For Protocol Amendment: 17

NCI Protocol #: 9950

NCI Version Date: 03-12-24
Protocol Date: 03-12-24

SUMMARY OF CHANGES – Protocol

1. Changes submitted by PI

#	Section	Comments
1.	**Corresponding Organization**	The Corresponding Organization has been updated to **LAO-MD017** / JHU Sidney Kimmel Comprehensive Cancer Center LAO as Dr. Owonikoko has recently transferred institutions.
2.	Principal Investigator	The address of the Principal Investigator has been updated as follows: Taofeek K. Owonikoko, MD/PhD/MSCR University of Maryland 22 S. Greene Street N9E22 Baltimore, MD 21201 Tel: 410-328-5506 towonikoko@som.umaryland.edu
3.	Study Contact	The Study Coordinator has been updated: **Study Contact:** Judy Murray Johns Hopkins University 201 N. Broadway, Suite 9130 Baltimore, MD 21287 Tel: 443-927-3568 jmurra33@jhmi.edu
4.	Pharmacist	Listed Pharmacist has been removed.
5.	Administrative Updates	Updates to the TITLE PAGE to match the NCI Protocol Template.

NCI Protocol #: 9950

ClinicalTrials.gov Identifier: NCT02567422

TITLE: A Phase I Study of M6620 (VX-970, berzosertib) in Combination with Cisplatin and XRT in Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC; SDC 10060121)

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

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LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / UPMC Hillman Cancer Center LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
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CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

Statistician:	**Study Contact:**
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NCI-Supplied Agent(s): M6620 (VX-970, berzosertib) (NSC 780162)

Other Agent(s): Cisplatin, NSC # 119875 commercial

IND #:

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: *Original / Version # 1 / October 23, 2015*

Protocol Type / Version # / Version Date: *Original / Revised Version #2 / December 9, 2015*

Protocol Type / Version # / Version Date: *Original / Revised Version #3 / May 18, 2016*

Protocol Type / Version # / Version Date: *Original / Revised Version #4 / June 23, 2016*

Protocol Type / Version # / Version Date: *Original / Revised Version #5 / August 16, 2016*

Protocol Type / Version # / Version Date: *Original / Revised Version #6 / October 03, 2016*

Protocol Type / Version # / Version Date: *Original / Revised Version #7 / May 24, 2017*

Protocol Type / Version # / Version Date: *Original / Revised Version #8 / June 7, 2017*

Protocol Type / Version # / Version Date: *Original / Revised Version #9 / January 26, 2018*

Protocol Type / Version # / Version Date: *Original / Revised Version #10 / March 22, 2018*

Protocol Type / Version # / Version Date: *Original / Revised Version #11 / May 04, 2018*

Protocol Type / Version # / Version Date: *Original / Revised Version #12 / July 05, 2018*

Protocol Type / Version # / Version Date: *Original / Revised Version #13 / October 09, 2018*

Protocol Type / Version # / Version Date: *Original / Revised Version #14 / November 21, 2018*

Protocol Type / Version # / Version Date: *Original / Revised Version #15 / June 24, 2019*

Protocol Type / Version # / Version Date: *Original / Revised Version #16 / July 17, 2019*

Protocol Type / Version # / Version Date: *Original / Revised Version #17 / November 24, 2020*

Protocol Type / Version # / Version Date: *Original / Revised Version #18 / March 23, 2021*

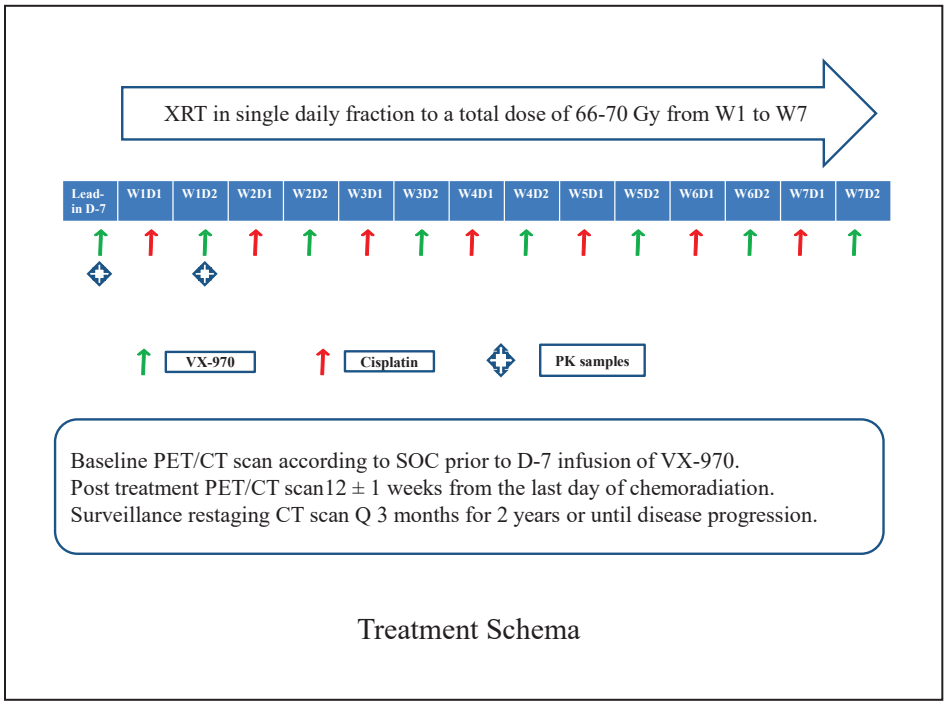
Protocol Type / Version # / Version Date: *Original / Revised Version #19 / June 21, 2021*

Protocol Type / Version # / Version Date: *Revised Version #20 / October 5, 2021*

Protocol Type / Version # / Version Date*: Revised Version #21 / November 09, 2021*

Protocol Type / Version # / Version Date*: Revised Version #22 / March 12, 2024*

SCHEMA



Treatment Schema

Dose Escalation Table:

Stage	Dose level	Cisplatin (mg/m^2) IV Q week	M6620 (VX-970, berzosertib)(VX-970, berzosertib) (mg/m^2) IV Q week	XRT over 6-7 weeks	Number of Patients
Stage I	-1	30	120	70Gy	0-6
	1 (starting dose level)	40	120*	70Gy	3-9
Stage II	2	40	160	70Gy	3-6
	3	40	200	70Gy	3-6
	4	40	240	70Gy	3-6
	5	40	280#	70Gy	3-6
Expansion	RP2D	40	200	70Gy	15

*:The starting dose of M6620 (VX-970, berzosertib)(VX-970, berzosertib) may be different than 120 mg/m^2 depending on the safety experience in the ongoing phase I study of cisplatin + M6620 (VX-970, berzosertib)(VX-970, berzosertib)
May test doses up to the single agent MTD of M6620 (VX-970, berzosertib)(VX-970, berzosertib) of 480mg/m^2 as tolerated
Up to 30 patients in the escalation phase and 15 patients in the expansion cohort treated at the RP2D
In case of DLT with the cisplatin starting dose of 40mg/m^2, a dose level -1 will be tested with cisplatin 30mg/m^2 and subsequent escalation of M6620 (VX-970, berzosertib)(VX-970, berzosertib) will be along with the reduced dose of cisplatin. There is no plan to deescalate the total dose of radiation in this study

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Assess the safety and tolerability of M6620 (VX-970, berzosertib)(VX-970, berzosertib) when administered along with weekly cisplatin and XRT in patients with locoregionally advanced HNSCC
1.1.2 Establish the recommended phase 2 dose (RP2D) of the combination

1.2 Secondary Objectives

1.2.1 Characterize the PK profile of M6620 (VX-970, berzosertib)(VX-970, berzosertib)
1.2.2 Assess for potential drug-drug interaction between M6620 (VX-970, berzosertib)(VX-970, berzosertib) and aprepitant
1.2.3 To observe and record anti-tumor activity. Although the clinical benefit of this combination regimen has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response in addition to safety and tolerability
1.2.4 To assess the rate of complete metabolic response (CMR) at 12 weeks post completion of chemoradiation using ^{18}Fluorodeoxy glucose (FDG) PET scans.
1.2.5 To collect archival tumor material for retrospective analysis of association between tissue-based biomarkers and clinical outcome.

2. BACKGROUND

2.1 *Study Disease(s)*

2.1.1 Head and Neck Squamous Cell Carcinoma (HNSCC)

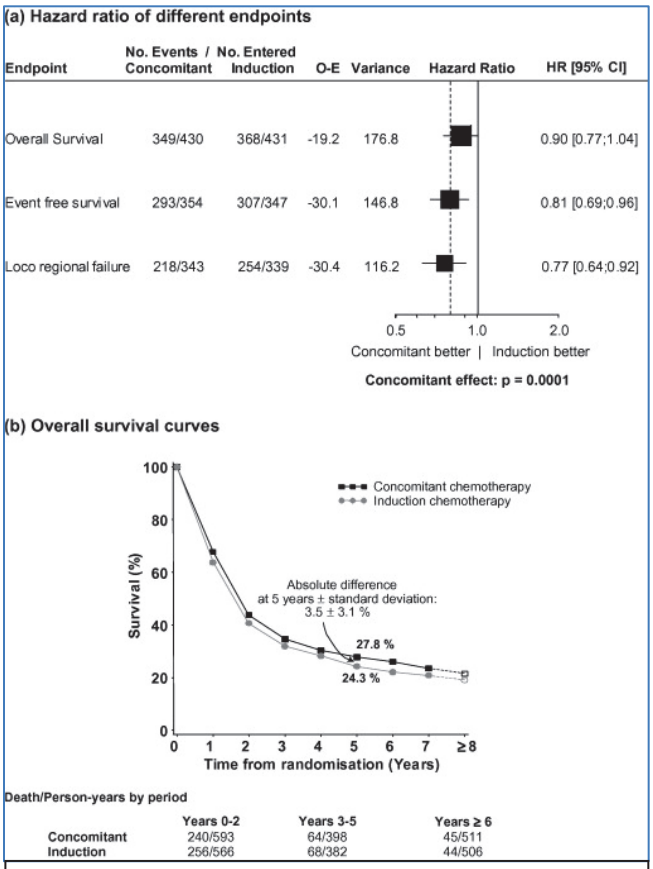
HNSCC is the 6th most common type of cancer with more than 500,000 new cases diagnosed annually worldwide.(Ferlay et al., 2015; Siegel et al., 2015) The disease can arise in any part of the head and neck region with the most common sites involving the oral cavity, oropharynx, hypopharynx, larynx and sinuses.(Bar-Ad et al., 2014) Excessive tobacco and alcohol use are well-established risk factors. In the last decade, the critical role of oncogenic human papilloma virus (HPV) infection in the development of a subset of oropharyngeal HNSCC became recognized.(D'Souza et al., 2007; Gillison et al., 2000)

Advances in the management of HNSCC have resulted in improved organ preservation and function, patient quality of life and survival.(Bar-Ad et al., 2014) Specifically, the use of primary chemoradiotherapy (CRT) for unresectable disease achieved the goal of organ preservation while the addition of chemotherapy to adjuvant radiotherapy for high risk disease along with improvement in surgical and radiation techniques resulted in better clinical outcome and improved survival.(Bar-Ad et al., 2014) While there has been a consistent improvement in local-regional control with these advanced techniques and novel treatment approaches, the impact on distant disease control remains modest.(Blanchard et al., 2011; Pignon et al., 2009) Indeed, 50% of all patients suffered disease recurrence within the local site.(Blanchard et al., 2011; Pignon et al., 2009) Single institution studies and case series of intensified chemoradiation regimens

suggest a shift in failure pattern to distant metastases; however, improved local control remains critical for establishing a significant improvement in survival of HNSCC patients.

2.1.2 Chemoradiation for locoregional HNSCC

Definitive chemoradiation therapy is an established standard for locally advanced HNSCC.(Bar-Ad et al., 2014) HPV (-) HNSCC is comparatively less sensitive to chemotherapy and radiation than HPV (+) disease. Moreover, HPV (+) HNSCC especially of oropharynx origin has shown consistently superior loco regional control over HPV (-) tumors both in retrospective and prospective studies employing chemoradiotherapy for HNSCC.(Ang et al., 2010; Bentzen et al., 2015b; Fakhry et al., 2008; Lassen et al., 2014) A retrospective analysis of survival outcome on the international phase III study, TAX324, showed locoregional failure to be significantly less common in HPV+ patients (13% versus 42%, P = 0.0006) while improved survival was noted in the HPV (+) patients (OS, HR: 0.20, P < 0.0001).(Posner et al., 2011) This observation has been reproduced in other studies,(Ang et al., 2010; Fakhry et al., 2008) and has informed the ongoing attempts at dose de-intensification for HPV (+) tumors. Competing approaches under evaluation in NCTN group studies include reduced chemotherapy dose in the good risk population, omission of platinum-based chemotherapy and reduced intensity of radiation (RTOG1016; ECOG1308; ECOG3311; NRG HN002). However, improving the clinical outcome for the HPV (-) subset of HNSCC is an area of unmet need and there is limited evaluation of novel treatment strategies in comparison to the HPV (+) tumors. The MACH-NC analysis looked at the benefit of the addition of chemotherapy to radiation therapy in patients with locoregional HNSCC. This individual patient metaanalysis employed data from approximately 17,346 patients and showed a modest overall benefit of 4.5% at 5 years with HR of 0.88 (0.85–0.92) when compared to radiation therapy alone.(Blanchard et al., 2011; Pignon et al., 2009) There was a larger effect of chemotherapy when administered concurrently with radiation rather than in the induction or adjuvant therapy setting. Similar impact of chemotherapy was observed on event-free survival with an absolute benefit of 4.1% at 5 years (from 26.8 to 30.9%) and HR of 0.87 (0.84–0.90; $p <$ 0.0001). Moreover, the benefit of chemotherapy was seen across all the major subsites of HNSCC including oropharynx, larynx, oral cavity and hypopharynx.(Blanchard et al., 2011) Furthermore, concurrent administration of chemotherapy along with radiation therapy conferred



Benefit of chemotherapy added to radiation therapy in HNSCC; MACH-NC analysis; adapted from Pignon et al. (Pignon et al., 2009)

the maximum clinical benefit with this strategy for the most common sites for HNSCC except hypopharynx and oral cavity.(Blanchard et al., 2011)

2.1.3 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 (Dickson and Schwartz, 2009; Pitts et al., 2014). 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 or progression. 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.

In summary, definitive chemoradiation therapy is an established standard for locally advanced HNSCC. HPV (-) HNSCC is comparatively less sensitive to chemotherapy and radiation than HPV (+) disease. Strategies for improved outcome for HNSCC continue to evolve but success remains a challenge especially with the use of standard cytotoxic chemotherapy while attempt to incorporate antiangiogenic agent resulted in increased toxicities. The addition of mechanistically rational biologic agent to chemoradiation in carefully selected patients is expected to improve outcome without excessive toxicities. Inactivating alterations of TP53 and ATM genes have been described in HNSCC and TP53 is the most frequent genetic alteration, described in up to 85% of HPV (-) HNSCC. TP53 mutation is associated with poor therapeutic response and decreased survival in HNSCC. However, inactive p53 sensitizes cancer cells to M6620 (VX-970, berzosertib)(VX-970, berzosertib) especially in combinations with XRT or cytotoxic chemotherapy. Moreover, M6620 (VX-970, berzosertib)(VX-970, berzosertib) showed strong and consistent synergy with cisplatin of all cytotoxic chemotherapy drugs tested to date. It is therefore anticipated that the addition of M6620 (VX-970, berzosertib)(VX-970, berzosertib) to standard chemoradiation will achieve increased efficacy and better patient outcome. This study is the initial step to establish the safety of this approach prior to conducting a larger efficacy phase II/III trial of this strategy in HNSCC.

2.2 CTEP IND Agent

2.2.1 M6620 (VX-970, berzosertib)(VX-970, berzosertib)

Mechanism of Action

M6620 (VX-970, berzosertib)(VX-970, berzosertib) (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, berzosertib)(VX-970, berzosertib) was >100-fold weaker inhibitor of ATM (Ki=34 nM) and >1000-fold less effective against other closely related kinases, such as DNA-dependent protein kinase (DNA-PK) (Ki>4 mcM), mTOR (Ki>1mcM), and PI3K-gamma (Ki=0.22 mcM) (Fokas et al., 2012). Overall, among 291 kinases tested, M6620 (VX-970, berzosertib)(VX-970, berzosertib)'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, berzosertib)(VX-970, berzosertib) concentration (IC_{50}) of 0.019 mcM, demonstrating >100-fold greater selectivity against ATR compared to ATM or DNA-PK (IC_{50} of 2.6 mcM or 18.1 mcM, respectively) (Fokas *et al.*, 2012).

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

Concurrent treatment of cancer cell lines with M6620 (VX-970, berzosertib)(VX-970, berzosertib) and various DNA-damaging agents led to sustained M6620 (VX-970, berzosertib)(VX-970, berzosertib)-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, berzosertib)(VX-970, berzosertib) in combination with DNA-damaging agents enhanced levels of the DNA-damage markers, *i.e*., γH2AX and $KAP1pS^{824}$, as compared to DNA-damaging agent alone (Hall *et al*., 2014; Investigator's Brochure, 2015). Sequential treatment of cells with DNA-damaging agent followed 15 h later by M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib). The rebound of phospho-CHK1 has been attributed to non-specific phosphorylation by an undefined kinase. However, despite the transient inhibition of phospho-CHK1, the sustained accumulation of γH2AX and $KAP1pS^{824}$ was observed. Together these data suggest that disruption of ATR-mediated DDR signaling by M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) activity.

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

Nonclinical studies

In vitro antitumor activity

In the absence of exogenous DNA-damaging agents, M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) 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,

berzosertib)(VX-970, berzosertib) (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, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) + carboplatin suggests >10-fold reduction in carboplatin IC_{50} for two non-small cell lung cancer (NSCLC) cell lines (H23 and HT1299) tested.

The impact of M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) in combination with cisplatin (84% of cell lines) or gemcitabine (76% of cell lines), demonstrating ≥3-fold reduction in the IC_{50} compared to IC_{50} of the cytotoxic agent alone (Hall et al., 2014a) 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, berzosertib)(VX-970, berzosertib). 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, berzosertib)(VX-970, berzosertib) with cisplatin or gemcitabine: antitumor IC_{50} was ≥3-fold lower for the M6620 (VX-970, berzosertib)(VX-970, berzosertib) + 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, berzosertib)(VX-970, berzosertib) were observed against two human pancreatic cancer cell lines with mutant KRAS and mutant p53 (MiaPaCa-2 and PSN1) (P<0.05), but not against non-cancerous fibroblast cell lines (Fokas *et al*., 2012). In addition, M6620 (VX-970, berzosertib)(VX-970, berzosertib) profoundly sensitized pancreatic tumor cells to gemcitabine-based chemoradiation.

Impact of defective ATM signaling on sensitivity of cells to M6620 (VX-970, berzosertib)(VX-970, berzosertib) in combination with a cytotoxic agent (cisplatin, gemcitabine, irinotecan, oxaliplatin, or etoposide) was examined in isogenic matched lung cancer cells (wild-type p53 A549 versus A549 transfected with p53 shRNA), using a cell viability assay (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, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) + 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, berzosertib)(VX-970, berzosertib) combined with cisplatin. Furthermore, no clear relationship between cellular response to M6620 (VX-970, berzosertib)(VX-970, berzosertib) + cisplatin and p53 status was observed in seven primary lung tumors.

In vivo antitumor activity

The *in vivo* activity of M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib). Single-agent M6620 (VX-970, berzosertib)(VX-970, berzosertib) had no significant effect on tumor growth in the experimental models. M6620 (VX-970, berzosertib)(VX-970, berzosertib) was generally well tolerated at efficacious doses in combination with DNA-damaging agents. Some body weight loss and enhanced changes in specific peripheral blood cell populations were observed with intensive and sustained dosing of M6620 (VX-970, berzosertib)(VX-970, berzosertib) in combination with cisplatin. This effect could be attributed to an increased growth arrest, which was observed *in vitro* in normal cells for combinations of M6620 (VX-970, berzosertib)(VX-970, berzosertib) with DNA-damaging agents. This effect was reversed when ATR activity was restored. M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) administered in combination with gemcitabine + IR was well tolerated.

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

Therapeutic human dose has been estimated based on the efficacious exposure achieved at 20 mg/kg/week of M6620 (VX-970, berzosertib)(VX-970, berzosertib) (given either as a single IV injection or as two IV injections of 10 mg/kg per week) 12-24 h after cytotoxic agent

(gemcitabine or cisplatin) in mice. The target M6620 (VX-970, berzosertib)(VX-970, berzosertib) plasma exposure, which corresponded to this dose, was an area under the concentration-time curve (AUC) of 4080 ng×h/mL/week. Allometry predicts that a human dose of 2.5 mg/kg (100 mg/mg^2) will be sufficient to achieve this exposure.

Nonclinical Pharmacokinetics

In all non-clinical species (the mouse, rat, dog, and monkey), M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) was extensively bound to plasma proteins; the free fraction of M6620 (VX-970, berzosertib)(VX-970, berzosertib) was only 2.1% in human blood.

M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib)(VX-970, berzosertib) kinetics and blood levels. Based on its minimal inhibition or induction effects on CYPs, M6620 (VX-970, berzosertib)(VX-970, berzosertib) is expected to have a low potential for drug-drug interactions. M6620 (VX-970, berzosertib)(VX-970, berzosertib) metabolites were excreted in the urine and bile. All metabolites observed in human hepatocyte incubations were also observed in either rat or dog hepatocyte incubations and in the blood, bile, or urine from rats or dogs. The systemic clearance of M6620 (VX-970, berzosertib)(VX-970, berzosertib) 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, berzosertib) 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, berzosertib) 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, berzosertib) in both rats and dogs.

M6620 (VX-970, berzosertib) had no cardiovascular liabilities, was not genotoxic in mutagenicity assay, had no hemolytic potential in human blood or compatibility issues in human plasma, and was well tolerated in an acute rabbit parenteral injection study. M6620 (VX-970, berzosertib) does absorb in the ultraviolet (UV) spectrum and has high tissue distribution in rats. M6620 (VX-970, berzosertib) has yet not been assessed in developmental and reproductive toxicity studies. However, M6620 (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, berzosertib) 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, berzosertib) phase 1 study with M6620 (VX-970, berzosertib) 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, berzosertib) in combination with either gemcitabine +/- cisplatin or cisplatin +/- etoposide. M6620 (VX-970, berzosertib) 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, berzosertib) PK, a 7-day lead-in treatment period of M6620 (VX-970, berzosertib) before cycle 1 has been included. Combinations of M6620 (VX-970, berzosertib) with gemcitabine or cisplatin are administered on a weekly schedule, with M6620 (VX-970, berzosertib) 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, berzosertib) 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, berzosertib) PK. M6620 (VX-970, berzosertib) exposures were similar for the agent administered alone and in combination with gemcitabine, suggesting no apparent drug-drug interactions. In the M6620 (VX-970, berzosertib) 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, berzosertib) in combination with gemcitabine or cisplatin (study 001) and for 11 patients treated with single-agent M6620 (VX-970, berzosertib) (study 002) (Investigator's Brochure, 2015). Of 29 evaluable patients (receiving M6620 (VX-970, berzosertib) +

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, berzosertib) + cisplatin demonstrated SD. Among 10 evaluable patients treated with M6620 (VX-970, berzosertib) 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, berzosertib) in combination with gemcitabine or cisplatin (Study 001) and 11 patients receiving M6620 (VX-970, berzosertib) 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, berzosertib) monotherapy in Study 001. There were no deaths attributable to treatment with M6620 (VX-970, berzosertib) 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, berzosertib) + gemcitabine, M6620 (VX-970, berzosertib) 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, berzosertib) 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, berzosertib) + cisplatin, six patients received M6620 (VX-970, berzosertib) (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, berzosertib) study (Study 002), M6620 (VX-970, berzosertib) 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, berzosertib). 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, berzosertib), has been identified as an adverse drug reaction for VX 970.

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

- M6620 (VX-970, berzosertib) absorbs in the UV-visible radiation spectrum and is widely distributed including skin, so patients receiving M6620 (VX-970, berzosertib) should

take protective measures to minimize sun exposure.

- To minimize the possibility of phlebitis, M6620 (VX-970, berzosertib) should be administered through a large-bore catheter into a large-caliber peripheral vein. 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, berzosertib) has not been fully characterized, caution should be used when co-administering medications with M6620 (VX 970). Because M6620 (VX-970, berzosertib) is primarily metabolized by CYP3A4, concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided.

- Preclinical studies suggested that M6620 (VX-970, berzosertib) 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, berzosertib).

2.3 *Other Agent(s)*

Cisplatin

2.3.1.1 Cisplatin and chemoradiation in HNSCC

The optimal partner systemic chemotherapy employed for definitive chemoradiation in HSNCC has not been established.(Bar-Ad et al., 2014) Options of chemotherapy are guided by investigator familiarity and institutional preference rather than by availability of prospective randomized comparative data. However, single agent cisplatin is the most widely accepted partner chemotherapy for HNSCC and the majority of randomized chemoradiation trials employed single agent cisplatin administered once every three weeks during the course of radiation. It is noteworthy that survival data from chemoradiation studies using the combination of cisplatin and 5-fluorouracil are generally comparable to cisplatin;(Rodriguez et al., 2014) albeit with greater frequency and severity of associated toxicities. Nonetheless, significant toxicities such as renal dysfunction, ototoxicity and peripheral neuropathy are also observed when cisplatin is administered as high-dose bolus infusion once every three weeks. This drawback of high dose cisplatin led to the evaluation and introduction of alternative chemotherapy regimens. Single agent cisplatin at a dose of 30-40mg/m^2 and carboplatin/ paclitaxel doublet administered on a weekly schedule during the course of radiation have been tested.(Bentzen et al., 2015a; Driessen et al., 2015b; Geiger et al., 2014; Gupta et al., 2009) Although there is no data from randomized comparison studies of high dose cisplatin and these alternative regimens, the clinical outcome is comparable. Driessen et al. reported on the outcome of one hundred six patients treated with concomitant cisplatin 40 mg/m2 weekly with accelerated radiation therapy up to a dose of 68 Gy over 5.5 weeks. Ninety-nine percent of the patients completed the planned RT and 90% received ≥5 cycles of cisplatin and only one patient developed nephrotoxicity. Three-year locoregional control, disease-free survival, and overall

survival were 72%, 54%, and 61%, respectively. Based on the increasing experience with weekly cisplatin and the reassurance that efficacy is not compromised, newly designed clinical trials are now employing weekly cisplatin as an acceptable chemotherapy regimen.

Until recently, high dose cisplatin has been the accepted concurrent systemic treatment of choice for large multi-institutional and cooperative group studies in HNSCC both for definitive chemoradiation and adjuvant study protocols.(Adelstein and Rodriguez, 2008) For example, NRG Oncology Group has traditionally employed high dose cisplatin given every 21 days for a lot of its HNSCC protocols as was the case with RTOG 0129, RTOG0522 and RTOG1016 studies, which used 2-3 cycles of high dose cisplatin at 100 mg/m^2. However, the emerging paradigm shows a shift towards more tolerable regimens. Weekly cisplatin at a dose of 40 mg/m^2 per week concurrent with radiation was selected as the chemotherapy regimen in recently activated NRG Oncology trials including NRG-HN001 for patients with nasopharyngeal cancer and RTOG1216 which is designed to compare different post operative adjuvant treatment strategies in patients with high-risk disease. Weekly cisplatin has been fairly well investigated as an alternative to high-dose cisplatin given once every three weeks and showed a lower overall toxicity profile.(Bentzen et al., 2015a; Driessen et al., 2015b; Geiger et al., 2014) It is also a well accepted regimen employed in prospective chemoradiation studies in nasopharyngeal cancer where it is associated with a survival advantage over radiotherapy alone, while producing lower toxicities than the standard high dose cisplatin schedule.(Chan et al., 2002; Chen et al., 2008; Qi et al., 2011) Randomized trials by Bachaud et al (flat dosing cisplatin at 50mg/week), by Jeremic et al (6mg/m^2/day) and Ghadjar et al. (20mg/m^2 daily for 5 days in weeks 1 and 5) all showed improved outcomes with chemoradiation over radiation alone.(Bachaud et al., 1996; Ghadjar et al., 2012; Jeremic et al., 2004) A retrospective study showed that weekly cisplatin achieved higher cumulative dose of 240mg compared to the cumulative dose of 200mg achieved with 100mg/m2 tri-weekly dosing due to a larger proportion of patients who were unable to complete the planned three doses of cisplatin given at the standard 100mg/m2 dose.(Ho et al., 2008) However, cisplatin at a cumulative dose of 20 mg/m^2/week or cumulative dose of 140mg was associated with inferior outcome and thus established a threshold at which the efficacy of cisplatin appears to be compromised. Indeed, a review of combined modality trials suggested that efficacy benefit of chemoradiation over radiation alone requires a cumulative cisplatin dose of approximately 200 mg/m^2 irrespective of the dosing schedule since a large proportion of patients could not tolerate the third planned dose of cisplatin.(Ang, 2004)

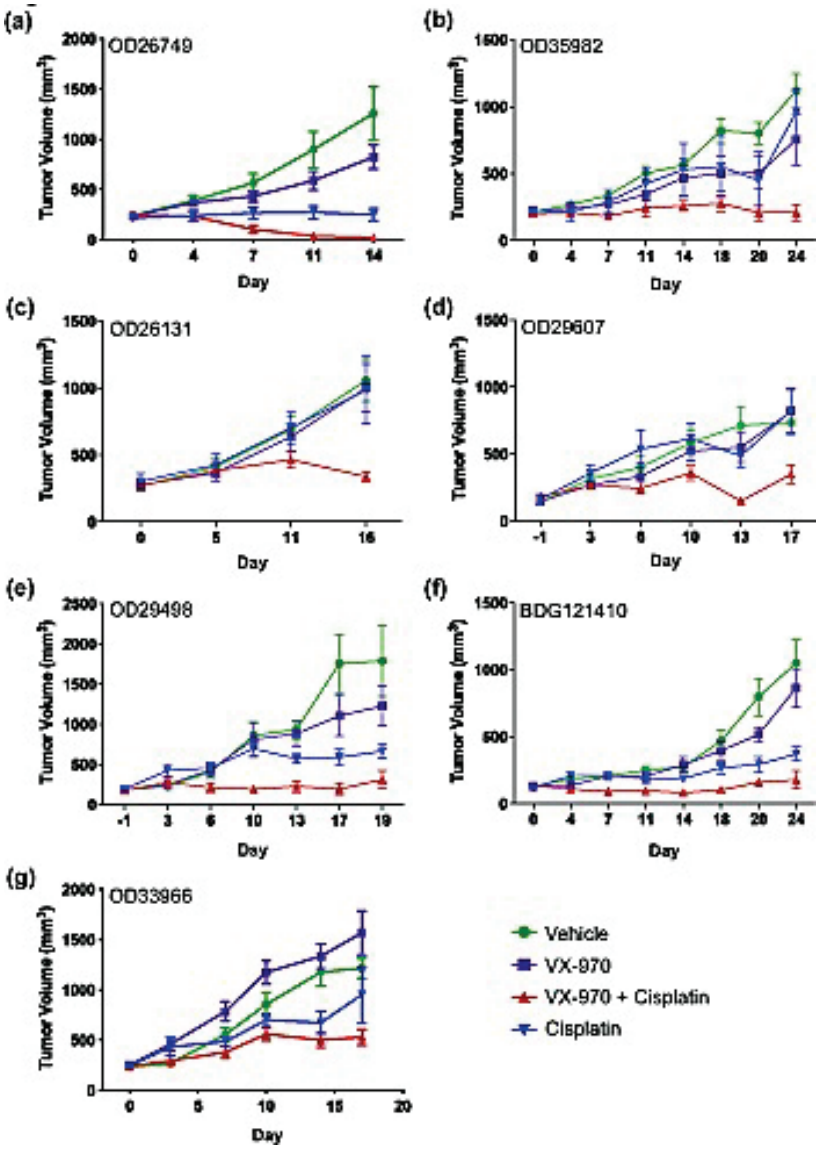
We recently conducted a meta-analysis of published studies comparing weekly to once every three weeks administration of cisplatin for chemoradiation of HNSCC.(Mohamed et al., 2015) We reviewed 1500 studies published between 1970 and 2013. Studies of induction therapy or studies using regimen that contained 5-FU or other targeted therapy or a total dose of cisplatin less than 180mg/m^2 or radiation dose less than 60 Gy were excluded. There were 51 studies that met the inclusion requirement for the analysis (25 weekly and 26 tri-weekly) with a total of 5,323 patients enrolled. The number of patients treated with weekly cisplatin was 1,797 (84% males) and tri-weekly was 3,526 (86% males). The median dose of radiation was 70 Gy for both groups while the median cumulative dose of cisplatin was 200 mg/m^2 and 300mg/m^2 respectively for the weekly and tri-weekly schedule. Overall response rate for weekly cisplatin was 89% (CI 79.6%-94.7%) versus 72% (CI 52%- 86%) for the tri-weekly schedule; p= 0.08.(Mohamed et al., 2015)

	Weekly Cisplatin (25 Studies, N=1797)	Tri-weekly Cisplatin (26 Studies, N=3526)	P-value
Study Characteristics			
Median age	57 years	57 years	
Males	84%	86%	
Stage IV	57%	69%	
Median radiation dose	70 Gy	70 Gy	
Median cisplatin dose	200 mg/m^2	300 mg/m^2	
Toxicities			
Grade 3-5 Toxicities	50% (CI 34%-65%)	69% (CI 54%-81%)	0.19
Grade 3-5 Mucositis	35% (CI 27%-44%)	36% (CI 28%- 44%)	0.73
PFS			
2-y PFS	70.5% (CI 58%- 80%)	67% (CI 59%- 74%)	0.90
3-y PFS	48.9% (CI 24%- 74%)	50% (CI 28%- 72%)	0.94
5-y PFS	62.6% (CI 47%- 76%)	59.4% (CI 36%-79.5%)	0.74
Median	24 months	44.8 months	0.45
OS			
2-y Survival rate	78.4% (CI 67%-86%)	73% (65%- 80%)	0.54
3-y Survival rate	59% (CI 32%- 82%)	66% (CI 41%- 84%)	0.77
5-y Survival rate	62% (CI 50%- 70%)	42% (CI 27%- 59%)	0.20
Overall Survival	21.2 months	27 months	0.77

The current study will employ the weekly cisplatin administration at 40 or 30 mg/m^2 due to the comparative efficacy to tri-weekly schedule and a trend toward better tolerability. Moreover, weekly administration allows greater flexibility to adjust dose delivery in the event of unanticipated toxicities occasioned by the addition of M6620 (VX-970, berzosertib) to standard chemoradiation. Future utility of this regimen is assured given the increased utilization of the weekly cisplatin regimen in prospective studies conducted by leading oncology groups and the emerging consensus in the field that the schedule of administration of cisplatin is less important than the achievement of a cumulative dose intensity of 200mg/m^2 in order to preserve the benefit of combined chemoradiation over radiation alone in locoregionally advanced HNSCC.(Strojan et al., 2015)

2.4 Rationale

Preclinical Considerations:
Replication checkpoint genes are amplified in genomically unstable cells. Notably, ATR and CHEK1 amplifications were predominantly observed in so-called "C-type" cancers, characterized by high levels of chromosomal instability, including lung squamous cell carcinoma, ovarian cancer and head-and-neck cancer.(Ciriello et al., 2013) The C class, identified by analysis of TCGA tumor maps, is characterized primarily by TP53 mutations and multiple recurrent chromosomal gains and losses. This class included almost all serous ovarian and breast (BRCA) carcinoma samples, as well as a large fraction of lung and HNSCC. Multimodality chemotherapy employing cisplatin in the neoadjuvant setting or given concurrently with radiation has become a standard of care for patients with locally advanced HNSCC. M6620 (VX-970, berzosertib) has the strongest and most consistent synergy with cisplatin of all cytotoxic chemotherapy drugs tested to date (M6620 (VX-970, berzosertib) Investigator Brochure); (Fokas et al., 2012; Hall et al., 2014b). Inactivation of p53 inactivates the G1/S checkpoint and further sensitizes cancer cells to M6620 (VX-970, berzosertib) combinations with XRT or cytotoxic chemotherapy. Loss of the ATM gene makes cancer cells more dependent on ATR signaling in conditions of replicative stress. Targeted inhibition of ATR reverses radioresistance in oral squamous cell carcinoma cells with distal chromosome arm 11q loss.(Sankunny et al., 2014) Distal 11q loss, marked by copy number loss of the ATM gene is observed in 25% of all Cancer Genome Atlas (TCGA) tumors, including 48% of HNSCC. The copy number loss of distal 11q is associated with resistance to ionizing radiation in oral squamous cell carcinoma (OSCC) cell lines. Expression studies at gene and protein levels revealed upregulation of ATR-CHEK1 pathway in these OSCC cell lines. Targeted knockdown of the ATR-CHEK1 pathway with siRNA resulted in increased sensitivity of the tumor cells to XRT. The results suggest that distal 11q loss is a useful marker for radio resistance that can be reversed by ATR-CHEK1 pathway inhibition.
M6620 (VX-970, berzosertib) (VE-822) has been used to target ATR in vivo, demonstrating selective sensitization of pancreatic tumors to radiation.(Josse et al., 2014) Treatment with VX-90 blocked ATR in vitro and in vivo, abrogated cell cycle checkpoints, enhanced persistence of residual DNA damage and blocked homologous recombination (HR) repair, as evidenced by a decrease in RAD51 foci.(Fokas et al., 2012) M6620 (VX-970, berzosertib) profoundly sensitized

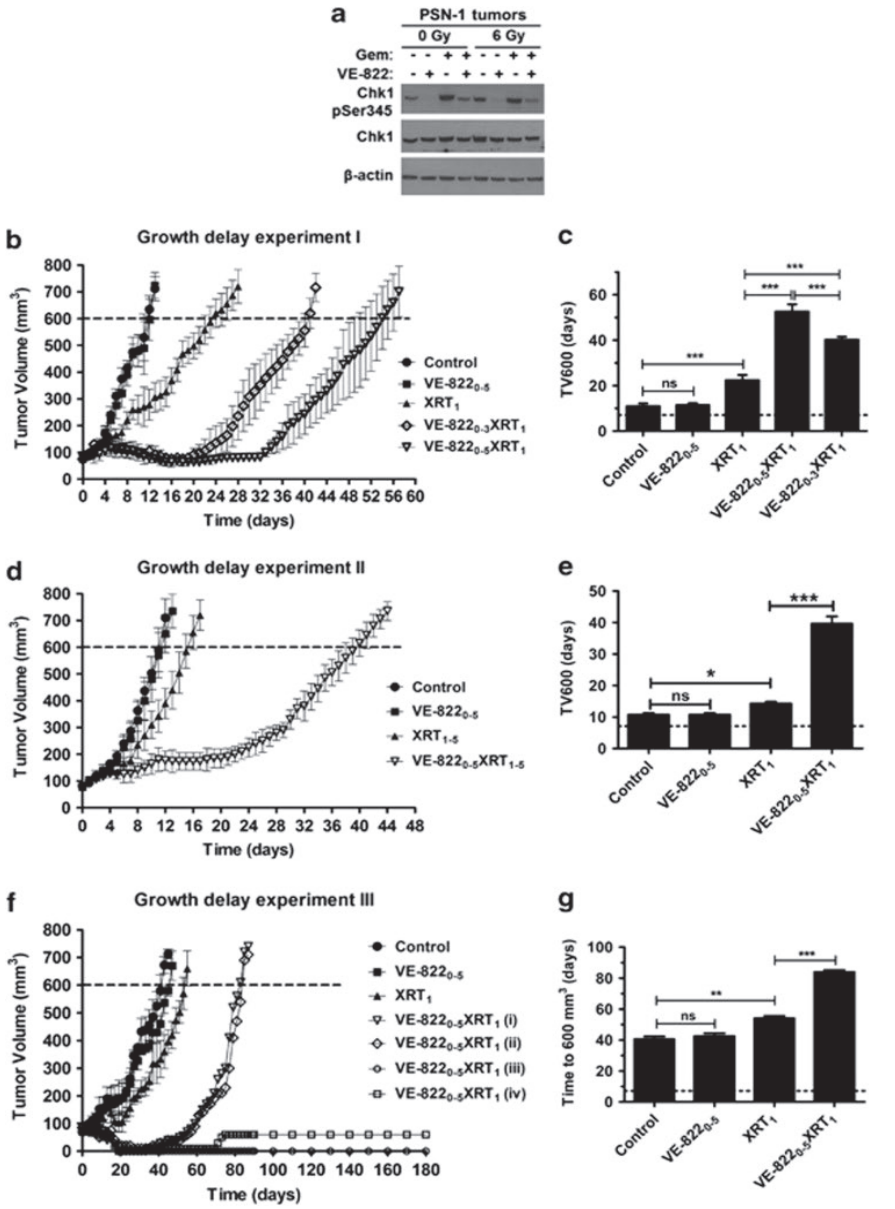


M6620 (VX-970, berzosertib) enhances the therapeutic efficacy of cisplatin in patient-derived lung tumor xenografts (A-G)
Human primary tumor tissues were passaged in SCID mice. Treatment started when the average tumor size was approximately 200 mm^3. Tumor bearing mice were treated with vehicle, M6620 (VX-970, berzosertib) (30 mg/kg in all models except 60 mg/kg in OD26749 and OD26131) PO, 4 consecutive days a week, alone and in combination with cisplatin (3 mg/kg IP, q7d), and cisplatin alone. Tumor volume and body weight were measured twice a week. Studies were terminated one or two days after the final dose of M6620 (VX-970, berzosertib). Points show the mean tumor volume (mm^3) for each treatment group (n=5-10). **Adapted from Hall A. B et al. Oncotarget. 2014 Jul 30;5(14):5674-85.(Hall et al., 2014b)**

pancreatic cancer cells and tumor xenografts to radiotherapy and gemcitabine-based chemoradiation without enhancing normal cells or tissue toxicity, as evidenced in an abdominal irrigation murine model.(Fokas et al., 2012; Prevo et al., 2012) VE-821 sensitized pancreatic cancer cells to radiation and gemcitabine and was associated with abrogation of the DNA damage-induced G2/M arrest and a decrease in RAD51 focus formation.(Hammond et al., 2004) Additionally, VE-821 blocked ATR-mediated signaling in tumor cells in response to replication

arrest in conditions of severe hypoxia and increased ATM-mediated phosphorylation of H2AX and KAP1.(Pires et al., 2012) It also decreased clonogenic survival of hypoxic tumor cells and sensitized them to radiation. ATR inhibition by VE-821 was associated with decreased HIF-1 stabilization and transcriptional activity. VE-821 resulted in significant chemo- and radiosensitization of hypoxic pancreatic cancer cells.

M6620 (VX-970, berzosertib) showed strong and consistent synergy with cisplatin of all cytotoxic chemotherapy drugs tested to date.(Fokas et al., 2012) It also displayed significant synergy in combination with radiation in *in vtro* and *in vivo* preclinical cancer models.(Fokas et al., 2012; Hall et al., 2014b) Additionally, cancer cells with inactive p53 are very sensitive to the cytotoxic effect of M6620 (VX-970, berzosertib) especially in combinations with XRT or chemotherapy. Inactivating alterations of TP53 and ATM genes have been described in HNSCC and TP53 is the most frequent genetic alteration, described in up to 85% of HPV (-) HNSCC (Agrawal et al., 2011; Stransky et al., 2011). Furthermore, TP53 gene mutation is associated with poor therapeutic response and decreased survival in HNSCC patients (Gross et al., 2014; Lindenbergh-van der Plas et al., 2011; Masica et al., 2015; Skinner et al., 2012). Cisplatin is the most widely employed chemotherapy backbone for chemoradiation therapy in HNSCC (Adelstein et al., 1997; Dimri et al., 2013; Driessen et al., 2015a; Gupta et al., 2009; Rodriguez et al., 2014). It is therefore reasonable to anticipate that the combination of M6620 (VX-970, berzosertib) and chemoradiation will result in superior clinical efficacy. We hypothesize that the strategy of combining a targeted DNA repair inhibitor, M6620 (VX-970, berzosertib), with standard chemoradiation will be safe and well tolerated by patients. Furthermore, we expected that such a combination will produce improved outcome over standard chemoradiation alone in HPV (-) HNSCC, an area of unmet need where currently available treatment approaches have achieved suboptimal clinical outcome.



E-822 enhances the therapeutic efficacy of radiation (XRT) in MiaPaCa-2 and PSN-1 xenograft models.

(**a**) Mice bearing PSN-1 tumors were treated with VE-822 (60 mg/kg; days 0 and 1) and/or gemcitabine (100 mg/kg; day 0) and/or XRT (6 Gy; day 1). Tumors were harvested 2 h post-XRT. Chk1 phosphorylation (Ser345) was examined by immunoblot in tumor homogenates. (**b**) mice were treated as indicated. Growth delay experiment I: mice bearing PSN-1 tumors (n=4–5) were treated daily with either vehicle (control), VE-822 (60 mg/kg) from days 0 to 5 (VE-8220–5), 6 Gy at day 1 (XRT1) or VE-822 plus 6 Gy by administering the drug for either 4 days (VE-8220–3XRT1) or 6 days (VE-8220–5XRT1). (**c**) Time in days, from day 0, to reach a tumor volume of 600 mm^3 (TV600) in the different groups. (**d**) Growth delay experiment II: mice bearing PSN-1 tumors (n=4) were treated with vehicle (control), VE-822 from days 0 to 5 (VE-8220–5), fractionated XRT using five daily doses of 2 Gy from day 1 to day 5 (XRT1–5) or the combination of VE-822+ fractionated XRT (VE-8220–5XRT1–5). (**e**) Time from day 0 to TV600 in the different groups. (**f**) Growth delay experiment III: mice bearing MiaPaCa-2 xenograft tumors (n=4) were treated as in (**b**) with the difference that only one VE-822+XRT combination was tested (VE-8220–5XRT1). (**g**) Time in days, from day 0, to TV600 in the different groups. In (**b**, **d** and **f**), points show the mean of tumor volume (mm^3) of each treatment group (n=4–5). ns, not significant; *P<0.05; ***P<0.001. **Adapted from Fokas et al. Cell Death Dis. 2012 Dec 6;3:e441.(Fokas et al., 2012)**

2.5 Correlative Studies Background

The following correlative analysis will be analyzed posthoc using tumor and surrogate samples collected from patients enrolled on this study.

2.5.1 FDG-PET: Response to chemoradiation assessed at 12-weeks post treatment is a strong predictor of long-term outcome.(Pfister et al., 2014) It is also an important tool for selecting patients in need of salvage neck dissection following definitive chemoradiation. The frequency of complete response on post treatment PET scan will be compared to historical evidence in order to obtain some preliminary evidence of improved therapeutic efficacy when M6620 (VX-970, berzosertib) is added to standard chemoradiation. **(NB: Decision regarding the need for salvage surgery post chemoradiation is left to the discretion of the investigators according to local institution standard practice and will not be dictated directly by the metabolic response assessment)**

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed head and neck squamous cell cancer (HNSCC) including paranasal sinus cancers but excluding nasopharyngeal carcinomas.

3.1.2 Clinical staged III or IV HNSCC, according to AJCC 7th Edition, that is not amenable to surgical resection.

3.1.3 Carcinoma of the neck of unknown primary site origin (regardless of HPV/p16 status) is eligible.

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

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.6 Life expectancy of greater than *3 months*

3.1.7 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.

3.1.8 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 normal institutional limits
–	AST(SGOT)/ALT(SGPT)	≤2.5 × institutional upper limit of normal
–	creatinine	within normal institutional limits
		OR
–	creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.9 The effects of M6620 (VX-970, berzosertib) 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 for 6 months after completion of M6620 (VX-970, berzosertib) administration.

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

3.1.11 Women of childbearing potential who are sexually active should be willing and able to use medically acceptable forms of contraception throughout the treatment phase of the trial and for up to 6 months following the last administration of study treatment. Men who are sexually active must be willing and able to use medically acceptable forms of contraception throughout the treatment phase of the trial and for 6 months after completion of M6620 (VX-970, berzosertib) administration.

3.2 Exclusion Criteria

3.2.1 Patients with nasopharyngeal carcinoma, skin SCC, and salivary gland carcinomas are not eligible

3.2.2 Patients who are receiving adjuvant chemoradiation after surgical resection of the primary site of disease

3.2.3 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.4 Patients who are receiving any other investigational agents.

3.2.5 Patients on tacrolimus or any other immunosuppressants with significant interaction with cisplatin

3.2.6 Patient who requires live vaccine administration

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

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

3.2.9 Prior systemic chemotherapy for the current cancer (prior chemotherapy for a different cancer is allowed)

3.2.10 Prior receipt of radiotherapy that would result in overlap of the new and old radiation therapy fields

3.2.11 Uncontrolled intercurrent illness including, but not limited to:

- Ongoing or active infection requiring intravenous antibiotics at the time of treatment initiation;
- Symptomatic congestive heart failure (requiring hospital stay within the last 6 months);
- Myocardial infarction within the last 6 months
- Unstable angina pectoris, cardiac arrhythmia
- Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 Pregnant women are excluded from this study because M6620 (VX-970, berzosertib) 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, berzosertib), breastfeeding should be discontinued if the mother is treated with M6620 (VX-970, berzosertib). These potential risks may also apply to other agents used in this study.

3.2.13 HIV-positive patients with well-controlled disease, as determined by CD4 count and viral load, who are on antiretroviral therapy that does not contain a strong inducer or inhibitor of CYP3A4 are allowed on trial. HIV-positive patients on combination antiretroviral therapy with strong inducers or inhibitors of CYP3A4 are ineligible because of the potential for pharmacokinetic interactions. Patients with poorly controlled HIV are not eligible due to the increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.14 Definitive clinical or radiographic evidence of distant metastasis or adenopathy below the clavicles.

3.2.15 M6620 (VX-970, berzosertib) 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.

3.3 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 at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

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

- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

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

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

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

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

4.2 Site Registration

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

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

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

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

Additional Requirements
Additional requirements to obtain an approved site registration status include:

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

4.2.1 Downloading Regulatory Documents

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

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-MD017, and protocol number 9950,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Requirements For 9950 Site Registration:

- Internal Site initiation teleconference (SIT) conducted by the Study PI with the site research team
    - SIV checklist and sign-in sheet must be completed and signed by site study PI and sent back to the Protocol Liaison of the lead LAO.
- Notification via email of the SEP2C Program Manager with the following information: Protocol #, Institution Name and CTEP ID, and a statement that the site has fulfilled the Site Initiation Teleconference

- Electronic notification of CTSU of site initiation by SEP2C Program Manager.
- For applicable ETCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

4.2.3 Submitting Regulatory Documents

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

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

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

4.2.4 Checking **Site** Registration Status

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

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment.

OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

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

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

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

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

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

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

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

4.3.2 OPEN/IWRS Questions?

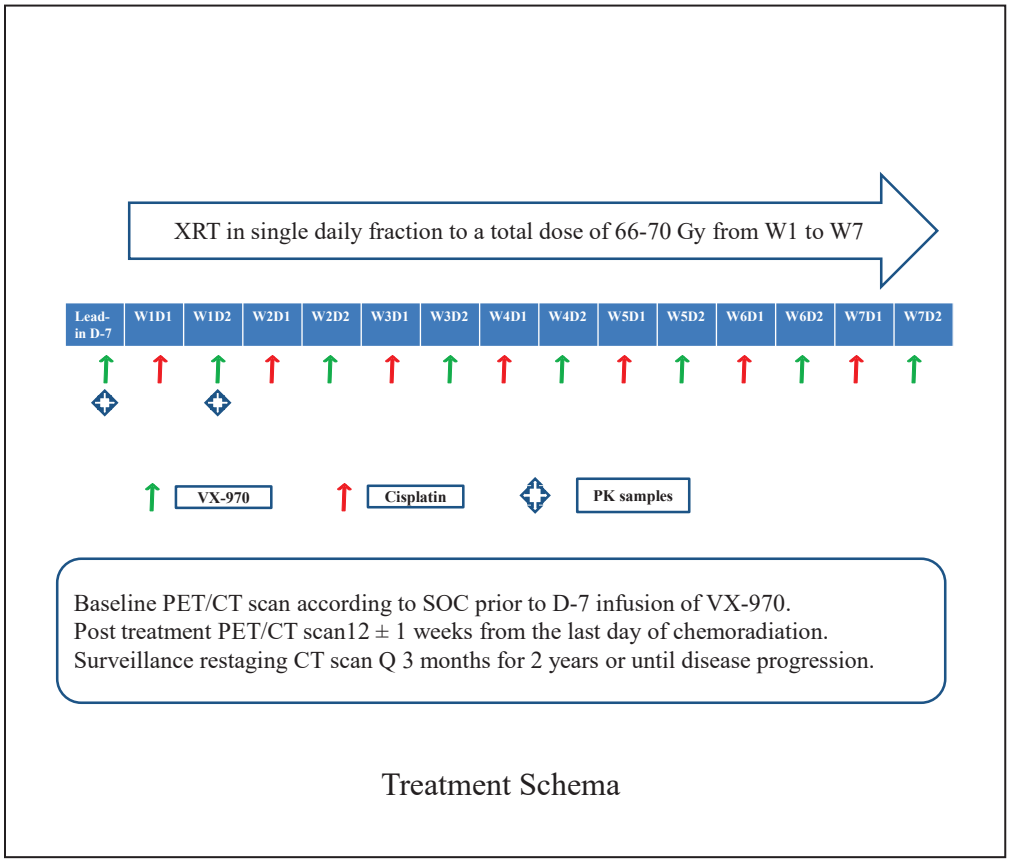
Further instructional information on OPEN is provided on the OPEN link of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *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

This is a phase I, open label, safety, tolerability and tolerability study of the combination of M6620 (VX-970, berzosertib) with cisplatin and XRT in locally advanced HNSCC. The study will employ a standard phase I design to enroll previously untreated patients with locally



Treatment Schema

advanced HNSCC patients (stage III or IV HNSCC of the larynx, oropharynx, hypopharynx, or oral or paranasal cavity but excluding nasopharyngeal cancer). Eligible patients will receive escalating doses of M6620 (VX-970, berzosertib) in combination with fixed doses of cisplatin and XRT (see dose escalation table). Intrapatient dose escalation will not be allowed on study. Toxicity will be assessed and graded according to NCI CTCAE version 5.0. Patients will be enrolled in cohorts of 3 subjects using a Bayesian adaptive design, Escalation with Overdose Control (EWOC).

The dose levels for the trial are summarized in the dose escalation table. The dose escalation will consist of two stages starting with stage 1, dose level 1 consisting of M6620 (VX-970,

berzosertib) (120 mg/m^2) and cisplatin (40 mg/m^2). Doses of M6620 (VX-970, berzosertib) up to 280mg/m^2 on D2 and D9 have been shown to be safely tolerated in combination with cisplatin (40mg/m^2) on D1 of a 21-day cycle. The planned maximum dose of M6620 (VX-970, berzosertib) may be extended depending on the safety experience in other studies of M6620 (VX-970, berzosertib) in combination with cisplatin. The starting dose of 120mg/m^2, which is approximately 57% of the maximum dose of M6620 (VX-970, berzosertib) already tested in combination with cisplatin (unpublished clinical trial experience, Vertex Pharmaceuticals) is therefore considered to be a safe starting dose in combination with weekly cisplatin and XRT. If none of the three patients in the first cohort experienced a DLT, the trial will proceed directly to stage 2, otherwise additional patients will be treated in cohorts of 3 either at dose level 1 or dose level -1 based on the EWOC recommended doses. We plan to enroll a maximum of 30 patients during this dose escalation phase.

Stage	Dose level	Cisplatin (mg/m^2) IV Q week	M6620 (VX-970, berzosertib) (mg/m^2) IV Q week	XRT over 6-7 weeks	Number of Patients
Stage I	-1	30	120	70Gy	0-6
	1: Starting dose level	40	120*	70Gy	3-9
Stage II	2	40	160	70Gy	3-6
	3	40	200	70Gy	3-6
	4	40	240	70Gy	3-6
	5	40	280#	70Gy	3-6
Expansion	RP2D	40	200	70Gy	15

*:The starting dose of M6620 (VX-970, berzosertib) may be different than 120 mg/m^2 depending on the safety experience in the ongoing phase I study of cisplatin + M6620 (VX-970, berzosertib)
May test doses up to the single agent MTD of M6620 (VX-970, berzosertib) of 480mg/m^2 as tolerated
Up to 30 patients in the escalation phase and 15 patients in the expansion cohort treated at the RP2D
In case of DLT with the cisplatin starting dose of 40mg/m^2, a dose level -1 will be tested with cisplatin 30mg/m^2 and subsequent escalation of M6620 (VX-970, berzosertib) will be along with the reduced dose of cisplatin. There is no plan to deescalate the total dose of radiation in this study

Exploratory correlative analysis will be carried out posthoc using baseline archival tissue samples.

This phase I dose escalation study of M6620 (VX-970, berzosertib) (120, 160, 200, 240 and 280 mg/m^2) in combination with standard doses of cisplatin (30 or 40mg/m^2) administered on a weekly schedule along with external beam radiation therapy to a total dose of 70 Gy will be conducted in HNSCC patients who are appropriate candidates for combined chemoradiation as definitive therapy for locally advanced disease. Immediate efficacy will be assessed at 12 weeks (± 1 week) post chemoradiation using FDG PET to be acquired according to local standard algorithm for image acquisition. Metabolic response will be correlated with long-term outcome. (**NB: Decision regarding the need for salvage surgery post chemoradiation is left to the**

discretion of the investigators according to local institution standard practice and will not be dictated directly by the metabolic response assessment)

The study will use the weekly administration of cisplatin (40 or 30mg/m^2) along with escalating does of M6620 (VX-970, berzosertib). A lead in administration of M6620 (VX-970, berzosertib) in the week preceding XRT will allow for single agent PK assessment followed by concurrent administration with cisplatin the following week. Given that M6620 (VX-970, berzosertib) is a CYP substrate and fosaprepitant (CYP3A4 inhibitor) is part of the standard premed for cisplatin, it would be critical to assess for DDI through comprehensive PK analysis during this phase I study. The PK sample collection is not mandatory and may be omitted if patient is unable to adhere to the schedule of sample collection. Dose limiting toxicity will be assessed over the entire duration of the chemoradiation and for up to 3 weeks beyond the last fraction of radiation.

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.

Regimen Description					
Agent	**Premedication**	**Dose**	**Route**	**Schedule**	Weeks
M6620 (VX-970, berzosertib)	As needed	** in D5W diluted to final concentration between 0.075 mg/mL to 1 mg/mL	IV over 1 hour	Day -7 Day 2	1 to 7
Cisplatin	See section 5.1.2	** in 250 cc NS	IV over 30-60 minutes	Day 1	1 to 7
XRT	As needed	Single daily fractionation of 2Gy	NA	Days 1-5	1 to 7
**** total dose**					

5.1.1 M6620 (VX-970, berzosertib)

5.1.1.1 Preparation

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

The maximum amount of betadex sulfobutyl ether sodium that will be administered is

8.5 g/week, based on a maximum 800 mg/week dose of M6620 (VX-970, berzosertib). This amount of betadex sulfobutyl ether sodium is less than the amount administered weekly based on the approved dose of intravenously administered Vfend® (voriconazole), which contains 3200 mg betadex sulfobutyl ether sodium per 200 mg/30 mL vial.

5.1.1.2 Administration and precautions

Administer as an intravenous infusion as a single agent on Day -7 and for up to 7 additional doses administered weekly concurrent with chemotherapy and radiation treatment at the dose appropriate for the patient cohort. Dose will be calculated using actual body weight. In order to obtain samples to characterize single agent PK characteristics of M6620 (VX-970, berzosertib), the first infusion (week -1) of M6620 (VX-970, berzosertib) will be administered 7 (±1) days prior to the initiation of cisplatin and radiation. Subsequent M6620 (VX-970, berzosertib) doses will be administered once weekly at least 24 (±4) hours from the end of cisplatin infusion. Note that M6620 (VX-970, berzosertib) may be administered before or after radiotherapy. No M6620 (VX-970, berzosertib) will be administered after the final week of radiation. M6620 (VX-970, berzosertib) should be administered on Tuesdays or Wednesdays to maximize overlap of daily radiation with exposure (strive to administer on the same day of the week within a variance of 1 day for scheduling challenges for vacation or holidays). If radiation treatments are held for toxicity, M6620 (VX-970, berzosertib) dosing should also be held. The dose of M6620 (VX-970, berzosertib) held due to toxicity will not be made up. If cisplatin is held due to a non-overlapping toxicity, M6620 (VX-970, berzosertib) may continue to be administered provided there is no discontinuation of radiation.

The dose of M6620 (VX-970, berzosertib) will be infused intravenously over 60 minutes (± 10 minutes). When the total volume of infusion exceeds 600 mL, the infusion time may be extended beyond 60 minutes (as tolerated), but no more than 90 minutes. Intravenous administration of M6620 (VX-970, berzosertib) is independent of food intake.

To minimize the possibility of phlebitis, M6620 (VX-970, berzosertib) 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, berzosertib) and of pruritus in 2 subjects at 480 mg/m^2 of VX-970, pre-medication with a corticosteroid and an antihistamine may be considered for all subjects receiving M6620 (VX-970, berzosertib) (to prophylax against possible acute hypersensitivity), and is strongly recommended for subjects receiving doses of M6620 (VX-970, berzosertib) above 240 mg/m^2 (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, berzosertib) infusion, and should be used prophylactically as pre-medication for all subjects who develop acute

hypersensitivity or pruritus with M6620 (VX-970, berzosertib) infusion and who continue to receive treatment with M6620 (VX-970, berzosertib). 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, berzosertib) infusion, and either 10 mg of chlorphenamine or 25 mg of diphenhydramine intravenously approximately 30 minutes (± 10 minutes) before M6620 (VX-970, berzosertib) 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.

M6620 (VX-970, berzosertib) absorbs in the UV-visible radiation spectrum and is widely distributed including skin, so patients receiving M6620 (VX-970, berzosertib) should take protective measures to minimize sun exposure. The potential genotoxicity of M6620 (VX-970, berzosertib) was assessed in a non-GLP bacterial mutagenicity (Ames) assay using 2 Salmonella strains (TA98 and TA100) with and without S9 metabolic activation. There was no increase in revertants at noncytotoxic concentrations, indicating that M6620 (VX-970, berzosertib) was not mutagenic under the conditions of this assay. The IV formulation of M6620 (VX-970, berzosertib) (5% betadex sulfobutyl ether sodium w/w and 3% mannitol w/v in water) has no in vitro hemolytic potential in human blood, and showed no evidence of precipitation or incompatibility with human plasma up to the maximum concentration evaluated (2 mg/mL). Furthermore, M6620 (VX-970, berzosertib) was well tolerated in an acute rabbit parenteral tolerability study when administered via IV, perivenous, intra-arterial, or subcutaneous injection at a dose of 2 mg/mL. Only slight to moderate dermal irritation at injection sites was observed. Microscopic findings noted following IV, perivenous and intra-arterial administration were limited to minimal to mild tissue damage that was not considered adverse based on the minimal extent and severity of the finding. Nonetheless, M6620 (VX-970, berzosertib) was considered to be mildly irritating upon injection.

M6620 (VX-970, berzosertib) 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.

5.1.1.3 Antiemetic regimen

The antiemetic regimen for day 2 post cisplatin will also serve as the premedication regimen for M6620 (VX-970, berzosertib) administration. At least 30 minutes prior to M6620 (VX-970, berzosertib) administration, administer the standard anti-emetic regimen for day 2 post cisplatin (see section 5.1.2.2)

5.1.2 *Cisplatin*

Cisplatin: administer weekly during radiation treatment for a maximum of 7 doses at a dose of 40 mg/m^2/week (alternatively 30mg/m^2/day if DLT observed with the protocol-

defined starting dose of cisplatin). Dose will be based on actual body weight.
The first cisplatin infusion should be started within 24 hours before or after the first scheduled radiation therapy administration. Note that treatment may be administered before or after radiotherapy. No cisplatin will be administered after the final week of radiation. **Cisplatin should be administered on Mondays or Tuesdays to maximize overlap of daily radiation with cisplatin exposure (strive to administer on the same day of the week within a variance of 1 day for scheduling challenges for vacation or holidays)**. Administration on Wednesday prior to that day's radiation dose is acceptable but not preferred. If radiation treatments are held for toxicity, cisplatin dosing should also be held. The dose of cisplatin held for toxicity will not be made up.

5.1.2.1 Cisplatin Administration Guidelines

High dose cisplatin is highly emetogenic. While this protocol is using the weekly dosing that may be considered moderately emetogenic, investigators should use aggressive prophylactic antiemetics and hydration as necessary. **For purposes of this protocol, individual investigators may use local guidelines for cisplatin administration provided the subject received the assigned dose of cisplatin for his cohort. The recommended approach below** may be modified based on local guidelines and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen is to be at the discretion of the local investigator, based on local practice guidelines.

5.1.2.2 Antiemetic regimen

A 5-HT3 antagonist, NK antagonist and dexamethasone should be employed in line with local practice for highly emetogenic chemotherapy:

i. ondansetron 16 mg PO prior to cisplatin and 8 mg PO up to 3 times daily on days 2 and 3 following cisplatin weekly and dexamethasone x 3 days starting prior to the cisplatin dose weekly, 12 mg on day 1 and 8 mg on days 2 and 3 each week
OR
ii. palonosetron 0.25 mgs IV and dexamethasone 12 mgs prior to cisplatin
iii. Due to the need to carry out DDI analysis for M6620 (VX-970, berzosertib), fosaprepitant (or aprepitant) must be administered as part of the antiemetic regimen prior to W1D1 cisplatin administration
iv. Subsequent use of fosaprepitant or aprepitant, metoclopramide, or prochlorperazine is left to the discretion of the investigator.

5.1.2.3 Pre-Hydration:

Give 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin may be given at the discretion of the investigator according to local practice.

5.1.2.4 Cisplatin administration:

Infuse cisplatin over 30-60 minutes intravenously in 250 cc NS at an infusion rate not to exceed 2 mgs per min.

5.1.2.5 Post-hydration:

Following the end of the cisplatin administration, an additional liter of D5½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours. Patient should be encouraged to take at least 2 liters of fluid per day orally for the next 2 days. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS. Note that the pre- and post-hydration is left to the discretion of the investigator.

5.1.3 Radiation

5.1.3.1 General Considerations

Radiation treatment must begin within 14 calendar days after registration.
Missed treatments due to holidays or logistic reasons can be compensated by delivering additional BID fractions, with a minimum inter-fraction interval of 6 hours, or by treating on Saturday or Sunday.

5.1.3.2 Required Criteria

- All patients will undergo computed tomography (CT) simulation with intravenous (IV) contrast unless medical contraindications to IV contrast exist (allergy, creatinine > 1.5)
- Intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) treatment technique will be utilized along with daily image guided radiation therapy (IGRT)
- Heterogeneity corrections must be utilized
- Non IMRT techniques may be used to treat the low neck, if it is the institution's practice. For IMRT planning, margin expansions will be set at a minimum of 0.5 cm from GTV to the high dose CTVs. Sites will have the option to use an additional 0.3 or 0.5 cm to the PTV, depending on the frequency of IGRT.
- If PTV margins of 0.3 cm are used, daily IGRT usage is required. If using 0.5 cm PTV margins, a minimum of weekly IGRT is required.

5.1.3.3 Target Volume Determination

- The initial gross tumor volume (GTV) will include all positron emission tomography (PET) positive areas of disease along with regions of disease seen on physical exam and fiberoptic laryngoscopy exam
- GTV to clinical target volume (CTV) expansion will be determined by the treating radiation oncologist, however at least 5 mm-1 cm is recommended
- The CTV will then be expanded by an additional 3-5 mm to create a planning target volume (PTV), depending on availability of IGRT.

5.1.3.4 Radiation Dose

- Gross disease will be treated to a maximum of 70 Gy in 2 Gy/day fractions
- Dose to high-risk nodal regions within the neck will be determined by the treating radiation oncologist, but must range from 50-60 Gy
- Dose to intermediate and low-risk nodal regions within the neck will be determined by the radiation oncologist, but must range from 44-60 Gy
- Simultaneous integrated boost or sequential IMRT/VMAT planning may be utilized.

5.1.3.5 Dose Prescription and Dose Constraints

- Isodose lines will be generated for both the primary and boost plans
- 95% of all PTVs will be covered by the 100% isodose line at minimum
- The mean dose to one parotid gland must be 26 Gy or less
- The maximum spinal cord dose must be 45 Gy or less
- The maximum brain stem dose must be 54 Gy or less
- The maximum dose must be located within the PTV and may not be greater than 110% of the prescription dose
- Other constraints (not mandatory but highly recommended) include a mean larynx dose of 40 Gy or less, a mean oral cavity dose of 30 Gy or less, and maximum dose of 72 Gy to the mandible

5.1.3.6 Patient Immobilization and Imaging

- All patients will be immobilized using a head and shoulder mask
- On board imaging (OBI) images will be obtained daily during throughout treatment if a minimum PTV margin of 3mm is utilized
- The use of a thermoplastic head and shoulder mask is mandatory for head and neck IMRT.
- Patients will be planned in the supine position with their arms at their sides.

5.1.3.7 Technical Factors

Image Guidance for IGRT When Using Reduced Margins

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy).

5.1.3.8 Planning CT scan

The treatment planning CT scan is mandatory for defining target volumes and normal organ at risk. The planning CT scan will be done with and without contrast, the one with no contrast is intended for use in heterogeneity corrected IMRT planning. The structuring scan with contrast is fused to the planning scan for the purposes of structure definition and so that the major vessels of the neck are easily visualized. An institution may elect to use the structuring scan as the planning scan. CT scan thickness should be at minimum 0.3 cm, and the CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be included in the CT scan limits. The scanning limits should at least encompass the orbits superiorly, and 1 cm below the supra-sternal notch inferiorly. For more accurate contouring, diagnostic CT scans and/or MRI may be fused with the planning CT scan.

5.2 Definition of Dose-Limiting Toxicity

Patients are considered evaluable for DLT determination if they have received at least 1 dose of

cisplatin and M6620 (VX-970, berzosertib) concurrent with 1 week (5 fractions) of XRT. Patients who discontinue from protocol treatment prior to meeting this requirement for DLT definition will be replaced unless they experience DLT prior to discontinuation.

Patients must have samples collected on D-7 and W1D2 to be evaluable for PK endpoints. The PK sample collection is not mandatory and may be omitted if patient is unable to adhere to the schedule of sample collection.

Dose limiting toxicities will be defined as follows:
The following will constitute DLT in this study consistent with DLT definition in other phase I studies of chemo-radiation plus novel agent in HNSCC.(Argiris et al., 2011; Gilbert et al., 2012)

- Grade 4 hematologic toxicity lasting more than 7 days
- Grade 4 Neutropenia of any duration with fever ≥ 38.5c
- Grade ≥4 nausea and or vomiting in spite of standard supportive therapy
- Grade ≥3 non-hematologic toxicity (exclude alopecia, anorexia, fatigue, infection without neutropenia, grade 3 elevation of transaminases, and grade 3 hypomagnesemia and grade 4 stomatitis, mucositis and/or dysphagia that resolves to grade 2 or less with a treatment break not to exceed 10 days from the scheduled day of chemotherapy); lab abnormalities will not be considered DLT if of no clinical consequence
- Inability to re-treat patient within 2 weeks of scheduled treatment due to treatment-related toxicity
- Grade 4 radiation induced rash
- Inability to deliver at least 90% of the total radiation dose due to treatment discontinuation as a result of intolerable treatment-related toxicity or a radiation treatment break of > 5 consecutive fractions

DLT assessment period will extend from W1D1 through the last day of radiation according to CTCAE v. 5.0 criteria. The maximum tolerated dose (MTD), recommended phase II dose (RP2D) and pharmacokinetic (PK) characteristics of M6620 (VX-970, berzosertib) will be established using a maximum of 30 patients treated in up to five possible dose cohorts. An expansion cohort of 15 patients will be treated at the RP2D in order to obtain preliminary evidence for efficacy. M6620 (VX-970, berzosertib) is a CYP3A4 substrate while premedication for cisplatin includes fosaprepitant, a possible CYP inhibitor. Therefore potential drug-drug interaction (DDI) between M6620 (VX-970, berzosertib) and cisplatin premedication regimen will be assessed by comparing the PK characteristics (Cmax, AUC, CL, t1/2, Vss) of M6620 (VX-970, berzosertib) collected on Day -7 (run-in period with single agent M6620 (VX-970, berzosertib)) and on Week 1 Day 2. PK samples will be collected:

- Baseline before start infusion
- 30 min (±5 min) after start of M6620 (VX-970, berzosertib) infusion
- 55 min (±5 min) after start of M6620 (VX-970, berzosertib) infusion
    - i.e. 5 min before end of M6620 (VX-970, berzosertib) infusion <1h; M6620 (VX-970, berzosertib) ends>
- 5 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 15 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 30 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion

- 1h (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 2h (±10 min) after end of M6620 (VX-970, berzosertib) infusion
- 4h (±10 min) after end of M6620 (VX-970, berzosertib) infusion
- 23h (±1 h) after end of M6620 (VX-970, berzosertib) infusion
- 48h (±2 h) after end of M6620 (VX-970, berzosertib) infusion
- 72h (±2 h) after end of M6620 (VX-970, berzosertib) infusion

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.3 General Concomitant Medication and Supportive Care Guidelines

M6620 (VX-970, berzosertib) is metabolized by cytochrome P450 (CYP) 3A4 isoenzyme (CYP3A4); exposure to M6620 (VX-970, berzosertib) may be affected by concomitantly administered drugs that are strong inhibitors or inducers of CYP3A4. Concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Sensitive substrates of CYP3A4 should be used with caution. 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, berzosertib) is a moderate inhibitor of P-gp and BCRP. It is a P-gp substrate but not BCRP. Based on in vitro data, there is low risk of drug-drug interaction with OATP1B3 and BCRP. Use caution when administered with sensitive substrates of OATP1B3 and BCRP transporters.

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

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

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until completion 70Gy of XRT concurrent with systemic therapy 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.

5.5 Duration of Follow Up

All patients on study will be followed for status assessment approximately every 2 weeks as necessary for the first 3 months post chemoradiation and then every 3 months for the next 2 years.

Safety: Patients removed from study due to adverse event(s) will be followed until resolution or stabilization of the adverse event or for a minimum of 30 days after removal from study or until death, whichever occurs first. Such patients will be followed for response assessment as appropriate.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form. There will be no requirement for long term follow-up for patients removed from study.

6. DOSING DELAYS/DOSE MODIFICATIONS

Note: *All treatment modifications must be expressed as a specific dose or amount rather than as a percentage of the starting or previous dose.*

Dose reduction plan	***M6620 [VX-970]* Dose**
-2	*40 mg/m^2, weekly*
-1	*80 mg/m^2, weekly*
1 (cohort 1 starting dose)	*120 mg/m^2, weekly*
+2	*160mg/m^2, weekly*
+3	*200 mg/m^2, weekly*
+4	*240 mg/m^2, weekly*
+5	*280 mg/m^2, weekly*

Dose reduction plan	***[Cisplatin]* Dose**
-1	*30 mg/m^2, weekly*
1 (starting dose level)	*40 mg/m^2, weekly*

Below are dose modification tables for M6620 (VX-970, berzosertib) in the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia. Please use as appropriate. Note that if a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the

dose to the lowest level.

The dose modification for M6620 (VX-970, berzosertib) will be based primarily on the recommendations specific related to this agent in the table below. Please note that a dose modification for cisplatin does NOT automatically call for M6620 (VX-970, berzosertib) dose reduction if the type and or severity of toxicity does not require M6620 (VX-970, berzosertib) dose modification.

Nausea	**Recommendation**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Vomiting	**Recommendation**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Diarrhea	**Recommendation**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Neutropenia	**Recommendation**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

Neutropenia	**Recommendation**
**Patients requiring > two dose reductions should go off protocol therapy.	

Thrombocytopenia	**Recommendation**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Cisplatin

NOTE: Dose reductions for all events are permanent and should be for all subsequent cycles. Patients may undergo a single dose reduction. If a second dose reduction is required, the patient should discontinue all protocol treatment.

If different dose reductions are required because of two different types of toxicities, the greater dose reduction should be effected.

Hematologic Toxicity

Neutropenia

Granulocyte or platelet counts for Day 1: Based on counts within 2 days of the start of each cycle, give the following:

Granulocytes/mm^3		Platelets/mm^3	Cisplatin
≥ 1,500	and	≥ 100,000	Maintain current dose level
< 1,500	and/or	< 100,000	0*

*Hold all protocol therapy; repeat counts at least once weekly and reinstitute therapy at current dose level when granulocytes ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3 (if within 7 days); reduce cisplatin by one dose level if more than 7 days.

If counts do not reach these levels within 3 weeks of the next scheduled treatment, discontinue all protocol therapy.

Neutropenia or Febrile Neutropenia

- For nadir neutropenia in the absence of fever or with fever that is successfully treated by oral antibiotics, there will be no dose adjustment.
- For treatment delays due to chemotherapy toxicities of more than 7 days (hold both cisplatin and M6620 (VX-970, berzosertib)), reduce both agents by one dose level as applicable for all subsequent doses of chemotherapy.
- For neutropenic fever (ANC < 500/mm^3 and temperature > 100.5ºF) requiring intravenous antibiotics, reduce dose by one dose level as applicable for the next and all subsequent doses. If counts do not recover within 2 weeks, remove patient from study and discontinue all protocol therapy.
- The use of growth factor for neutropenia is not allowed

Thrombocytopenia

- For grade 4 nadir platelet count decrease (thrombocytopenia) (platelets < 25,000 mm^3), reduce cisplatin by one dose level for the next dose and for all subsequent doses of chemotherapy.
- If counts do not recover within 2 weeks, remove from protocol therapy.

Anemia
- No dose reductions will be made for anemia.
- Patients should be supported per the treating physician's discretion.
- The use of blood transfusions for anemia will be allowed as indicated.
- The use of erythropoiesis growth factors for anemia is not permitted.

Non-Hematologic Toxicity

Gastrointestinal Toxicity, Nausea and Vomiting
All patients should receive antiemetics* to prevent nausea and vomiting. The specific choice of antiemetic therapy is left to the discretion of the treating physician (recommend steroids, NK1 and 5-HT3 antagonists as appropriate).
If severe vomiting, consider hospital admission and/or use of aprepitant if possible.

Do not modify chemotherapy doses.

*Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%.

NOTE: Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis.

Nephrotoxicity (based on measured or calculated creatinine clearance)

Creatinine Clearance (ml/min)	Cisplatin*
≥ 60	Current dose level
59 – 50	Reduce by one dose level
< 50	0**

*Please note that the cisplatin dose reduction below 30mg/m^2 is not allowed on this protocol.
**If serum creatinine clearance is < 50 ml/min on day 1 of the next dose, delay cisplatin treatment by up to 1 week (check creatinine at least weekly). If CrCl decrease persists beyond 2 weeks, discontinue protocol therapy and consider alternative standard systemic therapy.
NOTE: If the serum creatinine returns to ≥50 ml/min within 2 weeks of original hold, cisplatin may be reinstituted with one dose level reduction. A more aggressive hydration regimen (as tolerated by patient clinical state) should be instituted as well with all subsequent doses of cisplatin

Hypomagnesemia
Hypomagnesemia is not an indication for dose modification or stopping therapy. Oral or parenteral magnesium supplementation is indicated for serum magnesium levels < 1.5 mEq/1.

Nervous System Disorders (Neurologic Toxicity)

Grade	Cisplatin
0-1	maintain current dose level
2**	reduce by one dose level
3***	Omit cisplatin

**Patients with a grade 2 nervous system disorder (neurotoxicity) should hold cisplatin until recovery to grade 1 or less, then administer at one dose level reduction. If grade 2 neurotoxicity recurs after one dose level reduction, hold treatment until resolution to grade 1 or less and resume at the same dose. If grade 2 neurotoxicity persists for ≥2 weeks, remove the patient from all protocol therapy.
***Discontinue all protocol therapy for ≥ grade 3 neurotoxicity.

Allergic Reactions
Discontinue all protocol treatment promptly if ≥ grade 3 anaphylaxis develops.

Suggested Management of Allergic Reaction:
In case of mild allergic symptoms (e.g., appearance of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).
Patient experiencing significant allergic reaction should be managed according to local institutional standards. A combination of corticosteroids, antihistamines, nebulized respiratory therapy with beta (2) agonists and isotonic fluid support should be employed as appropriate based on patient's clinical condition.

For Grade 3 or Grade 4 symptoms: (Grade 3: severe reaction; prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]; Grade 4: life-threatening; pressor or ventilatory support indicated):

Immediately discontinue chemotherapy infusion. Begin an i.v. infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration, 0.3 mg of a 1:1,000 solution for intramuscular administration, or 0.1 to 0.25 mg of a 1:10,000 solution slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur.

Cisplatin will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

Ototoxicity
Remove patient from therapy for grade ≥ 3 ear and labyrinth disorder (ototoxicity).

Other grade 3 or 4 non-hematologic toxicity
If patient develops grade 3 or 4 non-hematologic toxicity not detailed above [excluding anorexia, dysphagia, fatigue and fever without grade 3 or 4 neutrophil count decrease (neutropenia) attributed to protocol therapy], hold all systemic therapy. Therapy can be restarted if the toxicity has resolved to ≤ grade 1 by the time of the next treatment. Doses of systemic therapy should then be reduced by 25% based on the preceding week dose. If systemic therapy has to be held for more than 2 weeks, remove the patient from all protocol therapy and consider alternative standard treatment.

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 (CAEPR)

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.

The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

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, berzosertib)

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

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

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

Version 1.4, April 30, 2019[1]

Adverse Events with Possible Relationship to M6620 (VX-970, berzosertib) (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS	
Diarrhea	***Diarrhea (Gr 2)***
Nausea	***Nausea (Gr 2)***
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	***Fatigue (Gr 2)***
IMMUNE SYSTEM DISORDERS	
Anaphylaxis	
INFECTIONS AND INFESTATIONS	
Urinary tract infection	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Infusion related reaction	***Infusion related reaction (Gr 2)***
INVESTIGATIONS	
Alanine aminotransferase increased	***Alanine aminotransferase increased (Gr 2)***
Aspartate aminotransferase increased	***Aspartate aminotransferase increased (Gr 2)***
Blood bilirubin increased	
Creatinine increased	
Lymphocyte count decreased	***Lymphocyte count decreased (Gr 2)***
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hyperglycemia	

Adverse Events with Possible Relationship to M6620 (VX-970, berzosertib) (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
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, berzosertib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Adverse Event List(s) for Cisplatin

Nephrotoxicity:
Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of cisplatin and renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and

severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given. Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage. The administration of cisplatin using a 6- to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity:
This has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Ototoxic effects may be more severe in children receiving cisplatin. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation. It is unclear whether cisplatin-induced ototoxicity is reversible. Ototoxic effects may be related to the peak plasma concentration of cisplatin. Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin. Vestibular toxicity has also been reported. Ototoxicity may become more severe in patients being treated with other drugs with nephrotoxic potential.

Hematologic:
Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician.
The development of acute leukemia coincident with the use of cisplatin has been reported. In these reports, cisplatin was generally given in combination with other leukemogenic agents.

Gastrointestinal:
Marked nausea and vomiting occur in almost all patients treated with cisplatin, and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy.
Diarrhea has also been reported.

Other toxicities
Vascular toxicities coincident with the use of cisplatin in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic-uremic syndrome [HUS]), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Serum Electrolyte Disturbances
Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin.
Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia
Reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity
Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) have also been reported.

Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively

advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity
Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuation. Steroids with or without mannitol have been used; however, efficacy has not been established.

Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions
Anaphylactic-like reactions have been reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Hepatotoxicity
Transient elevations of liver enzymes, especially SGOT, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

Other Events
Please refer to the package insert for a comprehensive listing of adverse reactions associated with the use of cisplatin

7.2 Adverse Event Characteristics

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

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

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

7.3 Expedited Adverse Event Reporting

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

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

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

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

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

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

Pregnancy loss is defined in CTCAE as "Death in utero." Any pregnancy loss should be reported expeditiously, as **Grade 4 "Pregnancy loss"** under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.1.2 Agent Ordering and Agent Accountability

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

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

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB 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.

8.1.3.3 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

8.1.3.4 Investigator Brochure Availability- The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent

Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

8.2 *Commercial Agent(s)*

8.2.1 Cisplatin

Refer to the package insert for detailed pharmacologic and safety information

Description: The active ingredient, cisplatin, is a yellow to orange crystalline powder with the molecular formula PtCl2H6N2, and a molecular weight of 300.1. Cisplatin is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is soluble in water or saline at 1 mg/mL and in dimethylformamide at 24 mg/mL. It has a melting point of 207° C. Cisplatin Injection is a sterile aqueous solution commercially available in amber vials with fill volumes of 50 and 100mL. Each ml contains 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

Mechanism of Action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

Solution preparation: Caution should be exercised in handling the powder and preparing the solution of cisplatin. Procedures for proper handling and disposal of anticancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials and IV sets containing cisplatin for injection.

Skin reactions associated with accidental exposure to cisplatin may occur. The use of gloves is recommended. If cisplatin powder or solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Cisplatin Injection should be further diluted prior to administration. Do not dilute cisplatin in just 5% Dextrose Injection. The infusion solution should have a final sodium chloride concentration ≥0.25%.

Route of administration: Cisplatin should be given as a slow intravenous infusion over 30-60 minutes along with appropriate hydration and anti-emetics. Sites may follow local administration guidelines and practice if different than the recommended infusion time.

Dose Specifics and Administration
Concurrent chemotherapy: 30 or 40 mg/m2 once every week for 6-7 weeks (IV infusion as per institutional standard). Cisplatin is usually administered as an intravenous infusion. The first infusion should be over 1 hour but after this the IV can be over 30 minutes. Cisplatin is highly

emetogenic. After administering appropriate antiemetics, cisplatin should be infused over 30-60 minutes for the 40 mg/m2 dose along with vigorous hydration.

Storage and Stability:
Cisplatin is a sterile, multidose vial, without preservatives. Store at 15° to 25°C. Do not refrigerate. Protect unopened container from light. If diluted solution is not to be used within 6 hours, protect solution from light. Further dilutions in NS, D_5/0.45% NaCl or D_5/NS to a concentration of 0.05 to 2 mg/mL are stable for up to 72 hours at room temperature. 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. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

Incompatibilities
Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

Compatibilities
Admixture: Amphotericin-B, aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride.
Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.
Consult your pharmacist regarding specific concentrations.

Availability
Commercially available as a mg/ml solution in 50 and 100mg vials. Vials of lyophilized powder are no longer commercially available, but may be obtained directly from the manufacturer for chemoembolization use.

Agent ordering and supply: Cisplatin is commercially available and not provided by study sponsor.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Integral Laboratory or Imaging Studies

Not Applicable

9.2 Integrated Correlative Studies (Pharmacokinetics)

M6620 (VX-970, berzosertib) PK (samples collected on D-7 and W1D2) will be performed to add to the present knowledge base of M6620 (VX-970, berzosertib) PK, to evaluate any effect of

platinum/aprepitant on M6620 (VX-970, berzosertib) PK, and to correlate exposure to PD metrics.

9.2.1 Collection of Specimens

Blood samples (approximately 5mls) 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 anti-coagulated blood samples will be obtained at the following timepoints:

- Baseline before start infusion
- 30 min (±5 min) after start of M6620 (VX-970, berzosertib) infusion
- 55 min (±5 min) after start of M6620 (VX-970, berzosertib) infusion
    - i.e. 5 min before end of M6620 (VX-970, berzosertib) infusion <1h; M6620 (VX-970, berzosertib) ends>
- 5 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 15 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 30 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 1h (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 2h (±10 min) after end of M6620 (VX-970, berzosertib) infusion
- 4h (±10 min) after end of M6620 (VX-970, berzosertib) infusion
- 23h (±1 h) after end of M6620 (VX-970, berzosertib) infusion
- 48h (±2 h) after end of M6620 (VX-970, berzosertib) infusion
- 72h (±2 h) after end of M6620 (VX-970, berzosertib) infusion

9.2.2 Handling of Specimens

Document the 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. Samples should be centrifuged within 20 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.

9.2.3 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
  UPMC Hillman Cancer Center
  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.

9.2.4 Site Performing Correlative Study

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

9.3 Exploratory/Ancillary Correlative Studies

9.3.1 *Correlative Genomic Analysis*
Original diagnostic archival tumor sample will be collected from each patient enrolled on the study. The tissue will be employed for posthoc correlative genomic and protein expression analysis to identify potential biomarker with reasonable possibility of serving as an enrichment strategy for future efficacy studies of M6620 (VX-970, berzosertib) in this patient population.

9.3.1.1 Mutations in TP53, ATM, FA, BRCA genes/p16 INK4A promoter methylation: These genes are involved in the orderly progression of cancer cells into S phase and or in the repair of genomic damage. p16 (product of CDKN2A gene) inhibits CDK4/6 binding to cyclin D1, preventing RB phosphorylation and liberation of E2F. Furthermore, p53-induced apoptosis following DNA damage may be mediated in part through modulation of Bcl2. The role of the phosphorylated form of Bcl2 (pBcl2), which is the biologically relevant molecule has not been clarified. Correlation of TP53 mutation with total Bcl2 and pBcl2 protein expression will be assessed and tested for significant association with outcome in all patients treated with chemoradiation and M6620 (VX-970, berzosertib) and more specifically in patients treated uniformly with the same dose of M6620 (VX970) in the expansion cohort.

9.3.1.2 Distal chromosome arm 11q loss: this locus harbors the ATM gene, which if lost could confer vulnerability of cancer cells to ATR inhibitor such as M6620 (VX-970, berzosertib).

9.3.1.3 ERCC1 and XRCC1 expression: A systematic screen to identify synthetic lethal interactions with ATR pathway-targeted drugs showed that loss of the endonuclease, ERCC1-XPF (ERCC4) is synthetic lethal with ATR pathway inhibitors.(24) ERCC1-XPF functions in the repair of bulky DNA adducts, DS breaks, interstrand crosslinks and separation of sister chromatids at fragile sites. Low ERCC1 expression was strongly associated with improved response in SCCHN patients treated with combined chemotherapy and radiotherapy.

9.3.1.4 Baseline tumor expression of XRCC1: ATR inhibition is synthetic lethal in XRCC1 deficient ovarian cancer cells.(26) Further, XRCC1 is a critical protein in single-strand break repair and base excision repair. XRCC1 is a molecular scaffold, which coordinates DNA repair by interacting with several components of BER/SSBR, including PARP1, DNA glycosylases and AP endonuclease (APE1). XRCC1 deficiency leads to accumulation of single strand DNA breaks. In the absence of ATR signaling, these SS breaks convert to lethal double strand breaks. ATR inhibition also blocks the repair of the DSBs by homologous recombination. A retrospective analysis of SCCHN patients treated with chemoradiation demonstrated a strong association between low levels of XRCC1 and improved PFS and OS.(27) We hypothesize that low levels of ERCC1 and XRCC1 in SCCHN tumor cells would predict a better response to M6620 (VX-970, berzosertib), as well as to platinum-based therapy.

9.3.1.5 HRD Score: This whole genome assessment of DNA damage repair deficiency has been shown to predict benefit of neoadjuvant platinum and DNA repair inhibitors in breast cancer patients. We hypothesize that tumors with high HRD Score would be more susceptible to the investigational therapy of chemoradiation plus M6620 (VX-970, berzosertib).(28)

9.3.1.6 Collection of Specimen(s)
Archival paraffin embedded tissue samples. Twenty unstained 4-5uM thick slides

should be submitted if unable to submit the entire block.

9.3.1.7 Handling of Specimens(s)
No special handling required

9.3.1.8 Shipping of Specimen(s)
Follow appropriate safeguards for shipping biological materials. Samples should be forwarded to the lab of the study PI:
Taofeek Owonikoko, MD/PhD
UPMC Hillman Cancer Center Research Pavilion
Ground Floor lab G.28
5117 Centre Avenue
Pittsburgh, PA 15213
Attn: Guojing Zhang, MS

9.3.1.9 Site(s) Performing Correlative Study
Myriad Genetics (HRD Score)

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 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 9	Wk 11	Wk 13	Wk 15	Wk 19	Off Study[h]
M6620 (VX-970, berzosertib)[a]		X	X	X	X	X	X	X	X						
Cisplatin[b]			X	X	X	X	X	X	X						
XRT[c]			X	X	X	X	X	X	X						
PK Samples[d]		X	X												
Informed consent	X														
Demographics	X														
Medical /Interval History	X		X		X		X		X	X	X		X	X[g]	
Concurrent meds	X	X	X----------											----------X	
Physical exam	X	X	X		X		X		X	X	X		X	X[g]	X
Vital signs	X	X	X	X	X	X	X	X	X			X			X
Height	X														
Weight	X	X	X	X	X	X	X	X	X		X		X		X
Performance status	X	X	X	X	X	X	X	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
Serum chemistry[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH/ free T4[e]	X								X					X	
EKG (as indicated)	X														
Adverse event evaluation		X----------												----------X	X
Tumor measurements	X	Tumor measurements are repeated every *12 (± 1)* weeks from the end of radiation.													
Radiologic evaluation	X		Standard of care radiologic measurements with CT or MRI should be performed every *12 (± 1)* weeks from the end of radiation. NB: The first assessment is the SOC PET/CT obtained at 12 weeks post chemoradiation.												
B-HCG	X[f]														
FDG PET	X*													X*	
Diagnostic Tumor Sample	X														

a: M6620 [VX-970]: Dose as assigned to patient cohort; see administration schedule; preferred start day is Tuesday
b: [Cisplatin]: Dose as assigned to patient cohort; see administration schedule; preferred start day is Monday
c: Daily fractionation Monday through Friday to a total of 70 Gy; preferred start day is Monday
d: Optional PK samples will be collected:
- Baseline before start infusion
- 30 min (±5 min) after start of M6620 (VX-970, berzosertib) infusion
- 55 min (±5 min) after start of M6620 (VX-970, berzosertib) infusion
  - i.e. 5 min before end of M6620 (VX-970, berzosertib) infusion <1h; M6620 (VX-970, berzosertib) ends>
- 5 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 15 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 30 min (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 1h (±5 min) after end of M6620 (VX-970, berzosertib) infusion
- 2h (±10 min) after end of M6620 (VX-970, berzosertib) infusion

	• 4h (±10 min) after end of M6620 (VX-970, berzosertib) infusion • 23h (±1 h) after end of M6620 (VX-970, berzosertib) infusion • 48h (±2 h) after end of M6620 (VX-970, berzosertib) infusion • 72h (±2 h) after end of M6620 (VX-970, berzosertib) infusion e: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], GGT, sodium; TSH and Free T4 (thyroid function test to be obtained at baseline, end of radiation, at 12 weeks post radiation and then as clinically indicated) f: Serum pregnancy test in women of childbearing potential; (repeat every 4 weeks while on active treatment). g: Repeat every 3 months for 2 years h: Off-study evaluation. *: SOC Images to be submitted for central review by designated radiologists; it is highly recommended that the baseline PET/CT is obtained within 4 weeks of treatment initiation.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of M6620 (VX-970, berzosertib) plus cisplatin over cisplatin alone has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 12±1 weeks. In addition to a baseline scan, a post-treatment PET/CT scan will be obtained 12±1 weeks following completion of chemoradiation for initial documentation of tumor response.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for disease status every 12 ± 1 week after the post chemoradiation PET/CT scan.
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 M6620 (VX-970, berzosertib) *and Cisplatin*.

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

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.
Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

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

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing

site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

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.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

11.1.5 Duration of 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 will be assessed. It will be defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

Baseline imaging and post treatment restaging scan obtained at 12 weeks after completion of chemoradiation will be independently reviewed centrally by the study designated radiologists.

12. DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and

statistician have access to the data at all times through the CTMS web-based reporting portal. 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.
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.

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

12.2 Data Reporting

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

Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
  Rave role requirements:
  - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
  - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
  - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

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

is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

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

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at 609-619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

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

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

) and CTSU websites.

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 Data Quality Portal

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

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

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

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

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

12.4 Data Monitoring and Safety Plan

A mandatory dose escalation conference call will take place before any decision on dose escalation or dose escalation is made. In addition, there will be a regularly scheduled monthly PI call to update participants on the current status of the trial. These calls will include investigators from all participating centers, CTEP, and representatives from Vertex. During the safety calls, any serious toxicities encountered will be discussed and appropriate action taken, and issues relating to the protocol, treatment, management, or other matters of importance that arise during the conduct of the study will be discussed. Between these regularly scheduled conference calls, unusual toxicities may be discussed among the Principal Investigator and CTEP senior investigators; however, all participants will routinely be updated on such calls via e-mail. Independent oversight of study conduct and safety will be provided by the Data Safety Monitoring Committee of the Winship Cancer Institute of Emory University, the home institution of the study PI.

12.5 CTEP Multicenter Guidelines

N/A

12.6 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

A maximum of 9 patients will be treated in stage I with a target probability of DLT θ set at 0.33 based on experience with weekly cisplatin and radiation in this patient population. The cohort size will be 3 patients per cohort in stage 1. The trial starts with the dose level 1. The dose for the first cohort of 3 patients will be Cisplatin (40 mg/m^2) and M6620 (VX-970, berzosertib) (120 mg/m^2). These doses have been previously established as safe doses. All other patients in stage 1 will receive 120 mg/m^2 M6620 (VX-970, berzosertib) and the highest level (30 or 40 mg/m^2) for Cisplatin as determined by EWOC based on all available data, satisfying the ethic constraint that the expected proportion of patients treated at doses above the MTD is less than or equal to a pre-specified value, α. We start at α = 0.25 and increase α in small increments of 0.05 until α = 0.5, this value being a compromise between the therapeutic aspect of the agent and its toxic side effects. The maximum sample size of stage 1 is 9. The three possible outcomes after completion of stage 1 are: 1) Dose level -1 is over-toxic without defining a MTD; 2) one of the 2 dose levels in stage 1 is determined as MTD; 3) Dose level 1 is still under-toxic. If dose level 1 is established to be under-toxic, the trial proceeds to the stage II; otherwise the dose level 1 is considered as MTD if the dose level 2 in stage 2 has been previously tested and determined to be over-toxic. If dose level 1 is established to be safe and lower than the MTD, the trial proceeds to the second stage.
Stage 2 will estimate the MTD from a fixed number of 5 dose levels (dose level 1, 2, 3, 4, or 5) specified in the dose escalation table. The minimum dosage and maximum dosage of M6620 (VX-970, berzosertib) will be 120 and 280 mg/m^2, respectively. The minimum dose increment of M6620 (VX-970, berzosertib) between consecutive dose levels to be explored will be 40 mg/m^2. Specifically, all patients in stage 2 will receive 40 mg/m^2 Cisplatin and the highest level (120, 160, 200, 240, or 280 mg/m^2) for M6620 (VX-970, berzosertib) is determined by EWOC so that, on the basis of all available data including the data of patients treated at the dose level 1, the probability that it exceeds the MTD is less than or equal to α. The starting α in stage 2 is set at 0.40 with small increments of 0.05 until α = 0.5, assuming that 3 cohorts of patients have been treated in the stage I before entering the stage II. To be conservative, the initial escalation will proceed only by single dose level increment unless a higher dose has ever been tested. The cohort size will also be 3 patients per cohort in stage 2. The dose level 1 will be included as a one of the dose levels in the stage 2. There is no maximum number of cohorts that can be explored at a dose level. The computation of the dose to be administered to each patient and the 95% highest posterior density credible interval estimate of the MTD will be carried out by study statistician. The EWOC design will be implemented by R programs which were programmed by the study statistician. Because it takes 4 weeks to resolve toxicity, a patient may be accrued to the trial before the responses of all previously treated patients have been determined. It will be at the discretion of the study PI along with the concurrence of the safety monitoring committee whether to treat the newly accrued patient at the dose level determined on the basis of the currently available data or to wait until one or more toxicities are resolved. In this case, however, no more than 2 cohorts of 6 patients will be treated at the same dose level. A maximum sample size of 30 is used in the stage 2 and the sample size of 30 includes the patients who have been treated at the dose level 1 in the stage I. Upon completion of the trial, the MTD will be estimated as the

median of the marginal posterior distribution of the MTD.

The three possible outcomes after completion of stage 2 are: 1) One of the 4 dose levels of stage 2 is determined as MTD; 2) Dose level 5 is still under-toxic without defining a MTD; 3) Dose level 2 is still over-toxic. In the case that the dose level 2 is determined to be over- toxic, the dose level 1 is determined as MTD if it is not over toxic. After the MTD has been estimated, another cohort of 15 patients will be further enrolled and treated at the MTD in the expansion cohort.

In the expansion cohort, we will treat 15 patients at MTD. For the expansion cohort, objective response rate will be presented as estimated percentage along with 95% exact confidence intervals. Using a one-sided binomial test, the sample size of more than 15 patients will achieve at least 80% power at the significance level of 0.05 to detect an improvement in objective response rate from 60% to 90% among the patients treated at MTD.

Design Operating Characteristics:
A flat prior was used for all parameters of EWOC, including the prior probability distribution associated with DLT rate for the starting dose level. We carried out some simulations under different scenarios for the "true" MTD and probability of DLT at the different dose levels. A total of 1000 trial replicates were generated. Five wide range representative simulation results under 5 different specific scenarios are summarized in the tables below.

Dose level	-1	1	2	3	4	5
True DLT probability	0.20	0.40	0.50	0.65	0.85	0.95
Percentage the dose level is recommended as MTD.	5%	92%	3%	0%	0%	0%
Estimated percentage of DLT probability.	5%	32%	65%	75%	90%	100%
Percentage of patients at the dose level.	15.7%	76.5%	7%	1%	0%	0%
Number of patients treated at the dose level.	1.8	8.8	0.8	0.1	0	0
Percentage of times that study stops early.	11.52 88%					
Percentage of times that study goes to the maximum of 30 patients.	12%					

Dose level	-1	1	2	3	4	5
True DLT probability	0.10	0.33	0.45	0.55	0.65	0.75
Percentage the dose level is recommended as MTD.	5%	75%	17%	3%	0%	0%
Estimated percentage of DLT probability.	8%	31%	41%	60%	70%	91%
Percentage of patients at the dose level.	4.7%	57.3%	29.0%	7.1%	1.8%	0%

Number of patients treated at the dose level.	0.8	9.7	4.9	1.2	0.3	
Percentage of times that study stops early.	16.92 58%					
Percentage of times that study goes to the maximum of 30 patients.	42%					

Dose level	-1	1	2	3	4	5
True DLT probability	0.01	0.20	0.33	0.45	0.55	0.65
Percentage the dose level is recommended as MTD.	0%	8%	80%	9%	3%	0%
Estimated percentage of DLT probability.	0%	13%	37%	48%	60%	73%
Percentage of patients at the dose level.	0.3%	32.4%	54%	11%	2.1%	0.3%
Number of patients treated at the dose level.	0.1	9.3	15.5	3.1	0.6	0.1
Percentage of times that study stops early.	28.74 6%					
Percentage of times that study goes to the maximum of 30 patients.	94%					

Dose level	-1	1	2	3	4	5
True DLT probability	0.01	0.05	0.15	0.23	0.33	0.55
Percentage the dose level is recommended as MTD.	0%	0%	1%	17%	67%	15%
Estimated percentage of DLT probability.	0	0.01	0.119	0.188	0.347	0.51
Percentage of patients at the dose level.	0%	30.6%	11.2%	15.0%	38.1%	5.1%
Number of patients treated at the dose level.	0	9	3.3	4.4	11.2	1.5
Percentage of times that study stops early.	2%					
Percentage of times that study goes to the maximum of 30 patients.	98%					

Dose level	-1	1	2	3	4	5
True DLT probability	0.001	0.02	0.10	0.20	0.28	0.33
Percentage the dose level is recommended as MTD.	%	0%	2%	5%	33%	60%
Estimated percentage of	0%	1%	7%	12%	23%	38%

DLT probability.						
Percentage of patients at the dose level.	0%	30%	10.3%	11.7%	14.3%	33.3%
Number of patients treated at the dose level.	0	9	3.1	3.5	4.3	10.1
Percentage of times that study stops early.	0%					
Percentage of times that study goes to the maximum of 30 patients.	100%					

In brief, the design has a probability of more than 50% to identify a correct MTD and more than 30% of patients are allocated to the true MTD in the trial. These operating characteristics are much better than those achieved by standard 3+3 design, which tends to underestimate MTD and treat patients at sub-optimal doses.

Safety evaluable population:
All patients who received any amount of the investigational agent will be evaluable for toxicity assessment.

Primary endpoints:
- Frequency and grade of toxicity according to NCI CTCAE v. 5.0
- DLT assessed over 6-7 weeks of chemo-radiation and through the last day of radiation delivery
- RP2D as the highest doses of cisplatin and M6620 (VX-970, berzosertib) safely combined with radiation

Demographic and other baseline data will be summarized descriptively. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics will be presented (i.e., mean, median, standard deviation, minimum, maximum).

13.2 Sample Size/Accrual Rate
The primary objective of this study is to investigate the safety, tolerability and the recommended dose for further clinical evaluation of M6620 (VX-970, berzosertib). Therefore, the projected sample size of 30 in the escalation phase is based on the need to obtain adequate tolerability, safety and pharmacokinetic data while exposing the minimum number of patients to the investigational product and procedures. Hence, cohorts of 3 to 6 evaluable patients will be required. The total number of patients will depend upon the number of dose escalations necessary.
Additionally, approximately 15 patients will be accrued at the defined recommended dose to further explore the tolerability, pharmacokinetics and clinical activity of the established dose.
The projected accrual rate is 3-4 patients per month across the five participating sites including 30 patients in the escalation phase and 15 in the expansion phase.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native					
Asian	1	1			**2**
Native Hawaiian or Other Pacific Islander					
Black or African American	2	6			**8**
White	8	22	2	3	**35**
More Than One Race					
Total	**11**	**29**	**2**	**3**	**45**

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13.3 Stratification Factors

NA.

13.4 Analysis of Secondary Endpoints

Secondary endpoints:

- PK characteristics of M6620 (VX-970, berzosertib) including Cmax, AUC, CL, t1/2, Vss
- DDI interaction between M6620 (VX-970, berzosertib) and aprepitant using AUC on D-7 and W1D2
- Overall response rate (CR + PR) by RECIST 1.1 criteria
- Metabolic response rate by FDG-PET by PERCIST criteria
- Exploratory tissue-based biomarkers as markers of DNA damage and predictors of clinical outcome.

13.4.1 Analysis of pharmacokinetic (PK) parameters of M6620 (VX-970, berzosertib)
Descriptive statistics (n, mean, standard deviation, median, geometric mean, coefficient of variation CV [%], geometric CV [%], minimum, and maximum) will be presented for all PK parameters with exception of Tmax, for which median, minimum and maximum values will be presented. Individual patient ratios (D-7: W1D2) and geometric mean ratio (90% CI) for M6620 (VX-970, berzosertib) PK parameters will be plotted. A graphical presentation of the PK profiles

will also be provided as appropriate using the arithmetic (± SD) and/or geometric mean values at each scheduled sample collection time point. We will perform within-subject comparisons of PK characteristics of M6620 (VX-970, berzosertib) (Cmax, AUC, t1/2, CL, and Vss) between day -7 and W1D2 using Wilcoxon signed rank test. We will also use Wilcoxon rank sum test to compare PK characteristics of M6620 (VX-970, berzosertib) between two cohorts treated at different dose levels. In the case of multiple groups, Kruskal–Wallis test will be used for comparison.

13.4.2 Analysis of Response Endpoints

Efficacy evaluable population - Response will be analyzed in the following patient groups:

i. All patients who received any amount of the investigational agent
ii. Patients who received at least 50% of the planned treatment delivery (radiation and systemic therapy)
iii. All patients enrolled in the expansion cohort treated at the RP2D.

Summaries of the number of patients with best objective response in each of the following categories will be provided:

Complete Response (CR)
Partial Response (PR)
Stable Disease (SD)
Progressive Disease (PD)
Non-Evaluable (NE)
Disease Control (DC = CR+PR+SD)

Objective response rate and disease control rate will be summarized. For the expansion cohorts, objective response rate will be presented along with 95% exact confidence intervals. The rate of complete response following combined chemoradiation for HNSCC is approximately 60%. We assume that the addition of M6620 (VX-970, berzosertib) at its RP2D to cisplatin is likely to improve this outcome by 50%. We therefore expect that a sample size of 15 patients treated in the expansion cohort will have 84% power to detect this degree of difference (P1-P0) of 0.3000 using a one-sided binomial test. The target significance level is 0.05 while the actual significance level achieved by this test is 0.0398 with the assumption that the population proportion under the null hypothesis is 0.6000.

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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, berzosertib) interacts with specific enzymes in the liver or other tissues like the gut and certain transport proteins that help move drugs in and out of the cell.

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

These are the things that you need to know:
The study drug M6620 (VX-970, berzosertib), may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors or inducers of CYP3A4 and substrates of CYP3A4, OATP1B3, and BCRP.

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

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** M6620 (VX-970, berzosertib) interacts with specific enzymes in your liver or other tissues like the gut and transport proteins that help move drugs in and out of cells and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):**	**Use caution and avoid the following drugs if possible:**	Your healthcare providers should be aware of any medicines that are strong inhibitors or inducers of CYP3A4, and sensitive substrates of CYP3A4, OATP1B3, and BCRP. • Strong inhibitors or inducers of CYP3A4 should be avoided. • Sensitive substrates of CYP3A4, OATP1B3,and BCRP should be used with caution. **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	Version Apr/2021
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov