key outcomes of ATR activation are inhibition of cell-cycle progression and suppression of late replicating origin firing (Zeman and Cimprich, 2014). ATR not only helps to stabilize but also restarts stalled replication forks, and suppresses recombination. ATR is recruited to the sites of SSB at stalled replication forks resulting from replication stress (Fokas *et al.*, 2014; Pitts *et al.*, 2014). ATR phosphorylates/activates checkpoint kinase 1 (CHK1) at serine 345 (CHK1pS^{345}), which stabilizes stalled replication forks until replication stress is resolved and DNA damage is repaired. Activated CHK1 phosphorylates and inhibits the cell division cycle 25A (CDC25A) phosphatase, which ultimately results in cell cycle arrest in intra-S-phase and/or G2-phase and blocks cells from entering mitosis until DNA is repaired and completely replicated [1,2]. The ATR function is not entirely restricted to CHK1 activation as it has been shown to be independently involved in replication of DNA and regulation of a DNA-damage protein network (Fokas *et al.*, 2014). Upon detecting DSBs, ATM activates CHK2, which controls p53-dependent G1-phase arrest. Unlike normal cells, cancer cells are often deficient in ATM signaling. It has been hypothesized that loss of the G1 checkpoint renders tumor cells more reliant on the ATR-controlled S/G2 checkpoints for repairing DNA damage and survival (Reaper *et al.*, 2011; Fokas *et al.*, 2014). Therefore, in tumor cells with defective ATM signaling, ATR inhibition may exacerbate replication stress leading to accumulation of DSBs, collapse of stalled replication forks, and eventually to lethal mitotic catastrophe. In contrast, normal cells which exhibit a low level of replicative stress and have functional ATM are expected to tolerate ATR inhibition. Indeed, preclinical studies have shown that disruption of the ATR pathway can exacerbate replication stress in oncogene-driven tumors and promotes cell killing. In addition, tumor cells, which proliferate rapidly, are more susceptible to the cytotoxic effects of chemotherapy and radiation than slowly proliferating normal cells (Fokas *et al.*, 2014; Weber and Ryan, 2015). However, the effectiveness of such DNA damage-inducing therapies in cancer treatment is attenuated by cells developing drug resistance, leading to tumor recurrence. Acquired resistance to cytotoxic therapies in tumors has been linked to the activation of DDR. There is accumulating preclinical evidence that ATR inhibition can sensitize tumor cells to the effects of radiation or chemotherapy.

2.2 CTEP IND Agent(s)

2.2.1 M6620 (VX-970)

Mechanism of Action

M6620 (VX-970) (former names VET-0768079 or VE-822) is a highly potent and selective ATP-competitive inhibitor of ATR, with an inhibition constant (Ki) <0.2 nmol/L (nM) (Fokas *et al.*, 2012; Investigator's Brochure 2015). In comparison, M6620 (VX-970) was >100-fold weaker inhibitor of ATM (Ki=34 nM) and >1000-fold less effective against other closely related kinases, such as DNA-dependent protein kinase (DNA-PK) (Ki>4 mcM), mTOR (Ki>1mcM), and PI3K-gamma (Ki=0.22 mcM) (Fokas et al., 2012). Overall, among 291 kinases tested, M6620 (VX-970)'s Ki values were >500-fold higher for 278 kinases (Ki>200 nM), >50-fold higher for 12

kinases (Ki>15 nM), and >25-fold higher for FLT4 (Ki=8 nM) than its Ki for ATR (Investigator's Brochure, 2015). A cellular 50% inhibition of ATR was attained at a M6620 (VX-970) concentration (IC_{50}) of 0.019 mcM, demonstrating >100-fold greater selectivity against ATR compared to ATM or DNA-PK (IC_{50} of 2.6 mcM or 18.1 mcM, respectively) (Fokas *et al.*, 2012).

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

Concurrent treatment of cancer cell lines with M6620 (VX-970) and various DNA-damaging agents led to sustained M6620 (VX-970)-dose-dependent decreases in levels of chemotherapy-induced CHK1pS^{345}, a major substrate of ATR (Fokas *et al*., 2012; Hall *et al*., 2014; Investigator's Brochure, 2015). In the presence of DNA damage, primarily DSBs, histone H2AX is phosphorylated at serine 139 to produce γH2AX (H2AXpS^{139}). Although all three DDR regulatory kinases, ATM, ATR, and DNA-PK phosphorylate H2AX to γH2AX, they are variably activated during different DNA-damage repair mechanisms (*e.g*., HR repair, non-homologous end joining [NHEJ] repair, base excision repair due induced by stalled replication forks, *etc*.) (Kuo and Yang, 2008). In addition, for efficient DNA-damage repair, the DDR regulatory kinases must be able to access damaged sites in the chromatin environment. ATM has been shown to phosphorylate the heterochromatin protein KAP1 at serine 824 (KAP1pS^{824}) in response to DNA damage (White *et al.*, 2012). Exposure of lung cancer cell lines as well as primary tumors to M6620 (VX-970) in combination with DNA-damaging agents enhanced levels of the DNA-damage markers, *i.e*., γH2AX and KAP1pS^{824}, as compared to DNA-damaging agent alone (Hall *et al*., 2014; Investigator's Brochure, 2015). Sequential treatment of cells with DNA-damaging agent followed 15 h later by M6620 (VX-970) resulted in an initial inhibition of phospho-CHK1 (for 1 to 2 h) (Investigator's Brochure, 2015). However, over time, phospho-CHK1 reappeared despite continued exposure to M6620 (VX-970). The rebound of phospho-CHK1 has been attributed to non-specific phosphorylation by an undefined kinase. However, despite the transient inhibition of phospho-CHK1, the sustained accumulation of γH2AX and KAP1pS^{824} was observed. Together these data suggest that disruption of ATR-mediated DDR signaling by M6620 (VX-970) leads to sustained accumulation of DNA damage in cancer cells exposed to DNA-damaging agents. Failure to repair chemotherapy-induced DNA damage in the presence of M6620 (VX-970) has been hypothesized to drive enhanced cytotoxicity in cancer cells. These data support using γH2AX and KAP1pS^{824} as pharmacodynamic markers of M6620 (VX-970) activity.

M6620 (VX-970)-mediated radiosensitivity of pancreatic ductal adenocarcinoma cells was associated with inhibition of HR repair (Fokas *et al*., 2012). M6620 (VX-970) caused increased persistence of γH2AX levels both *in vitro* and *in vivo*. Adding M6620 (VX-970) to gemcitabine and ionizing radiation (IR) dramatically enhanced antitumor effects, with early and late apoptosis and abrogation of IR-induced G2 checkpoint in cell culture experiments. It has been suggested that by promoting strong S-phase arrest, chemoradiation may further increase dependence of tumor cells on ATR-mediated homologous recombination (HR) repair of DNA double strand breaks (DSBs) and for survival.

Nonclinical studies

In vitro antitumor activity

In the absence of exogenous DNA-damaging agents, M6620 (VX-970) demonstrated stronger antiproliferative effects against three cancer cell lines tested (HCT116, HT29, and NCI-H23 with IC_{50s} of 35, 48, and 170 nM, respectively) compared to noncancerous fibroblast and epithelial cells (IC_{50}=110-200 nM) (Investigator's Brochure, 2015). However, among the three cancer cell lines, potent cytotoxicity by single-agent M6620 (VX-970) was seen only in a colorectal cancer [CRC] cell line HCT116: a 50% effect (death in 50% of cells) was observed at a concentration of 61 nM M6620 (VX-970) (EC_{50}). This suggests that certain cancer cells may be particularly reliant on ATR for survival even in the absence of an exogenous DNA-damaging agent.

In the cell proliferation assay with the HCT116 cell line, M6620 (VX-970) synergized with cisplatin (cross-linking agent), gemcitabine (anti-metabolite), irinotecan (topoisomerase I inhibitor), and etoposide (topoisomerase II inhibitor) (Investigator's Brochure, 2015). The most dramatic response was observed in combination with cisplatin (a 20-fold lower IC_{50} compared to the IC_{50} of cisplatin alone). Preliminary data from cell proliferation studies with M6620 (VX-970) + carboplatin suggests >10-fold reduction in carboplatin IC_{50} for two non-small cell lung cancer (NSCLC) cell lines (H23 and HT1299) tested.

The impact of M6620 (VX-970) on chemotherapy-induced cytotoxicity was further examined against a panel of 37 lung cancer cell lines (including squamous NSCLC and small cell lung cancer [SCLC] histotypes) and 15 pancreatic cancer cell lines (Investigator's Brochure, 2015). Most lung cancer cell lines responded well to M6620 (VX-970) in combination with cisplatin (84% of cell lines) or gemcitabine (76% of cell lines), demonstrating ≥3-fold reduction in the IC_{50} compared to IC_{50} of the cytotoxic agent alone [3] and (Investigator's Brochure, 2015). Enhanced sensitivity was also observed with etoposide (53% of cell lines), irinotecan (49% of cell lines) and oxaliplatin (39% of cell lines). About 40% of cell lines were hypersensitized (>10-fold reduction in IC_{50} observed) to cisplatin by M6620 (VX-970). Marked synergy between the two agents was also seen against four of seven human NSCLC primary tumors tested *in vitro* (Hall *et al.*, 2014). The greatest antitumor synergistic effect was demonstrated by tumors with poor response to cisplatin alone. Similarly, most pancreatic cancer lines responded well to combination of M6620 (VX-970) with cisplatin or gemcitabine: antitumor IC_{50} was ≥3-fold lower for the M6620 (VX-970) + cytotoxic agent in >70% of cell lines as compared to IC_{50} of cytotoxic agent alone (Investigator's Brochure, 2015).

In addition, significant radiosensitization effects by M6620 (VX-970) were observed against two human pancreatic cancer cell lines with mutant KRAS and mutant p53 (MiaPaCa-2 and PSN1) (P<0.05), but not against non-cancerous fibroblast cell lines (Fokas *et al*., 2012). In addition, M6620 (VX-970) profoundly sensitized pancreatic tumor cells to gemcitabine-based chemoradiation.

Impact of defective ATM signaling on sensitivity of cells to M6620 (VX-970) in combination with a cytotoxic agent (cisplatin, gemcitabine, irinotecan, oxaliplatin, or etoposide) was examined in isogenic matched lung cancer cells (wild-type p53 A549 versus A549 transfected with p53 shRNA), using a cell viability assay (Hall *et al.*, 2014; Investigator's Brochure, 2015). Loss of p53 promoted sensitivity to ATR inhibition in combination with all five cytotoxic agents in contrast with the effects in wild-type A549. M6620 (VX-970) also synergized with cisplatin

resulting in cytotoxicity in ATM-null primary skin fibroblasts, but no cytotoxicity was observed against wild-type fibroblasts (Investigator's Brochure, 2015). This suggests that the functional status of the ATM pathway is a contributing factor in the cellular response to the inhibition of ATR.

Of note, the response/p53 status relationship was unclear in the panel of heterogeneous cancer cell lines exposed to M6620 (VX-970) + chemotherapy (Hall *et al.*, 2014). Although not significant, there was a trend of causality between response and p53 status (P=0.08) for M6620 (VX-970) combined with cisplatin. Furthermore, no clear relationship between cellular response to M6620 (VX-970) + cisplatin and p53 status was observed in seven primary lung tumors.

In vivo antitumor activity

The *in vivo* activity of M6620 (VX-970) was tested in multiple mouse xenograft models derived from human hung cancer cell lines and primary human tumor cells (Hall *et al.*, 2014; Investigator's Brochure, 2015). M6620 (VX-970) potentiated antitumor effects of cisplatin, gemcitabine, irinotecan, and IR in a dose-dependent as well as dosing schedule-dependent manner. Antitumor efficacy correlated with inhibition of phospho-CHK1 and an increase in DNA-damage markers. This supports ATR inhibition as a primary mechanism of action for M6620 (VX-970). Single-agent M6620 (VX-970) had no significant effect on tumor growth in the experimental models. M6620 (VX-970) was generally well tolerated at efficacious doses in combination with DNA-damaging agents. Some body weight loss and enhanced changes in specific peripheral blood cell populations were observed with intensive and sustained dosing of M6620 (VX-970) in combination with cisplatin. This effect could be attributed to an increased growth arrest, which was observed *in vitro* in normal cells for combinations of M6620 (VX-970) with DNA-damaging agents. This effect was reversed when ATR activity was restored. M6620 (VX-970) sensitized pancreatic tumor xenografts to the cytotoxic effects of gemcitabine-based chemoradiation (Fokas *et al*., 2012). The combination treatment was effective even at gemcitabine doses with no single-agent activity. M6620 (VX-970) administered in combination with gemcitabine + IR was well tolerated.

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

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

Nonclinical Pharmacokinetics

In all non-clinical species (the mouse, rat, dog, and monkey), M6620 (VX-970) exhibited a high volume of distribution (V_d); tissue exposure, including tumor, was high. In rats, no accumulation or retention was observed in tissues and the elimination half-lives ($t_{1/2}$) were similar across all tissues and whole blood (Investigator's Brochure, 2015). The whole blood $t_{1/2}$ was 11.6 h in rats and 9.8 h in dogs. M6620 (VX-970) was extensively bound to plasma proteins; the free fraction of M6620 (VX-970) was only 2.1% in human blood.

M6620 (VX-970) is primarily eliminated by oxidative metabolism, with a cytochrome 450 (CYP) 3A4 isoform being the principle isoform responsible. Strong inducers or inhibitors of CYP3A4 may alter M6620 (VX-970) kinetics and blood levels. Based on its minimal inhibition or induction effects on CYPs, M6620 (VX-970) is expected to have a low potential for drug-drug interactions. M6620 (VX-970) metabolites were excreted in the urine and bile. All metabolites observed in human hepatocyte incubations were also observed in either rat or dog hepatocyte incubations and in the blood, bile, or urine from rats or dogs. The systemic clearance of M6620 (VX-970) following IV administration was 26 and 13 mL/min/kg in the rat and dog, respectively.

Nonclinical Safety Pharmacology

An in-house manual patch-clamp human ether-a-go-go-related gene (hERG) assay demonstrated moderate inhibition of the hERG channel (Investigator's Brochure, 2015). However, a telemetry dog study did not demonstrate any cardiovascular (CV) effects at exposures greatly exceeding the target human exposure.

Nonclinical Toxicology

M6620 (VX-970) was administered PO or IV for up to 28 days in rats and dogs. The oral studies used an aggressive dosing regimen (every 2 days) to define the toxicity profile, while IV studies (dosed twice per week) were more representative of the planned clinical dosing schedule (Investigator's Brochure, 2015). In the rat, the severely toxic dose in 10% of animals (STD_{10}) was 30 mg/kg/day IV. The highest non-severely toxic dose (HNSTD) in dogs was 20 mg/kg/day IV. The target organs for M6620 (VX-970) toxicity in rats included testes and peripheral blood cell populations (red cell mass, eosinophils, and platelets). Target organs in the dog included the liver, testes, and peripheral blood cell populations (red cell mass and eosinophils); changes in these organs appeared to be reversible after discontinuing of M6620 (VX-970) in both rats and dogs.

M6620 (VX-970) had no cardiovascular liabilities, was not genotoxic in mutagenicity assay, had no hemolytic potential in human blood or compatibility issues in human plasma, and was well tolerated in an acute rabbit parenteral injection study. M6620 (VX-970) does absorb in the ultraviolet (UV) spectrum and has high tissue distribution in rats.

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

Clinical Studies

The suggested starting dose of M6620 (VX-970) in humans, 18 mg/m^2 IV, was equivalent to 1/10 of the rat STD_{10} (30 mg/kg or 180 mg/m^2) (Investigator's Brochure, 2015). This dose represents a more conservative estimate than 37 mg/m^2 IV which would an estimate corresponding to the 1/6 of the dog HNSTD (20 mg/kg or 222 mg/m^2).

Vertex Pharmaceuticals, Inc. has sponsored the first-in-human M6620 (VX-970) phase 1 study withM6620 (VX-970) being administered in combination with DNA-damaging agents to patients with advanced solid malignancies (Study 001); the study is ongoing (Investigator's Brochure, 2015). This study evaluates M6620 (VX-970) in combination with either gemcitabine +/- cisplatin or cisplatin +/- etoposide. M6620 (VX-970) is dose-escalated (18, 36, 60, 72 mg/m^2 IV) following the standard 3+3 design. To allow for the single-agent M6620 (VX-970) PK, a 7-day lead-in treatment period of M6620 (VX-970) before cycle 1 has been included. Combinations of M6620 (VX-970) with gemcitabine or cisplatin are administered on a weekly schedule, with M6620 (VX-970) being dosed 24 h after a DNA-damaging agent.

Clinical Pharmacokinetics

Clinical PK have been evaluated both in whole blood and plasma (Investigator's Brochure, 2015). Preliminary clinical PK data are available from the lead-in period for the first two cohorts (M6620 (VX-970) 18 mg/m^2 and 36 mg/m^2). Mean exposure (AUC) profiles were similar in whole blood and plasma. The terminal elimination $t_{1/2}$ was approximately 16 h across all doses. Overall, the C_{max} was 1.36x greater and $AUC_{0-\infty}$ 1.43x greater in whole blood than in plasma. The results suggest that plasma is an appropriate matrix to characterize the M6620 (VX-970) PK. M6620 (VX-970) exposures were similar for the agent administered alone and in combination with gemcitabine, suggesting no apparent drug-drug interactions. In the M6620 (VX-970) single dose studies, the plasma C_{max} and $AUC_{0-\infty}$ increase in linear fashion with dose up to 480 mg/m^2.

Clinical Efficacy

Preliminary efficacy data (cut off February 27, 2015) are available for 38 patients treated with M6620 (VX-970) in combination with gemcitabine or cisplatin (study 001) and for 11 patients treated with single-agent M6620 (VX-970) (study 002) (Investigator's Brochure, 2015). Of 29 evaluable patients (receiving M6620 (VX-970) + gemcitabine, 16 patients had stable disease (SD) (5/6, 4/9, and 7/13 patients with NSCLC, CRC, or other cancers, respectively) and 1 patient with EBV^+ nasopharyngeal cancer demonstrated a 51% tumor reduction corresponding to a partial response (PR). Four of seven evaluable patients receiving M6620 (VX-970) + cisplatin demonstrated SD. Among 10 evaluable patients treated with M6620 (VX-970) monotherapy, there were 3 SD and 1 PR. The CRC patient who achieved a PR (80% reduction of the lesion) on monotherapy continues on treatment after completing 11 cycles.

Clinical Safety

Preliminary safety data for 38 patients receiving M6620 (VX-970) in combination with

gemcitabine or cisplatin (Study 001) and 11 patients receiving M6620 (VX-970) alone (Study 002) can be found in Investigator's Brochure (2015). No dose-limiting toxicities (DLTs) were observed during either 7-14-day or 21-days lead-in period of M6620 (VX-970) monotherapy in Study 001. There were no deaths attributable to treatment with M6620 (VX-970) alone. There were no grade 3+ AEs; serious AEs (SAEs) were experienced by 2 patients (palpitation, pyrexia, and dyspnea). In the combination phase evaluating M6620 (VX-970) + gemcitabine, M6620 (VX-970) was administered at 18-140 mg/m^2 IV and gemcitabine at 500-875 mg/m^2 IV. Of 27 patients included in the DLT analysis, 4 patients (14.8%) experienced 7 DLTs (2 alanine aminotransferase [ALT], 2 aspartate aminotransferase [AST], 1 alkaline phosphatase, 1 thrombocytopenia, 1 fatigue). A total of 16 patients (2 during the M6620 (VX-970) lead-in phase and 14 during the combination treatment) experienced serious SAEs; 9 of them were assessed as related to treatment. The most common AEs regardless causality were nausea (65%), vomiting (55%), and fatigue (48%). In the sub-study evaluating M6620 (VX-970) + cisplatin, six patients received M6620 (VX-970) (90-140 mg/m^2) with cisplatin 40 mg/m^2. There were no DLTs and two SAEs (1 patient with metastases to CNS treated during the lead-in period and 1 patient with dyspnea), none of which were related to treatment. The most common AEs, regardless of causality, were nausea and fatigue, both observed in 4/6 patients (67%).

In the single-agent M6620 (VX-970) study (Study 002), M6620 (VX-970) was administered IV at doses ranging from 60-480 mg/m^2. There were no DLTs among 11 patients evaluated for toxicities (cut-off February 10, 2015). One SAE of grade 3 fatigue was classified as possibly related to M6620 (VX-970). The most common AE was fatigue (5/11 patients [46%]); nausea, urinary infection, headache, and flushing were observed in 3 patients (28%).

As of April 17, 2015, acute hypersensitivity, reported in 2/66 patients (3.0%) during administering M6620 (VX-970), has been identified as an adverse drug reaction for VX 970.

Safety Summary and Guidance for Investigators (Investigator's Brochure, 2015)

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

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

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

- Preclinical studies suggested that M6620 (VX-970) causes testicular changes with signs of reversibility after the drug discontinuation. Developmental and reproductive toxicity studies have not been conducted yet. Therefore, patients should take stringent measures to

avoid fathering or bearing children while on study drug and for 6 months after discontinuation of M6620 (VX-970).

2.3 Commercially Available Agents

The current protocol will use the combination of cisplatin and gemcitabine as a standard of care regimen, and patients will be treated with these drugs alone or in combination with M6620 (VX-970) (as subsequently discussed). Cisplatin is a platinating agent which works through the formation of monoadducts with cellular DNA. Cisplatin reacts preferentially with the N7 position of guanine. Interstrand cross links formed by a multiple monoadducts ultimately result in cumulative DNA damage and cellular death. Cisplatin is principally renally excreted. In contrast to cisplatin, gemcitabine is an antimetabolite. Gemcitabine requires a nuclear transporter for intracellular accumulation. Once in the cell, gemcitabine is phosphorylated to 2,2-difluorodeoxycytidine-phosphate, and this moiety inhibits ribonucleotide reductase. As a consequence, pools of deoxynucleotide triphosphates occur and subsequent cell death is encountered. The combination of cisplatin and gemcitabine was established as a standard in advanced bladder cancer through a randomized, phase III study comparing the regimen to the aforementioned 4 drug regimen, MVAC (Robert *et al* Ann Oncol 2006) In total, the study included 405 patients, with 203 randomized to cisplatin/gemcitabine and 202 randomized to MVAC. Overall survival was similar in both arms, with a median survival of 14.0 months with cisplatin/gemcitabine and 15.2 months in the MVAC arm (P=0.66). Median PFS was 7.7 months with cisplatin/gemcitabine and 8.3 months with MVAC. Several prognostic factors were noted in this study which correlated with overall survival. These included performance status (>70), TNM stage (M0 v M1), low/normal alkaline phosphatase expression, number of sites of disease < 3, and the absence of visceral metastases. Ultimately, the toxicity profile of cisplatin/gemcitabine appeared to be more favorable, particularly from the standpoint of a lesser incidence of neutropenic fever and sepsis. Thus, most modern trials of first-line therapy for advanced urothelial cancer utilized cisplatin/gemcitabine as a base.

2.4 Rationale for the combination of cisplatin/gemcitabine with M6620 (VX-970) in advanced bladder cancer

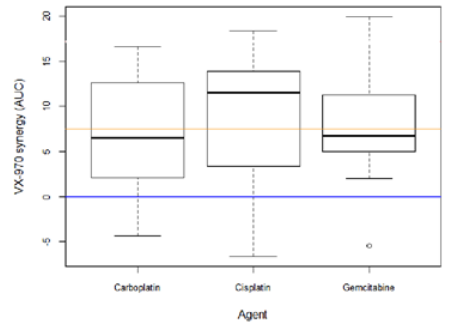

Figure 2. Synergy of M6620 (VX-970) in combination with multiple DNA damaging agents in a panel of 10 bladder cancer cell lines. Figure legend: The blue line indicates no interaction between the specified agent and M6620 (VX-970) (additivity). The orange line indicates synergy (Sum of AUC synergy of 7.5). Figure legend: The blue line indicates no interaction between the specified agent and M6620 (VX-970) (additivity). The orange line indicates synergy (Sum of AUC synergy of 7.5).

It is hypothesized that M6620 (VX-970) may improve the efficacy of cisplatin and gemcitabine. As previously described (see Section 2.1), cisplatin/gemcitabine represents a standard first-line regimen for metastatic urothelial carcinoma.

Data supplied by Vertex Pharmaceuticals suggests that M6620 (VX-970) appears to have *in vivo* synergy with cisplatin; Figure 1a outlines the activity of M6620 (VX-970) with cisplatin in a cisplatin-resistant xenograft, while Figure 1b reflects the synergy of cisplatin with M6620 (VX-970) in a non-small cell lung cancer PDX model. In the context of bladder cancer, inhibition of Chk1 (a downstream mediator of ATR) may augment the

activity of gemcitabine in the TCC-sup urothelial cancer cell line. (Wang *et al* 2014) Notably, this synergy is optimal when M6620 (VX-970) is administered 24 hours after cisplatin or gemcitabine in cellular models (Vertex Pharmaceuticals; data on file.)

Furthermore, Vertex Pharmaceuticals evaluated the activity of M6620 (VX-970) in combination with carboplatin, cisplatin, and gemcitabine in a panel of 10 bladder cancer cell lines. Synergy or antagonism was calculated using the sum of AUC difference for each combination in each cell line. Synergy (AUC of greater than 7.5) was seen when M6620 (VX-970) was combined with carboplatin (in 5/10 lines), cisplatin (in 7/10 lines), and gemcitabine (in 3/10 lines). In the rest of the cell lines tested, additivity was observed. These results are summarized in Figure 2. (data on file, Vertex Pharmaceuticals)

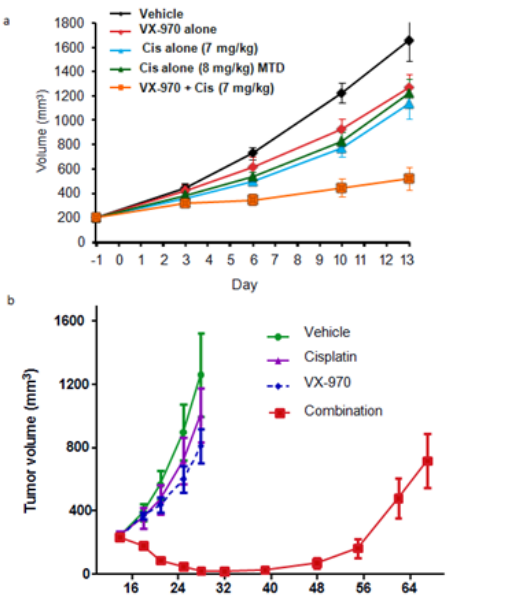

Figure 1. (a) VX-970 with cisplatin provides improved antitumor efficacy vs MTD of cisplatin alone in a HCT116 cisplatin resistant xenograft. (b) VX-970 markedly improves tumor responses to cisplatin in a PDX NSCLC model.

Collectively, these data provide rationale to investigate cisplatin and gemcitabine in combination with M6620 (VX-970) in metastatic urothelial carcinoma.
This protocol proposes a randomized, phase II study comparing cisplatin and gemcitabine with M6620 (VX-970) to cisplatin and gemcitabine alone. A phase I trial is evaluating the M6620 (VX-970) monotherapy (NCT02157792). Integrated in this phase I experience is a dose escalation portion for the combination of M6620 (VX-970) with gemcitabine, and a further dose escalation of the combination of cisplatin, gemcitabine and M6620 (VX-970). It has been hypothesized that M6620 (VX-970) may optimally synergize with cytotoxic therapy if delivered in a latent fashion – therefore, this current study will evaluate M6620 (VX-970) one day following cytotoxic treatment (i.e., on days 2 and 9 on a conventional 21 day cycle of cisplatin with gemcitabine).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed metastatic urothelial carcinoma. Urothelial cancer derived from the bladder, ureter or upper tract is permitted.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.3 Patients must have access to archival tumor tissue for proposed correlative studies. These may be derived from TURBT, cystectomy, or biopsy. If archival tissue is not available for proposed correlatives, patients may be enrolled at the discretion of the study PI (SKP).

3.1.4 No prior cytotoxic chemotherapy for metastatic disease. Prior immunotherapy is permitted.

3.1.5 At least 12 months have elapsed since platinum-based peri-operative treatment.

3.1.6 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of M6620 (VX-970) in combination with cisplatin and gemcitabine in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.7 Karnofsky ≥70% (ECOG performance status 0-1, see Appendix A).

3.1.8 Life expectancy of greater than 3 months

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	within institutional upper limit of normal
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
– creatinine clearance	≥50 mL/min by either measured (using the Cockcroft-Gault, MDRD or CKD-EPI formula) or calculated clearance (i.e. GFR)(See Appendix C for formulas)

3.1.10 The effects of M6620 (VX-970) on the developing human fetus are unknown. For this reason and because DNA-damage response (DDR) inhibitors as well as other therapeutic agents used in this trial may have teratogenic potential, 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 and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of M6620 (VX-970) administration.

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

3.2 Exclusion Criteria

3.2.1 Radiotherapy within 4 weeks of protocol therapy.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to M6620 (VX-970), cisplatin, or gemcitabine.

3.2.4 M6620 (VX-970) is primarily metabolized by CYP3A4; therefore, concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

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

3.2.6 Pregnant women are excluded from this study because M6620 (VX-970) as a DNA-damage response (DDR) inhibitor 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 M6620 (VX-970), breastfeeding should be discontinued if the mother is treated with M6620 (VX-970). These potential risks may also apply to other agents used in this study.

3.2.7 Patients with ≥ Grade 2 neuropathy.

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 and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their

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

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

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

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

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

4.2 Site Registration

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

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

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

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572

An active status on a participating roster at the registering site.

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

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI protocol # 9947 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select by LAO-CA043, and protocol #9947.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 9947 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Local informed consent document

4.2.3 Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office

1818 Market Street, Suite 3000

Philadelphia, PA 19103

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

4.2.4 Checking **Site** Registration Status

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

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

• Site staff with the appropriate roles will reserve slots using IWRS (https://open.ctsu.org/).
• City of Hope Cancer Center will receive notification via the IWRS when a slot has been reserved. An email will be sent from the City of Hope Cancer Center to the site requesting further information such as: the patient initials, tumor type and potential start date. The spot will show as 'pending approval' in the system until the site sends a REGISTRATION FORM/ELIGIBILITY CHECKLIST (see CTSU website) accompanied with the signed consent, baseline labs, pathology report, CT/x-ray reports to the City of Hope Cancer Center at ccc@coh.org for review and confirmation of eligibility.
• Once the Registration has been reviewed, the City of Hope Cancer Center will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the City of Hope Cancer Centre will update the spot to 'reserved' in IWRS.
• The site can now enroll the patient into the study in OPEN
* At the time of registration the treatment arm will be randomly assigned

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL. (*Note: A DTL is NOT required for this study.)*
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

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: 609-619-7862 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. TREATMENT PLAN

5.1 Agent Administration

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

Eligible patients will be randomized on either on Arm A or Arm B in OPEN; in order for randomization to be completed, the following information will be required: (1) KPS and (2) visceral metastases (present or absent).

Arm A – Cisplatin/Gemcitabine with M6620 (VX-970)

Arm B – Cisplatin and Gemcitabine

Please note that the dosing for the combination of cisplatin/gemcitabine with M6620 (VX-970) will utilized the recommended phase 2 dose (RP2D) from an ongoing phase I trial combining these agents (NCT02157792). The preferred dosing of cisplatin and gemcitabine are 60 mg/m^2 and 875 mg/m^2 on day 1 and days 1/8, respectively, of a 21 day cycle. This dosing regimen reflects other randomized, phase II studies employing a CG backbone (e.g., NCT01524991). M6620 (VX-970) at 90 mg/m^2 will be administered on days 2 and 9 of the 21 day cycle intravenously, as follows:

Arm A – Cisplatin/Gemcitabine with M6620 (VX-970) Dosing Table

Agent	Route	Dose	Administration	Frequency * (± 3 days)	Cycle Length	# Cycles
M6620 (VX-970)	IV	90 mg/m^2 (*in D5W to a final concentration between 0.075 mg/ml to 1 mg/ml)*	Over 1 hour	Day 2, 9	21 days	1-6
Gemcitabine	IV	875 mg/m^2 (*per institutional guidelines)*	Over 30 minutes according to institutional guidelines	Day 1, 8		
Cisplatin	IV	60 mg/m^2 (*per institutional guidelines)*	As per institutional guidelines	Day 1		

Arm B – Cisplatin/Gemcitabine Dosing Table

Agent	Route	Dose	Administration	Frequency * (± 3 days)	Cycle Length	# Cycles
Gemcitabine	IV	1000 mg/m^2 (*per institutional guidelines)*	Over 30 minutes according to institutional guidelines	Day 1, 8	21 days	1-6
Cisplatin	IV	70 mg/m^2 (*per institutional guidelines)*	As per institutional guidelines	Day 1		

Note: * Infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. It should be clearly documented in patient's chart and case report forms.

5.1.1 M6620 (VX-970)

Prophylactic or supportive care regimens will be administered in accordance with those established in NCT02157792. See Appendix E.

M6620 (VX-970) should not come in contact with 0.9% Sodium Chloride due to incompatibility. 5% dextrose in water solution must be used for IV line priming and flushing. Infuse using an infusion set containing low-sorption, or non-PVC, DEHP-free tubing and an in-line 0.2 micron filter.

5.1.2 Cisplatin

The antiemetic regimen is at the discretion of the treating physician and according to institutional standards. Hydration before and after cisplatin should be rendered as per institutional standards (including use of mannitol and addition of sodium, potassium or other electrolytes to intravenous fluids).

5.1.3 Gemcitabine

No pre-medications are required for gemcitabine therapy.

5.1.4 Growth factor support

Prophylactic use of filgrastim or pegfilgrastim on day 9 of each cycle is encouraged but not mandated. If patients develop neutropenia or other neutropenic complications and remain on protocol-based treatment, then filgrastim or pegfilgrastim use beginning on day 9 of each cycle is mandated. Dosing of these agents should follow institutional policies.

5.2 General Concomitant Medication and Supportive Care Guidelines

M6620 (VX-970) is metabolized by cytochrome P450 (CYP) 3A4 isoenzyme (CYP3A4); exposure to M6620 (VX-970) may be affected by concomitantly administered drugs that are strong inhibitors or inducers of CYP3A4. Because of the potential for drug interactions through CYP3A4, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients.

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

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

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

In the event of infusion reaction, the investigator may use dexamethasone 8 mg (or equivalent) intravenous 30 minutes prior to infusion and/or diphenhydramine 25 mg intravenous or oral 30 minutes prior to infusion.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 6 cycles or until one of the following criteria applies:

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

5.4 Duration of Follow Up

Patients will be followed for up to 36 months after removal from protocol therapy or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

For patients who have not progressed at the time that they are removed from treatment will be followed for progression; for those who begin another treatment prior to progression, the type of treatment will be recorded, as well as the time to 1st progression.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria apply:
- Follow-up for 36 months after removal from protocol therapy
- Withdrawal of consent for further follow-up
- Death

The reason for protocol therapy termination and study removal and the dates the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose-modifications for treatment-related hematological toxicity

Dose modifications for Day 1 Treatment (Cycle 2 through Cycle 6)

The following dose modifications will be based on blood counts within 3 days prior to **Day 1** of each cycle of therapy.

<table>
<tr><th>ANC</th><th></th><th>Platelets</th><th>Cisplatin dose</th><th>Lowest gemcitabine dose in prior cycle</th><th>Day 1 dose of gemcitabine</th></tr>
<tr><td>≥1.5K/ mm^3</td><td>And</td><td>≥ 100 K/mm^3</td><td rowspan="3">Continue dose of cisplatin from prior cycle (eg, if no prior dose reductions, continue at 60 mg/m^2)</td><td>1000 mg/m^2</td><td>1000 mg/m^2</td></tr>
<tr><td>≥ 1.5K/m m^3</td><td>And</td><td>≥ 100 K/mm^3</td><td>875 mg/m^2</td><td>875 mg/m^2</td></tr>
<tr><td>≥ 1.5K/m m^3</td><td>And</td><td>≥ 100 K/mm^3</td><td>600 mg/m^2</td><td>600 mg/m^2</td></tr>
<tr><td><1.5K/ mm^3</td><td>Or</td><td><100 K/mm^3</td><td>*Hold and recheck in 1 week</td><td>Any</td><td>*Hold and recheck in 1 week</td></tr>
<tr><td colspan="6">*Once ANC ≥ 1500 and platelets ≥ 100,000, resume therapy with gemcitabine reduced by 1 dose level. If gemcitabine has already been reduced by 1 dose level, discuss further dose reduction with principal investigator. Granulocyte colony stimulating factors may be used at the discretion of the treating physician; however, growth factors should be not used during cycle #1 or in lieu of recommended dose reductions. Treatment with M6620 (VX-970) will also be HELD until patients meet criteria to resume dosing with gemcitabine and cisplatin.</td></tr>
</table>

Dose modifications for Day 8 Treatment (any cycle)

The following dose modifications of gemcitabine will be based on blood counts within 3 days prior to day 8 of each cycle of therapy.

ANC		**Platelets**	**if Day 1 dose level of gemcitabine was:**	**then Day 8 dose level of gemcitabine will be:**
≥ 1.5K/mm^3	And	≥ 100 K/mm^3	1000 mg/m^2	1000 mg/m^2
≥1.5K/mm^3	And	≥ 100,000	875 mg/m^2	875 mg/m^2
≥ 1.5K/mm^3	And	≥ 100 K/mm^3	600 mg/m^2	600 mg/m^2
1.0K/mm^3- 1.4 K/mm^3	And	≥ 100 K/mm^3	1000 mg/m^2	875 mg/m^2
1.0K/mm^3- 1.4 K/mm^3	And	≥ 100 K/mm^3	875 mg/m^2	600 mg/m^2
<1.0 K/mm^3	Or	<100,000 K/mm^3	Any	Hold and recheck in 1 week*
*Treatment held on Day 8 should not be made up at a later date; resume next cycle as scheduled with gemcitabine reduced by 1 dose level.				

There should be no dose re-escalation after a dose reduction.

Febrile neutropenia

If febrile neutropenia develops in a given cycle, hold gemcitabine, cisplatin, and M6620 (VX-970) during febrile neutropenia.

NOTE: Doses missed on Days 8 of therapy will not be made up.

Resume gemcitabine and cisplatin at one dose lower than the dose administered in the last cycle. This dose should be used for all subsequent cycles. The dose of M6620 (VX-970) will be unchanged. Granulocyte colony stimulating factors may be used at the discretion of the treating physician.

6.2 Dose Modifications for Other Treatment Related Non-Hematological Toxicity Secondary to Gemcitabine or Cisplatin

Dose reductions for non-hematologic toxicities attributable to gemcitabine or cisplatin (with the exception of alopecia or nausea/vomiting not optimally managed with antiemetics) are outlined in the table below. Only the drugs felt to be contributing to the toxicity per the Treating Physician should be dose reduced. Patients with treatment-related nausea that is grade ≥ 2 despite optimal use of antiemetics will be dose reduced by 1 level.

If nonhematologic toxicity occurs mid-cycle, and is attributed to gemcitabine, the Day 8 gemcitabine dose should be held and resumed with the subsequent cycle as scheduled.

Dose reductions for nonhematologic toxicities	
Nonhematologic toxicity	**Gemcitabine/Cisplatin**
Grade 0-2	No change
Grade 3	Hold until Grade ≤1 and resume treatment reduced by 1 dose level
Grade 4	Hold until Grade ≤1 and resume treatment reduced by 1 dose level

Dose modifications for gemcitabine and cisplatin for Arm A		
Dose level	Gemcitabine	Cisplatin
Dose level -1	600 mg/m2	50 mg/m2
Dose level -2	500 mg/m2	40 mg/m2

Dose modifications for gemcitabine and cisplatin for Arm B		
Dose level	Gemcitabine	Cisplatin
Dose level -1	875 mg/m2	60 mg/m2
Dose level -2	600 mg/m2	50 mg/m2

Dose re-escalation after a dose reduction for non-hematologic toxicity should not occur without discussion with the Study Investigator.

If toxicity is specifically attributable to cisplatin and warrants discontinuation of cisplatin, patients may be considered for continuation on treatment with gemcitabine and M6620 (VX-970) but this must be discussed with the Study Investigator.

Treatment may be delayed for up to 7 days. If more than 7 days, this must be discussed with the Study Investigator.

6.3 Dose Modifications for M6620 (VX-970)

Dose reductions for toxicities attributable to M6620 (VX-970) (with the exception of alopecia or nausea/vomiting not optimally managed with antiemetics) are outlined in the table below. Only the drugs felt to be contributing to the toxicity per the Treating Physician should be dose reduced. Patients with treatment-related nausea that is grade ≥ 2 despite optimal use of antiemetics will be dose reduced by 1 level.

Dose modifications for M6620 (VX-970) are as follows (acknowledging a starting dose of 90 mg/m^2):

Dose reductions for nonhematologic toxicities	
Nonhematologic toxicity	**M6620 (VX-970)**
Grade 0-2	No change
Grade 3	Hold until Grade ≤1 and resume treatment reduced by 1 dose level
Grade 4	Hold until Grade ≤1 and resume treatment reduced by 1 dose level

Dose modifications for M6620 (VX-970)	
Dose level	M6620 (VX-970)
Dose level -1	72 mg/m2
Dose level -2	60 mg/m2

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event 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 of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The 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/adverse_effects.htm for further clarification.

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

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for M6620 (VX-970)

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for M6620 (VX-970).

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

Version 1.4, April 30, 2019[1]

Adverse Events with Possible Relationship to M6620 (VX-970) (CTCAE 5.0 Term)	**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS	
Diarrhea	***Diarrhea (Gr 2)***
Nausea	***Nausea (Gr 2)***
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	***Fatigue (Gr 2)***
IMMUNE SYSTEM DISORDERS	
Anaphylaxis	
INFECTIONS AND INFESTATIONS	
Urinary tract infection	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Infusion related reaction	***Infusion related reaction (Gr 2)***
INVESTIGATIONS	

Adverse Events with Possible Relationship to M6620 (VX-970) (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Alanine aminotransferase increased	***Alanine aminotransferase increased (Gr 2)***
Aspartate aminotransferase increased	***Aspartate aminotransferase increased (Gr 2)***
Blood bilirubin increased	
Creatinine increased	
Lymphocyte count decreased	***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hyperglycemia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
Tumor pain	
NERVOUS SYSTEM DISORDERS	
Dizziness	
Headache	***Headache (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Pruritus	
Rash maculo-papular	
VASCULAR DISORDERS	
Flushing	

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

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

CARDIAC DISORDERS - Palpitations
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Colonic obstruction; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever
IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (lower respiratory tract infection); Otitis externa; Sepsis; Soft tissue infection
INVESTIGATIONS - GGT increased; Hemoglobin increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression)
NERVOUS SYSTEM DISORDERS - Lethargy; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Atelectasis; Dyspnea
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: M6620 (VX-970) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Adverse Event List(s) for Commercial Agent(s)

7.1.2.1 Gemcitabine

>10%: Cardiovascular: Peripheral edema (20%), edema (13%) Central nervous system: Pain (10% to 48%), fever (30% to 41%), somnolence (5% to 11%) Dermatologic: Rash (24% to 30%), alopecia (15% to 18%), pruritus (13%) Gastrointestinal: Nausea/vomiting (64% to 71%; grades 3/4: 1% to 13%), constipation (10% to 31%), diarrhea (19% to 30%), stomatitis (10% to 14%) Hematologic: Anemia (65% to 73%; grade 4: 1% to 3%), leukopenia (62% to 71%; grade 4: ≤1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 47%; grade 4: ≤1%), hemorrhage (4% to 17%; grades 3/4: <1% to 2%); myelosuppression is the dose-limiting toxicity Hepatic: Transaminases increased (67% to 78%; grades 3/4: 1% to 12%), alkaline phosphatase increased (55% to 77%; grades 3/4: 2% to 16%), bilirubin increased (13% to 26%; grades 3/4: <1% to 6%) Renal: Proteinuria (10% to 45%; grades 3/4: <1%), hematuria (13% to 35%; grades 3/4: <1%), BUN increased (8% to 16%; grades 3/4: 0%) Respiratory: Dyspnea (6% to 23%) Miscellaneous: Flu-like syndrome (19%), infection (8% to 16%; grades 3/4: <1% to 2%)

1% to 10%: Local: Injection site reactions (4%) Neuromuscular & skeletal: Paresthesia (2% to 10%) Renal: Creatinine increased (2% to 8%) Respiratory: Bronchospasm (<2%)

<1% (Limited to important or life-threatening; reported with single-agent use or with combination therapy, all reported rarely): Adult respiratory distress syndrome, anaphylactoid reaction, anorexia, arrhythmias, bullous skin eruptions, cellulitis,

cerebrovascular accident, CHF, chills, cough, desquamation, diaphoresis, gangrene, GGT increased, headache, hemolytic uremic syndrome (HUS), hepatotoxic reaction (rare), hypertension, insomnia, interstitial pneumonitis, liver failure, malaise, MI, peripheral vasculitis, petechiae, pulmonary edema, pulmonary fibrosis, radiation recall, renal failure, respiratory failure, rhinitis, sepsis, supraventricular arrhythmia, weakness

Please refer the reader to the package insert(s) for the comprehensive list of adverse events

7.1.2.2 Cisplatin

Renal: A dose-related cumulative renal tubular injury can occur. Adequate hydration and diuresis usually minimize the risk. Salt-wasting nephropathy and/or orthostatic hypotension with hyporeninemic hypoaldosteronism can occur in up to 10% of patients.

Neurologic: A dose-related ototoxicity, manifested by high-frequency hearing loss and tinnitus, occurs in about 30% of patients. Paresthesias, decreased vibratory, position, and touch sensations are less common, particularly at cumulative doses < 400 mg/m^2.

Hematologic: Mild leukopenia and thrombocytopenia occur in 25-30% of patients but is rarely dose limiting. Anemia is less common. A potentially fatal hemolytic uremic syndrome has been reported.

Gastrointestinal: Severe, dose-limiting nausea and vomiting occur in almost 100% of patients unless adequate antiemetic prophylaxis is given. Even with successful prophylaxis of acute nausea, a delayed (72-96 hour) reaction may occur, requiring additional therapy. Anorexia and taste changes may also occur.

Hypersensitivity: Allergic reactions are reported in up to 20% of patients. Symptoms include: rash, facial edema, wheezing, hypotension, and tachycardia. Severe anaphylaxis is rare.

Extravasation: Extravasation can occur with cisplatin administration. Treatment should be per institutional policy on extravasation.

Other: Raynaud's phenomena and digital ischemia has been described.

Rare complications are alopecia, seizures, loss of taste, allergic reactions and loss of muscle or nerve function. Tetany may occur due to hypomagnesinemia and/or hypocalcemia. Other electrolyte disturbances may occur.

At high doses patients have experienced optic neuritis, papilledema, cerebral blindness, blurred vision and altered color perception. Patients have experienced cardiac abnormalities, elevated SGOT and rash. Subsequent courses should not be given until serum creatinine returns to normal, if elevated. Audiometric analyses should be

monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy. Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryogenic. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

Please refer to the approved package labeling for complete toxicity information.

7.2 Adverse Event Characteristics

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

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

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

7.3 Expedited Adverse Event Reporting

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

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

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

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

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

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

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment,

they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

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

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

N/A

7.4 Routine Adverse Event Reporting

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

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

7.5 Secondary Malignancy

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

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

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

7.6 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent(s)

8.1.1 VRT-0768079, MSC2527093A, VX-970NSC 780162

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

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

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

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

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

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

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

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

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

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

Route of Administration: Intravenous (IV) infusion.

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

administered through a large bore catheter into a large caliber peripheral vein or central venous access.

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

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

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

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

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

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by the 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 responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB

anytime. 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 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 and 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
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)
IB Coordinator: IBCoordinator@mail.nih.gov

8.2 Commercial Agent(s)

8.2.1 Gemcitabine

Drug Name: Gemcitabine
Other: 1" – Deoxy – 2, 2" – difluorocytidine monohydrochloride, Gemzar, NSC #613327

Classification: Nucleoside analogue

Action: Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of

gemcitabine is attributed to a combination of 2 actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only 1 additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination).

Availability: Commercially available and FDA approved for pancreatic cancer. Also, recently approved for locally unresectable or metastatic non-small cell lung cancer in combination with cisplatin.

Storage: Unopened vials of Gemzar are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F). When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.

Reconstitution: The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer. Gemzar should be administered by intravenous infusion at a dose of 1000 or 875 mg/m^2 (depending on Arm) over 30 minutes.

Administration: Gemzar should be administered by intravenous infusion over 30 minutes.

Product description and storage: Gemcitabine will not be provided by the PMB and should be obtained from commercial sources. Gemcitabine is commercially available in vials containing 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. The recommended diluent for reconstitution of gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided. When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur. Please refer to the commercial package insert for complete drug information.

8.2.2 Cisplatin

Drug Name: Cisplatin
Other: Platinol (NSC-119875); Cis-diamminedichloroplatinum

Classification: Aklylating agent

Action: Cisplatin forms covalent bonds with nucleophilic sites on guanine present in all DNA. As cisplatin is a bifunctional agent, it is able to bind to 2 sites in a DNA strand. This results in the formation of inter- and intra- chain cross-linkings, which interferes with cellular transcription and replication. Regulatory mechanisms detect the abnormal DNA and so activate a chain of responses to try and correct it. This, ultimately, causes cell death (apoptosis).

Availability: Cisplatin is commercially available.

Storage: Cisplatin Injection is a sterile, multi-dose vial without preservatives. Store at 15° to 25°C (59° to 77°F). Note: Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

Reconstitution: The aqueous solution should be used intravenously only and should be administered by IV. Cisplatin is a cytotoxic chemotherapeutic agent. Appropriate precautions for hazardous drug handling should be taken during handling, preparation, administration and disposal of this agent. As with other potentially toxic compounds, caution should be exercised in handling the aqueous solution. Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If

cisplatin contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Administration: Cisplatin will be administered IV according to institutional guidelines.

Hydration
Hydration for cisplatin can be administered at the discretion of the treating physician and according to institutional standards.

Product description and storage: Cisplatin will not be provided by the PMB and should be obtained from commercial sources. Cis-diamminedichloroplatinum (Platinol or cisplatin) is a heavy metal complex and is water soluble. It is a white lyphilized powder with a molecular weight of 300.1. Cisplatin is available as 50mg/50ml and 100mg/100ml multi-dose vials. Each ml also contains 9mg sodium chloride. Hydrochloric acid and/or sodium hydroxide is added to adjust the pH. The intact vials may be stored at room temperature (15° - 25°C), protected from light, for the lot life indicated on the package. Do not refrigerate. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2NS (precipitate occurs in D5W) and stored at room temperature for up to 24 hours. Cisplatin should be given immediately after preparation as slow intravenous infusion over 60 minutes. Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin (Platinol) should not be used for preparation or administration, as a black precipitate is formed within 30 minutes. Please refer to the approved package labeling for complete prescribing and toxicity information.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The proposed randomized phase II study offers ample opportunity to understand biomarkers of response to the combination of cisplatin/gemcitabine with M6620 (VX-970). Alteration of p53 will be investigated as a potential biomarker for response. Cells deficient in p53 may potentially rely more heavily on ATR-mediated checkpoint signaling in the face of DNA damage (Reinhardt *et al* 2007). Data from The Cancer Genome Atlas (TCGA) investigators suggest that p53 genomic alterations (either homozygous deletion or mutation) occur in roughly 52% of patients (TCGA Investigators 2014). While previous prospective clinical studies have shown little predictive capability of p53 immunohistochemistry, there is preclinical data to suggest that inhibition of the ATR pathway may be more active in the setting of p53 mutation (Liu *et al* 2015). The same studies identify even more potent inhibition in patients with mutations in both p53 and p21. We therefore propose p53 mutation as a post-hoc stratification factor in our study, and we will retrospectively assess p21 as well. ATM, a distinct mediator of double-stranded DNA break repair, and γ-H2AX, a surrogate for DNA damage, will also be explored as putative biomarkers of M6620 (VX-970) response (Wang *et al* Oncogene 2014). We will develop patient-derived xenograft (PDX) models in collaboration with the UC Davis PDX Development and Trial Center (UM54CA233306, C-X Chong, PI). To generate these models, fresh tissue will be collected prior to initiation of therapy and at the time of resistance. In this manner, detailed studies can be performed to better understand *in vivo* the development of ATR-inhibitor resistance.
Given evidence suggesting the role of *ERCC2* mutation in modulating response to platinum-based therapies, this phenomenon will be assessed as well (Van Allen *et al* 2014).

Finally, we will obtain limited pharmacokinetic samples in all patients to explore relationships between exposure to M6620 (VX-970) (and gemcitabine), and toxicity or efficacy.

9.1 Integrated Laboratory Studies

9.1.1 Cytidine Deaminase (CDA) phenotype

Cytidine Deaminase (CDA) phenotype will be correlated with gemcitabine PK parameters observed.

9.1.1.1 Collection of Specimens
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.

A single serum tube will be collected prior to dosing (NO THU added !!!), (e.g. BD vacutainer 367812 plastic 13x75 4.0 mL tube).

9.1.1.2 Handling of Specimens
-Allow the blood to clot for 30 min at room temperature
-Centrifuge at 1800 x g for 10 min
-Freeze 2 serum aliquots at -80 C until shipment on dry-ice / analysis.

9.1.1.3 Shipping of Specimens
See Pharmacokinetics section below.

9.1.2 Pharmacokinetics

Gemcitabine PK (D1 and D8, with baseline assessment) will be correlated with toxicity observed, and response.

M6620 (VX-970) PK (D0, 2, 4, 9, 11) will be correlated with toxicity observed, and response performed, and possibly to add to the present knowledge base of M6620 (VX-970) PK by means of incorporation into a population pharmacokinetic model to be developed across studies.

9.1.1.4 Collection of Specimens

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:

Prepare a stock solution of tetrahydrouridine (THU) at 10 mg/mL (may be frozen for up to a year). THU can be added to Vacutainer tubes up to several days in advance without causing

significant loss of vacuum (no more than 7 days, and keep in fridge). Using a 3/10 cc insulin syringe or other similar sized syringe with a fine needle, draw up 10 µL of the THU solution for each 1 mL of blood to be drawn and transfer it to a Vacutainer tube by piercing the stopper. 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. Because of the fine needle, you will not lose the vacuum (apart from the volume added) in the collection tube.

Pre-treatment of cycle 1 (all patients)
EDTA anti-coagulated blood samples will be obtained at the following timepoints:
At baseline, prior to infusion

Day 1 and day 8 of cycle 1 (all patients)
EDTA anti-coagulated blood samples will be obtained at the following timepoints:
25 (±5) min after start of gemcitabine infusion = 5 min before end gemcitabine infusion

Day 2 and day 9 of cycle 1 (ARM A patients only)
EDTA anti-coagulated blood samples will be obtained at the following timepoints:
55 min (±5 min) after start of M6620 (VX-970) infusion = 5 min before end M6620 (VX-970) infusion

Day 4 and day 11 of cycle 1 (ARM A patients only)
EDTA anti-coagulated blood samples will be obtained at the following timepoints:
47 h (±3 h) after end of M6620 (VX-970) infusion

9.1.1.5 Handling of Specimens

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

Vacutainer tubes shall be inverted several times to mix blood with EDTA anticoagulant and placed on ice. Processing should begin within 20 minutes of collection. Samples should be centrifuged for 10 min at approximately 1000 x g in a refrigerated tabletop centrifuge so as to produce plasma.

The resulting plasma should be aspirated from the tubes, placed into appropriately-labeled microcentrifuge tubes, and stored at -70 °C.

9.1.1.6 Shipping of Specimens

Preparing the shipment
*Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH).
*Please organize the samples by Patient and Time point in the box.
*Do not store in plastic bags (they break on dry-ice and labels will detach).
*A copy of each of the pharmacokinetic sample collection forms for the respective patients or a sample list should be included with each shipment. 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 samples so that receipt can be acknowledged.
*Please notify the lab by telephone (412-623-3248) or fax (412-623-1212) at least 24 hours prior to shipment.

Shipping
*All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state (if samples are to be shipped frozen). All specimens are to be shipped on either Monday, Tuesday or Wednesday to:

Cancer Pharmacokinetics and Pharmacodynamics Facility
University of Pittsburgh Cancer Institute
Room G27 Hillman Research Laboratories
5117 Centre Avenue
Pittsburgh, PA 15213.

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.

9.1.1.7 Site Performing Correlative Study

Cancer Pharmacokinetics and Pharmacodynamics Facility
University of Pittsburgh Cancer Institute
Room G27 Hillman Research Laboratories
5117 Centre Avenue
Pittsburgh, PA 15213

9.2 Exploratory Correlative Studies

9.2.1 *Understanding the role of p53, CDKN1a (p21) and ERCC2 mutation in predicting differential response to cisplatin/gemcitabine versus cisplatin/gemcitabine with M6620 (VX-970)*

9.2.1.1 Collection of Specimen: Archival FFPE specimens from prior TURBT or cystectomy will be submitted to the California Cancer Consortium Biobank at UC Davis to be accessioned and stored prior to analysis.

9.2.1.2 Handling of Specimens(s): A total of 10 unstained slides (4 micrometer thickness) along with 2 reference H&E slide with representative tumor specimens should be submitted. Tissue should be mounted on positively charged (+) slides, coverslips may be used on H&E stained slides only.

All submissions must be accompanied by a completed CCC specimen submission form (available on the CTSU website) and a copy of the corresponding pathology report. Forms must be submitted to both the bank and the CCC data center.

If no tissue is available, participating sites must submit a CCC specimen submission form stating the reason for the unavailability of tissue. Forms must be submitted to both the bank and the CCC data center.

9.2.1.3 Shipping of Specimen(s):
All FFPE tissue should be send at ambient temperature and slides should be packed appropriately to protect from breakage. For summer shipments, please include a room temperature cool pack to insulate the specimen and protect paraffin from melting. Specimens should be shipped to the following address:

Dr. Philip Mack/Anthony Martinez
UC Davis Comprehensive Cancer Center
4501 X Street, Suite 1009
Sacramento, CA 95817

Phone: 916-734-0162
Email: axmartinez@ucdavis.edu or pcmack@ucdavis.edu

Please notify the bank at the time of shipping via email **(**axmartinez@ucdavis.edu**)**

9.2.1.4 Analysis of Specimens: Targeted sequencing will be performed using a BROCA-like sequencing platform developed at Yale, including a large panel of DDR and HRD genes. The panel includes genes of interest in the current study, including *p53, CDKN1a* and *ERCC2*.

9.2.1.5 Site(s) Performing Correlative Study: Yale University Comprehensive Cancer Center

9.2.2 *Assessment of DNA damage and ATM pathway activation with cisplatin/gemcitabine +/- M6620 (VX-970) and generation of PDX models*

9.2.2.1 Collection of Specimen(s): Patients treated at City of Hope and UC Davis will be offered biopsies prior to treatment initiation (to be performed from day -14 to day -1) and at the time of documented treatment progression (to be performed +/- 14 days from the documented date of progression). Notably, these biopsies are not mandatory.

9.2.2.2 Handling of Specimens: At least 24 hours prior to the biopsy, the research coordinator is to notify the institutional research team involved in this protocol, of the scheduled sample collections. A laboratory technician should prepare cryomolds prior to the biopsy, by labeling them, using the provided alcohol-proof marker, with the following information:

Clinical protocol number
Specimen ID
Biopsy time and Date

The laboratory technician should arrive at the biopsy collection site at least 15 min ahead of the scheduled biopsy to allow sufficient time to set up laboratory supplies and ensure rapid transport of specimens to the laboratory after collection. He should also, immediately before the biopsy, fill the insulated bucket with dry ice and isopentane.

Immediately after the biopsy is performed, the freshly collected specimen should be placed in the cryomold. A single drop of Tissue Tek™ OCT should be placed on the specimen, and the sterile tweezers should be used to gently hold one end of the freshly collected needle biopsy and to push the biopsy to the bottom of the cryomold cassette with forceps. Make sure biopsy is as flat as possible. The cryomold should then be filled with OCT, and the cryomold should be immediately placed in direct contact with the dry ice/isopentane cocktail until the bottom of the OCT freezes and turns white. Only the bottom of the cryomold should contact the dry ice/isopentane--none of the dry ice/isopentane should spill inside the cryomold itself and contact the specimen.

This process can be repeated using separate cryomold cassettes for separate biopsy samples.

Once frozen, place cryomolds on dry ice for transport. The used isopentane should be poured back into its bottle using funnel.

The cryopreserved biopsy should be stored at -80°C until shipment. After completion of each biopsy, the following information should be recorded:

Biopsy collection
Date:
Specimen ID:
Time guide needle placement confirmed:
Needle Type:
Needle diameter: gauge; and length: cm
Time biopsy needle introduced:
Time biopsy snap-frozen on dry ice:
Number of specimens:
Time aspirate performed (for bone lesions):
Time aspirate snap-frozen on dry ice:

Date/time of biopsy specimen(s) (and aspirate specimens, if applicable) placed at -80°C:
Date/time of biopsy specimen(s) (and aspirate specimens, if applicable) shipped:
Notes, including any deviations from the standard operating procedure:

PDX models will be generated using previously published methods (Lin T-Y *et al* 2014). Assessment of ATM P1981 and γ-H2AX will be performed via IHC using previously published methods (Wang *et al* 2014). Importantly, these exploratory studies are being done on tissue derived from PDX models, not on primary patient derived tissues (where the persistence of labile phospho-moieties would be low).

Shipping of Specimens: Specimens will be stored at UC Davis; if additional centers are chosen to participate in these correlative studies, these specimens will be shipped to UC Davis. Ideally, shipment should occur on the same day as the biopsy, unless the biopsy occurs on a Friday, in which case the specimen should be preserved at -80°C until shipment on the following Monday.

9.2.2.3 Site(s) Performing Correlative Study: City of Hope and UC Davis

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Off Study[c]
Cisplatin		A			A			A			A			A			A			
Gemcitabine		B	B		B	B		B	B		B	B		B	B		B	B		
M6620 (VX-970)		C	C		C	C		C	C		C	C		C	C		C	C		
Informed consent & history	X																			
Concurrent meds	X	X----------																		X
Physical exam	X	X			X			X			X			X			X			X
Vital signs	X	X			X			X			X			X			X			X
Height	X																			
Weight	X	X			X			X			X			X			X			X
Performance status	X	X			X			X			X			X			X			X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-HCG	X[b]																			
Adverse event evaluation		X----------																		X
Radiologic evaluation[d]	X	Radiologic measurements should be performed every 9 weeks during the first six months of treatment and every 12 weeks thereafter until the time of progression.																		X
Biopsy (optional)[e]	X																			
Tissue submission[f]	X																			
PK Draws[g]	X	X	X																	

A: Arm A - Cisplatin to be initiated at 60 mg/m2 on day 1 of each 21 day cycle (dose modification as specified in Section 6). Arm B – Cisplatin to be initiated at 70 mg/m2 on day 1 of each 21 day cycle (dose modification as specified in Section 6).

B: Arm A - Gemcitabine to be initiated at 875 mg/m2 on days 1 and 8 of each 21 day cycle (dose modification as specified in Section 6). Arm B – Gemcitabine to be initiated at 1000 mg/m2 on days 1 and 8 of each 21 day cycle (dose modification as specified in Section 6).

C: Arm A - For patients randomized to M6620 (VX-970) at 90 mg/m2, dosing on days 2 and 9 of each 21 day (dose modification as specified in Section 6). Notably, M6620 (VX-970) is administered over 1 hour.

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

b: Serum pregnancy test (women of childbearing potential).

c: Off-study evaluation. Following completion of 6 cycles of chemotherapy, patients should be evaluated every 9 weeks with the noted off-study assessments (including radiologic evaluation).

d: Radiologic evaluation should include CT of the chest, abdomen and pelvis for all patients. If there is clinical suspicion for bone metastases at the time of enrollment (at the discretion of the

investigator), bone scan should be performed at baseline. If bone metastases are detected, a bone scan should be conducted at the time of each radiologic evaluation. Window for scans is +/- 7 days.

e: Optional biopsies will be offered to patients treated at UC Davis. Please see specimen shipping and handling instructions in Section 9.

f: A total of 10 unstained slides and 2 H&E slides (4 micrometer thickness) derived from previous TURBT or cystectomy (and including tumor tissue) should be submitted. See Section 9.

g. Please refer to Section 9.1.1 for a schedule of blood draws for PK analyses. All patients will have blood drawn at baseline, and on Days 1 and 8 of Cycle 1, and patients on Arm A will have additional blood days on days 2, 4, 9 and 11.

11. MEASUREMENT OF EFFECT

11.1 Response Criteria

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

11.1.1 Definitions

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

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

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥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 may be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions,

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

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

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

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

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

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. 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 PET-CT (or PET alone; e.g., ^{18}FDG-PET) is not permitted in the current study as a means of radiologic assessment.

Ultrasound Ultrasound is not permitted in the current study as a means of radiologic assessment.

Tumor markers As there are no reliable tumor markers for bladder cancer, tumor markers are not permitted as a means of disease assessment.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target

lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-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).

11.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**

CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In this randomized trial, confirmation will not be required for Best Overall Response.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

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

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival (PFS)

PFS is defined as the duration of time from randomization to time of progression or death, whichever occurs first. For patients who have not progressed at the time that they are removed from treatment (for completion of 6 courses or reasons described in Section 5.3) will be followed for progression; for those who begin another treatment prior to progression, the type of treatment will be recorded, as well as the time to 1st progression.

11.1.7 Overall Survival (OS)

OS is defined as the duration of time from randomization to death from any cause. Patients who have not died at the time of analysis, will be censored at the date of they were last documented to be alive.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

See also Section 14 'CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS,' Subsection 14.1 '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.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second

stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician through IWRS and Medidata Rave.

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

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

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL. *(Note: A DTL is NOT required for this study.)*

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right -corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality

if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

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

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

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

Further information on data submission procedures can be found in the ETCTN Program Guidelines

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

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

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 **Study Design:** This study will employ a randomized, phase II design in which patients who have no prior cytotoxic chemotherapy for metastatic bladder cancer will be randomized 1:1 to receive either cisplatin/gemcitabine alone or cisplatin/gemcitabine with M6620 (VX-970). Prior to randomization, patients will be stratified according the Bajorin risk category: 0=KPS≥80 and no visceral metastases; 1=KPS <80 or visceral metastases (but not both); 2=both KPS<80 and presence of visceral metastases. Randomization will be done using a (stratified) permuted block design with randomly varying block sizes.

A total of 90 patients will be enrolled and randomized; a single interim analysis will occur when 60% of the expected events have been observed; toxicity will be monitored monthly and reviewed formally twice a year.

13.1.2 **Primary Endpoint:** Progression-free survival (PFS) as defined in Section 11.1.6.

13.1.3 **Secondary Endpoints:** Response rate (RR) as defined in Section 11.1, overall survival (OS) as defined in Section 11.1.7, and toxicity graded according the CTCAE v4.

13.2 Sample Size/Accrual Rate

The primary objective of the study is to determine if PFS is improved with the addition of M6620 (VX-970) to the combination of cisplatin/gemcitabine as compared to cisplatin/gemcitabine alone. Based on a meta-analysis including multiple trials of cisplatin-based chemotherapy, we estimate a median PFS of 5.3 months with cisplatin/gemcitabine (Galsky *et al* Cancer 2013). With 90 patients accrued and 80 evaluable for this primary endpoint, we will have 90% power to detect an improvement in median PFS from 5.3 months with cisplatin/gemcitabine alone to a median PFS of 10.1 months with cisplatin, gemcitabine and M6620 (VX-970) (i.e. a hazard ratio of 0.52). This assumes a 1-sided α of 0.1, exponential failure, and uniform accrual over 2 years with 9 additional months of follow-up – with 66 events at the time of the final analysis.

The number of patients required for this study will be a low of ≈71 (if the hypothesis that M6620 (VX-970) is not active is true and the trial is stopped at the time of the interim analysis) to a maximum of 90 (if the trial continues to completion).

13.3 Study Monitoring and Interim Analysis

13.3.1 Toxicity and Safety Monitoring

The DCC (Data Coordinating Center) will review cumulative toxicities on a monthly basis. Twice a year, the CCC (California Cancer Consortium) will prepare reports for the independent DSMC. At these semi-annual reviews, the two arms will be compared in terms of toxicities (by any type of Grade 3+ toxicity). Those toxicities resulting in a 2-sided p-value of 0.10 or less will be flagged for examination. While there are no formal rules for stopping because of toxicities, based on these reviews, the protocol may be modified or even closed, after discussion with CTEP.

All deaths within 30 days of last treatment will be reviewed; all deaths due to treatment will be reviewed and compared across arms.

13.3.2 Interim Analysis

As described above, under the alternative hypothesis that the addition of M6620 (VX-970) nearly doubles the median PFS, we expect 66 events after 24 months of accrual and 9 additional months of follow-up. In this setting, we plan a single interim analysis after 40

events have been observed – which should occur after about 19 months of accrual (if the hypothesis that M6620 (VX-970) is not active is true). Accrual will not be paused to wait for 40 events. At the time of the interim analysis, we will use two rules to guide our decision to continue or halt accrual.

- **Stopping for futility:** The two arms will be compared using the logrank test. If overall the Cisplatin/Gemcitabine+M6620 (VX-970) PFS is not nominally superior to the Cisplatin/Gemcitabine arm and the corresponding one-sided p-value is less than or equal to 0.50, then consideration will be given to stopping for futility (Wieand S *et al* Statistics in Medicine 1994).
- **Stopping for success:** The two arms will be compared using the logrank test. If overall the Cisplatin/Gemcitabine+M6620 (VX-970) PFS is superior to the Cisplatin/Gemcitabine arm and the corresponding one-sided p-value is less than (but not equal to) 0.005, then consideration will be given to stopping for success, using the Haybittle-Peto approach (Peto R *et al* British Journal of Medicine 1976).

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	**1**
Asian	2	6	0	0	**8**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	1	12	0	0	**13**
White	14	46	2	6	**68**
More Than One Race	0	0	0	0	**0**
Total	**17**	**65**	**2**	**6**	**90**

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13.4 Stratification Factors

Prior to randomization, patients will be stratified according to the Bajorin risk category: 0=KPS≥80 and no visceral metastases; 1=KPS <80 or visceral metastases (but not both); 2=both KPS<80 and presence of visceral metastases.

13.5 Analysis of Results

The outcome status (in terms of toxicity, number of course begun, amount of each of the planned drugs received (and percent of planned), reason off treatment, tumor response, and progression and survival status) of all randomized patients, will be reported. All eligible randomized patients will be included in the primary analysis of progression-free survival and response. All toxicities experienced by patients who begin treatment will be reported.

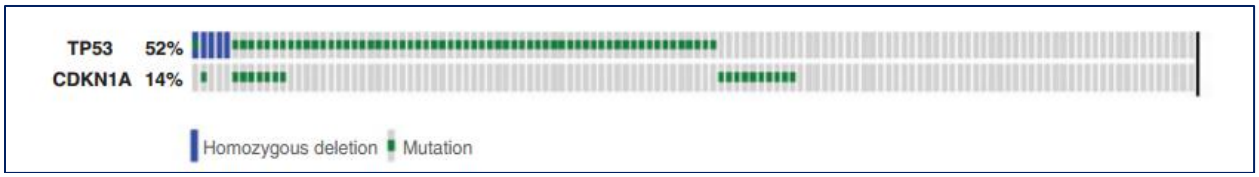
Toxicity. All observed toxicities will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by the CTCAE v5.0), and time of onset (i.e. course of treatment). Tables will be created to summarize these toxicities and side effects, overall by arm and by course. Proportions and associated 95% confidence intervals will be calculated for each arm separately and if indicated, for the difference between the arms. The two treatment arms will be compared using Fisher's exact test when the presence of toxicities is dichotomized and by the Cochran-Armitage test for trend if all grades are considered.

Clinical Outcome. PFS will be measured from the day of randomization, until progression, death, or the start of another treatment. In the primary analysis, patients who have not progressed, but who begin another treatment, will be censored at that time, for the measure of PFS; in the secondary analysis, all patients who begin another treatment prior to progression on this protocol, will be followed for the first progression on the subsequent treatment. PFS for each arm will be summarized with a Kaplan-Meier plot and 95% confidence intervals (at 3, 6, 9, and 12 months); the one-sided 0.10-level logrank test will be used to compare the two arms.

Overall survival, in which all patients will be followed until death (due to any cause) or for 36 months, will be summarized in a manner similar to PFS. The overall response rate will be calculated as the ratio of the number of eligible randomized patients who experienced a confirmed CR or PR (by RECIST v1.1) divided by the total number of randomized eligible patients who began treatment; 95% confidence intervals will be constructed. Pearson chi-square test will be used to compare the two arms in terms of the overall response rate.

Analysis of Potential Predictors of Response. Archival tumor tissue will be analyzed for the presence of p53, p21, and ERCC2 mutations. It is expected that the majority of patients will provide adequate specimens for analysis – conservatively we will assume that 75% (or 30/arm) of the evaluable patients will provide specimens. For each gene, each tumor will be coded as 1 (having a mutation) or 0 (having no mutation) for that gene. For each treatment arm separately and for each of the 3 indicators (one each for the presence of p53, p21, and ERCC2 mutations), the hazard ratio will be used to quantify the overall association between that gene and PFS. The Cox proportional hazards model (assuming that the assumption of proportional hazards is not unreasonable – which it should not be for PFS over the 1st year) will be used to estimate the interactions between the genes and PFS as well as the interaction between the treatment arm and each of the genes. Although associations will be tested, it is possible that that resulting p-values are not less than 0.05 simply due to small numbers. Based on the TCGA project (see the Figure below) we would expect about 50% of tumors to harbor p53 mutations, 14% to harbor p21 mutations, and 12% to harbor ERCC2 mutations; with 30 specimens per arm, that should yield

about 15, 4, and 3-4 tumors with mutations, respectively. Nonetheless, these analyses will guide the design of future studies. To analyze the patterns further, the association between more frequent specific mutations for each gene and PFS (as well as objective response) will be quantified with an estimate of the hazard ratio and displayed with Kaplan-Meier plots.



For patients treated at UC Davis, every attempt will be made to obtain fresh tumor biopsies prior to start of treatment as well as at the time of progression. The primary purpose of these biopsies is to develop PDX models. While the goal is to obtain as many models as possible, even one new model will be useful for future studies. Practically speaking we expect that 4-6 patients will provide matched specimens. Tissue from these biopsies will also be analyzed for changes in ATM activation and γH2AX.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment on their respective arm.

13.6.2 Evaluation of Response

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

All of the patients who met the eligibility criteria (with the 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. A secondary analysis will be undertaken which will include all patients who are evaluable for objective response (as defined in Section 11.1). The 95% confidence intervals should also be provided.

14. CCC POLICIES FOR MONITORING CONSORTIUM TRIALS

This protocol is monitored at several levels, as described in more detail below. To

summarize: The trial PI has access to the data at all times. The CCC Data Coordinating Center reviews accrual and toxicities monthly. An external, independent DSMC reviews the study progress twice yearly. In addition, for Phase I trials or the Phase I portion of a trial, the PI will have monthly - and as needed - conference calls with study investigators to review accrual, progress, and any unforeseen issues. Dose escalation/expansion/de-escalation decisions require sign-off by the PI (or his designee) and the study statistician (or designee). During the Phase II trial or a Phase II portion of a trial, the PI will have quarterly - and as needed - conference calls with study investigators to review accrual, progress, and any unforeseen issues. Decisions to proceed to the second stage of the Phase II trial will require sign-off by the study PI and the trial statistician.

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase II trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7) and case report forms. The Data Coordinating Center for the CCC Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCC that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCC initiated trial on the CCC website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCC teleconference meeting for review and approval.

14.1 Oversight

Oversight of the conduct of CCC trials occurs at several levels:

1. The Data Coordinating Center for the CCC flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism or his or her designee, and are communicated to the participating centers by the CCC Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. For CTEP sponsored Phase I trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCC institution; this audit is initiated by CTEP.

3. An independent CCC DSMC will review CCC trials every 6 months. This DSMC will consist of 6 voting members (3 medical oncologists or hematologists involved in Phase I/II cancer clinical trials but not participating in CCC studies, a patient representative and a statistician) and a non-voting CCC statistician.

    a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.

    b. This DSMC will review each CCC trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.

    c. The DSMC will report to the CCC leadership.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

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

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

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

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

These are the things that you need to know:
The study drug 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 substrates of P-gp and BCRP.

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

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** M6620 (VX-970) 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 substrates of P-gp and BCRP. • Strong inhibitors or inducers of CYP3A4 should be avoided. • Substrates of P-gp and BCRP should be used with caution. **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	Version Feb/2019
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

APPENDIX C COCKROFT-GAULT, MDRD AND CKD-EPI FORMULAS

Cockcroft-Gault Formula

$$\text{Calculated Creatinine Clearance} = \frac{[140 - \text{age (yrs)}] \times [\text{actual weight (kg)}]}{72 \times \text{serum creatinine (mg/dl)}}$$

Females = 0.85 x male value

Modification of Diet in Renal Disease Formula (MDRD)

$$eGFR = [186 \times \text{serum creatinine (mg/dl)}]^{-1.154} \times [\text{age (yrs)}]^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI)

$$eGFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

APPENDIX D SPECIMEN COLLECTION FOR PHARMACOKINETIC STUDIES FOR PHII-135 (NCI# 9947)

Title: A Randomized Phase 2 Trial of Cisplatin/Gemcitabine with or without M6620 (VX-970) in Metastatic Urothelial Carcinoma

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:

Prepare a stock solution of tetrahydrouridine (THU) at 10 mg/mL (may be frozen). THU can be added to Vacutainer tubes up to several days in advance without causing significant loss of vacuum. Using a 3/10 cc insulin syringe or other similar sized syringe with a fine needle, draw up 10 µL of the THU solution for each 1 mL of blood to be drawn and transfer it to a Vacutainer tube by piercing the stopper. 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. Because of the fine needle, you will not lose the vacuum (apart from the volume added) in the collection tube.

Day 1 and day 8 of cycle 1 (all patients)
EDTA anti-coagulated blood samples will be obtained at the following timepoints:
25 (±5) min after start of gemcitabine infusion = 5 min before end gemcitabine infusion

Day 2 and day 9 of cycle 1 (ARM A patients only)
EDTA anti-coagulated blood samples will be obtained at the following timepoints:
55 min (±5 min) after start of M6620 (VX-970) infusion = 5 min before end M6620 (VX-970) infusion

Day 4 and day 11 of cycle 1 (ARM A patients only)
EDTA anti-coagulated blood samples will be obtained at the following timepoints:
47 h (±3 h) after end of M6620 (VX-970) infusion

Handling of Specimens

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

Vacutainer tubes shall be inverted several times to mix blood with EDTA anticoagulant and placed on ice. Processing should begin within 20 minutes of collection. Samples should be centrifuged for 10 minutes at approximately 1000 x g in a refrigerated tabletop centrifuge so as to produce plasma.

The resulting plasma should be aspirated from the tubes, placed into appropriately-labeled microcentrifuge tubes, and stored at -70 °C.

Pharmacokinetic Sample Collection Schedule

Title: A Randomized Phase 2 Trial of Cisplatin/Gemcitabine with or without M6620 (VX-970) in Metastatic Urothelial Carcinoma (NCI 9947, PhII-135)

Patient's Initials _____ _____ Patient Accession # _____ _____
(first) (last)

Study Site _____ Height _____ cm Weight: ____ . ____ kg BSA ____ . ____ ____ m^2

Check one: ☐ Arm A (Cisplatin/Gemcitabine with M6620 (VX-970)) ☐ Arm B (Cisplatin/Gemcitabine)

Baseline Sample Date/time _____

Day 1 Gemcitabine Dose _____ mg/m^2 IV infusion

Day 1 Infusion Start Date/time _____ **Infusion End time** _____

Day 8 Gemcitabine Dose _____ mg/m^2 IV infusion

Day 8 Infusion Start Date/time _____ **Infusion End time** _____

Day 2 M6620 (VX-970) Dose _____ mg/m^2 IV infusion

Day 2 Infusion Start Date/time _____ **Infusion End time** _____

Day 9 M6620 (VX-970) Dose _____ mg/m^2 IV infusion

Day 9 Infusion Start Date/time _____ **Infusion End time** _____

Sample Name	Planned Collection Time Relative to Gemcitabine Infusion All Patients	Planned Collection Time Relative to M6620 (VX-970) Infusion Arm A Patients Only	Sample Date (mm:dd:yy)	Expected Time (hh:mm)	Actual Time (hh:mm)	Drawn By (initials)	Comments
P0	Baseline (prior to infusion)						
P1	Day 1 - 25 min (± 5 min) after start of Gemcitabine						
P2		Day 2 - 55 min (± 5 min) after start of M6620 (VX-970)					
P3		Day 4 - 47 h (±3 h) after end of M6620 (VX-970)					

P4	Day 8 - 25 min (± 5 min) after start of Gemcitabine						
P5		Day 9 - 55 min (± 5 min) after start of M6620 (VX-970)					
P6		Day 11 - 47 h (±3 h) after end of M6620 (VX-970)					

Preparing the shipment

*Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH).
*Please organize the samples by Patient and time point in the box.
*Do not store in plastic bags (they break on dry-ice and labels will detach).
*A copy of each of the pharmacokinetic sample collection forms for the respective patients or a sample list should be included with each shipment. 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 samples so that receipt can be acknowledged.
*Please notify the lab by telephone (412-623-3248) or fax (412-623-1212) at least 24 hours prior to shipment.

Shipping

*All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state (if samples are to be shipped frozen).
All specimens are to be shipped on either Monday, Tuesday or Wednesday to:

Cancer Pharmacokinetics and Pharmacodynamics Facility
University of Pittsburgh Cancer Institute
Room G27E Hillman Research Laboratories
5117 Centre Avenue
Pittsburgh, PA 15213

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.

APPENDIX E SUPPORTIVE CARE GUIDELINES FOR M6620 (VX-970)

To minimize the possibility of phlebitis, 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.

If any subject develops phlebitis, or signs or symptoms of inflammation that may progress to phlebitis or that the patient cannot tolerate, standard measures should be employed to ameliorate these symptoms (including removal of the infusion catheter and resumption of infusion through a different vein).

Based on the observation of acute hypersensitivity in 3 subjects at various doses of M6620 (VX-970) and of pruritus in 2 subjects at 480 mg/m2 of M6620 (VX-970), pre-medication with a corticosteroid and an antihistamine may be considered for all subjects receiving M6620 (VX-970) (to prophylax against possible acute hypersensitivity), and is strongly recommended for subjects receiving doses of M6620 (VX-970) above 240 mg/m2 (to prophylax against pruritus). In addition, corticosteroids and antihistamine should be used for treatment of subjects that develop acute hypersensitivity or pruritus after M6620 (VX-970) infusion, and should be used prophylactically as pre-medication for all subjects who develop acute hypersensitivity or pruritus with M6620 (VX-970) infusion and who continue to receive treatment with M6620 (VX-970).

Corticosteroid and antihistamine combinations that may be used include: 100 mg to 200 mg hydrocortisone intravenously approximately 60 minutes (± 15 minutes) before M6620 (VX-970) infusion, and either 10 mg of chlorphenamine or 25 mg of diphenhydramine intravenously approximately 30 minutes (± 10 minutes) before M6620 (VX-970) infusion. Alternative antihistamine and steroid doses, timing, routes of administration, and agents may be considered, as long as not prohibited by protocol. In addition, treatment with an H2-blocker (e.g., ranitidine) may be considered for subjects not responsive to a regimen with an H1 blocker.

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