To: CTEP Protocol and Information Office

From: Pranshu Mohindra, M.D., M.B.B.S., D.A.B.R

Date: June 21, 2021

Re: Amendment in response to Dr. Wu's April 22, 2021 notice to investigators using M6620 (VX-970, berzosertib).

SUMMARY OF CHANGES – Protocol

I. In response to the Notice to Investigators dated 04/22/2021:

#	Section	Comments
1.	5.3, 8.1.1, Appendix C, ICD	The purpose of the notice is to alert investigators of the change to the drug monograph and the Patient Drug Interactions Handout and Wallet Card for M6620 (VX-970, berzosertib). The following sections of the protocol should be amended to include the updated information or replaced in its entirety: • Potential Drug Interactions section under the Pharmaceutical Agent Information section of the protocol. • The Patient Selection and the General Concomitant Medication and Supportive Care Guidelines sections of the protocol. • The Patient Drug Interactions Handout and Wallet Card appendix in the protocol. • The agent name should be updated throughout the protocol and consent. **PI Response: The relevant sections of the protocol have been updated and the agent name revised throughout.**

II. Changes requested by the PI:

#	Section	Comments
2.	Header, Title Page	Updated protocol version date.

SUMMARY OF CHANGES – Consent Forms (Groups 1 and 2)

#	Section	Comments
3.	Header	Updated protocol version date.
4.	All	Updated agent name throughout the consent as specified in change #1.

Phase 1 Trial to Determine the Recommended Phase 2 Dose (RP2D) of M6620 (VX-970, berzosertib) When Combined with Whole Brain Radiotherapy (WBRT) in Patients with Brain Metastases from Lung Cancer

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

Principal Investigator: Pranshu Mohindra, M.D., M.B.B.S., D.A.B.R. ®
Associate Professor, Department Of Radiation Oncology,
University of Maryland School of Medicine, Baltimore
22 South Greene Street, Room GGJ 35
Baltimore, MD 21201
Telephone: (410) 328-9155
Telefax: (410) 328-5279
Email: pmohindra@som.umaryland.edu

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
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-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
EDDOP / Early Drug Development Opportunity Program

Co-Investigators:

Medical Oncology
Aaron Mansfield, M.D.
Mayo Clinic
Email: mansfield.aaron@mayo.edu

Radiation Oncology
Rao Gullapalli, M.D.
University of Maryland
Email: rpg@umm.edu

Prashant Raghavan, M.D.
University of Maryland
Email: praghavan@umm.edu

Timothy Kaufmann, M.D.
Mayo Clinic
Email: kaufmann.timothy@mayo.edu

Statisticians:
Søren M. Bentzen, PhD, D.M.Sc
University of Maryland
Telephone: (410) 706-8505
Email: sbentzen@som.umaryland.edu

Jun (Vivien) Yin, Ph.D.
Mayo Clinic
Telephone: (507) 538-6252
Email: yin.jun@mayo.edu

Protocol Manager:
Judy Murray
JHU Sidney Kimmel Comprehensive Cancer Center
Telephone: 410-955-4044
Email: jmurra33@jhmi.edu

ClinicalTrials.gov Identifier: NCT02589522

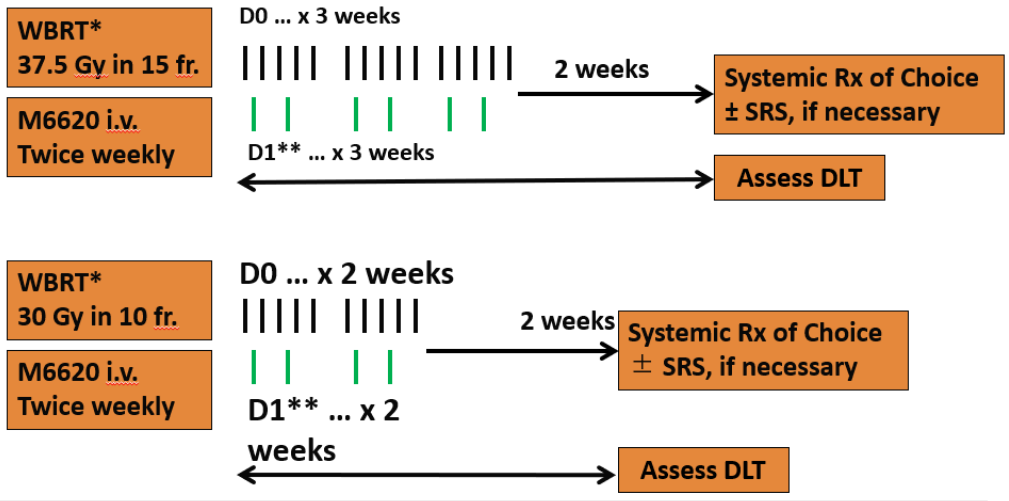
NCI-Supplied Agent: M6620 (VX-970, berzosertib) (NSC 780162)
IND #: [redacted]
IND Sponsor: DCTD, NCI.

Protocol Type / Version # / Version Date:
Original / Version 1 / September 22, 2015
Resubmission / Version 2 / November 20, 2015
Resubmission / Version 3 / January 8, 2016

Resubmission / Version 4 / May 23, 2016
Resubmission / Amendment 1 / October 7, 2016
Resubmission / Amendment 2 / November 23, 2016
Resubmission / Amendment 3 / July 26, 2017
Resubmission / Amendment 4 / July 2, 2018
Amendment 5 / Version 1 / January 31, 2020
Amendment 6 / Version 1 / July 7, 2020
Amendment 7 / Version 1 / June 6, 2021

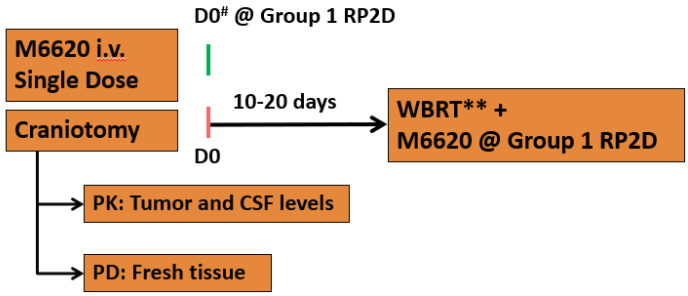
PROTOCOL SYNOPSIS

Title:	**Phase 1 Trial to Determine the Recommended Phase 2 Dose (RP2D) of M6620 (VX-970) when Combined with Whole Brain Radiotherapy (WBRT) in Patients with Brain Metastases from Lung Cancer**
Study Objectives:	**Primary Objective:** To determine the RP2D of twice weekly intravenous (i.v.) M6620 (VX-970, berzosertib) administered concurrent with conventionally fractionated whole brain radiotherapy (WBRT), with M6620 (VX-970, berzosertib) starting 18-30 hours after the first dose of radiation (but prior to the second fraction of radiation). Dose-limiting toxicities (DLTs) will be defined as any grade 3 or more non-hematological toxicity requiring more than 5-day interruption in therapy or any grade 4 or higher hematological toxicity that is attributable to the M6620 (VX-970, berzosertib) and/or whole brain radiotherapy. DLTs will be assessed from the day of the start of WBRT until 3 weeks post completion of WBRT. **Secondary Objectives:** • To estimate the incidence of ≥ Grade 3 delayed neurological toxicity at 2, 4 and 6-months post-completion of WBRT (for patients without intracranial progression). This will include testing for delayed-recall through Hopkins Verbal Learning Test-Revised (HVLT-R) and Functional Assessment of Cancer Therapy-Brain (FACT-BR) assessments. • To observe and record anti-tumor activity. o To estimate the radiological response rates (RR) at 6 months including bi-directional and volumetric measurements of lesion size. All patient accrued in group 1 (except the first three dose-levels) will be included in the imaging objective. o To estimate the intracranial 6-month progression-free survival (PFS). **Exploratory/ Hypothesis generating objectives:** • **Group 1** (patients accrued beyond dose-level 3): Magnetic resonance imaging (MRI): Changes in dynamic susceptibility contrast enhancement (DSC-MRI) perfusion and mean apparent diffusion coefficient (ADC) measurements in diffusion-weighted magnetic resonance imaging (DWI)

	• **Group 2: Restricted to the University of Maryland only** In an exploratory study involving a small cohort of 6 patients who are scheduled to undergo a craniotomy, a single dose of M6620 (VX-970, berzosertib) at the above-identified RP2D will be administered 2 to 4 hours prior to the planned craniotomy. The objective of this cohort is to measure plasma and CSF M6620 (VX-970, berzosertib) levels, tumor M6620 (VX-970, berzosertib) levels and pATR T1989, pCHK1 S345 and RAD51 multiplex foci. For patients with identifiable target lesion (other than the resected lesion): Changes in DSC-MRI perfusion and mean ADC measurements in DWI A parallel study at the PI's institution would be conducted wherein fresh tumor biopsies from 12 matched control patients who are scheduled to undergo a craniotomy but not accrued to the proposed study will be collected as a separate IRB approved study for assessments of pATR T1989, pCHK1 S345 and RAD51 multiplex foci. Expression of these markers will be compared with the data from 6 patients in the group 2 of the proposed study.
Study Design:	**Group 1: Newly detected Brain Metastases** **• No plan for immediate SRS/craniotomy (or have already had SRS/neurosurgery prior to trial accrual) (N = Up to 40 patients)**  *Hippocampal avoidance WBRT is allowed. **M6620 to start 18-30 hours after the first fraction of WBRT but prior to the second fraction of WBRT

Group 2: Translational Group (after Group 1 completed)

- **Planned craniotomy prior to initiation of WBRT* (N = 6 patients)**



* Pts. who have already had craniotomy can be enrolled directly into Group 1, if eligible
# To be administered 2-4 hours prior to craniotomy to allow maximal assessment of PD markers. t ½ M6620: 6 hrs
** 37.5 Gy in 15 fractions or 30 Gy in 10 fractions, Hippocampal avoidance WBRT is allowed

Treatment Interventions

M6620 (VX-970, berzosertib)
Group 1:

Dose Escalation Schedule [1]	
Dose Level	**Dose of M6620 (VX-970, berzosertib) (mg) [2]**
Level 1	50 mg twice weekly
Level 2	100 mg twice weekly
Level n	Estimated using the EWOC algorithm, ≤ 2 times the dose level (n-1)[3]
Highest level	800 mg twice weekly [4]

1. Once enrollment at level one has been completed, the subsequent dose escalation will be based on the Bayesian adaptive design, Escalation With Overdose Control (EWOC) algorithm, with all DLT data from all tested dose levels being part of the data set for defining dose levels for new trial participants.
2. See Section 13.2.2 for special early stoppage and slow convergence scenarios
3. In case of no toxicities at prior levels the EWOC may escalate the dose quite rapidly. As an added precaution, dose level n will not exceed the dose at level n-1 by more than a factor of 2, see section 13.2.2 for further details.
4. Highest dose-level may be increased if the MTD in the single agent 002 study turns out to be higher before the commencement of our phase I trial.

WBRT will be allowed to start on any day from Monday through Thursday, with

M6620 (VX-970, berzosertib) administered as follows:

- Monday or Thursday WBRT start: M6620 (VX-970, berzosertib) administered Tuesday and Friday
- Tuesday WBRT start: M6620 (VX-970, berzosertib) administered Wednesday and Friday in week 1 followed by Tuesday and Friday from week 2 onwards
- Wednesday WBRT start: M6620 (VX-970, berzosertib) administered Thursday in week 1 and then Monday and Thursday from week 2 onwards.

This will also allow patients to get 6 doses of M6620 (VX-970, berzosertib) over 3 weeks course of WBRT.

For the protocol purpose and due to the logistic difficulties of M6620 (VX-970, berzosertib) administration on Saturdays, the study calendar will include a comment to avoid a Friday start of WBRT, when clinically appropriate.

The second and subsequent doses of M6620 (VX-970, berzosertib), the drug will be administered after the day's administration of radiation treatment with no specified time interval.

Group 2: Restricted to the University of Maryland only
Single dose of M6620 (VX-970, berzosertib) administered intravenously at the above identified RP2D, 2 to 4 hours prior to the planned craniotomy. Patients will receive M6620 (VX-970, berzosertib) at the same dose, twice weekly during WBRT, as done for the group 1 patients.

M6620 (VX-970, berzosertib) Administration

Premedication/ Precautions	Dose [1]	Route	Schedule	Duration
Premedicate with dexamethasone as per institutional guidelines	[redacted]	IV over 60 minutes	Twice weekly	Three weeks

1. [redacted]

	[redacted] **Whole brain radiation therapy (WBRT):** One treatment of 2.5 Gy will be given daily not more than 5 days per week (15 fractions), once daily fractionation, Monday through Friday, without any planned interruptions for a total of 37.5 Gy over three weeks.

Study Hypothesis:	**Hypothesis for Primary Objective:** The combination of concurrent M6620 (VX-970, berzosertib) administered as twice weekly infusion at the identified RP2D can be safely administered with whole brain radiotherapy in patients with brain metastases from NSCLC. The recommended phase 2 dose (RP2D) using this dosing schedule will be established as the primary objective.
	
	Hypothesis for Secondary Objectives:
	• ≤ 10% incidence of Grade 3 or higher 6-month neurological toxicity in absence of intracranial progression;
	
	• Anti-tumor activity measured as
	  • ≥ 50% radiological RR at 6 months.
	  • ≥ 70% intra-cranial PFS at 6-months.

Sample Size:	**Group 1:** A maximum of 40 patients will be enrolled in the group 1 of this protocol using a Bayesian adaptive design, Escalation With Overdose Control (EWOC). If the convergence toward the RP2D is unexpectedly slow, accrual will be halted and the dose-response data will be analyzed and published once the maximum sample size is reached. **Group 2: Restricted to the University of Maryland only** A maximum of 6 patients will be enrolled in the group 2 of this protocol.

Endpoints:	**Primary:** Dose-limiting toxicity defined as any grade 3 or more non-hematological toxicity requiring more than 5-day interruption in therapy or any grade 4 or higher hematological toxicity that is attributable to the M6620 (VX-970, berzosertib) and/or whole brain radiotherapy.
	
	Secondary:
	• Incidence of delayed neurological toxicity at 2, 4 and 6-months post-completion of WBRT (for patients without intracranial progression) including:
	  • Delayed-recall through HVLT-R
	  • Quality of life as measured by the FACT-BR.
	
	• Radiological RR at 6 months including bi-directional and volumetric measurements of lesion size

	• Intracranial 6-month PFS.
	
	Exploratory:
	• Group 1 (Patients accrued beyond dose level 3): Changes in DSC-MRI perfusion, mean ADC measurements in DWI
	
	• Group 2: **Restricted to the University of Maryland only**
	
	  • Pharmacokinetic measurements: Intra-operative blood and CSF M6620 (VX-970, berzosertib) levels and craniotomy tumor specimen M6620 (VX-970, berzosertib) concentration
	  • Biomarker (Pharmacodynamic) end-point: Percentage pATR T1989, pCHK1 S345and RAD51 multiplex in post-M6620 (VX-970, berzosertib) administration intra-cranial tumor tissue specimen
	  • MRI end-points (For patients with identifiable target lesion, other than the resected lesion): Changes in DSC-MRI perfusion, mean ADC measurements in DWI

Sponsor:	DCTD, NCI.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To conduct a phase 1 dose escalation trial in patients with brain metastases from non-small cell lung cancer (NSCLC) to determine the recommended phase 2 dose (RP2D) of twice weekly intravenous (i.v.) M6620 (VX-970, berzosertib) administered concurrent with conventionally fractionated whole brain radiotherapy (WBRT), with M6620 (VX-970, berzosertib) starting 18-30 hours after the first dose of radiation (but prior to the second fraction of radiation).

Dose-limiting toxicities (DLTs) will be defined as any grade 3 or more non-hematological toxicity requiring more than 5-day interruption in therapy or any grade 4 or higher hematological toxicity that is attributable to the M6620 (VX-970, berzosertib) and/or whole brain radiotherapy.

DLTs will be assessed from the day of the start of WBRT until 3 weeks post completion of WBRT.

1.2 Secondary Objectives

In patients with brain metastases from NSCLC undergoing therapy with a combination of twice weekly intravenous (i.v.) M6620 (VX-970, berzosertib) administered concurrent with conventionally fractionated whole brain radiotherapy (WBRT), with M6620 (VX-970, berzosertib) starting 18-30 hours after the first dose of radiation:

- To estimate the incidence of ≥ Grade 3 delayed neurological toxicity at 2, 4 and 6-months post-completion of whole-brain radiotherapy (for patients without intracranial progression). This will include testing for delayed-recall through Hopkins Verbal Learning Test-Revised (HVLT-R) and Functional Assessment of Cancer Therapy-Brain (FACT-BR) assessments.

- To observe and record anti-tumor activity. Although the clinical benefit of M6620 (VX-970, berzosertib) 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. The objectives will be:

    - To estimate the radiological response rates (RR) at 6 months including bi-directional and volumetric measurements of lesion size. All patients accrued in group 1 (except the first three dose-levels) will be included in the imaging objective.

    - To estimate the intracranial 6-month progression-free survival (PFS).

1.3 Exploratory/ Hypothesis Generating Objectives

As exploratory, hypothesis generating objectives, we will collect observational data as below:

Group 1: For patients accrued beyond dose-level 3 only

Magnetic resonance imaging (MRI): Changes in dynamic susceptibility contrast enhancement (DSC-MRI) perfusion and mean apparent diffusion coefficient (ADC) measurements in diffusion-weighted magnetic resonance imaging (DWI)

Group 2: Restricted to the University of Maryland only

- In an exploratory study involving a small cohort of 6 patients who are scheduled to undergo a craniotomy, a single dose of M6620 (VX-970, berzosertib) at the above-identified RP2D will be administered 2-4 hours prior to the planned craniotomy. The objective of this cohort is to measure CSF M6620 (VX-970, berzosertib) levels, tumor M6620 (VX-970, berzosertib) levels, and pATR T1989, pCHK1 S345 and RAD51 multiplex foci.

- For patients with identifiable target lesion (other than the resected lesion): Changes in DSC-MRI perfusion and mean ADC measurements in DWI

2. BACKGROUND

2.1 Brain Metastases from Non-Small Cell Lung Cancer (NSCLC)

Brain metastases continue to be a major health problem for cancer patients. While the exact incidence is not known, a range of 8.3-14.3 per 100,000 populations has been reported [1-3]. The incidence in cancer population has been described from 9% to 17%. Increased used of high resolution diagnostic imaging such as magnetic resonance imaging (MRI) combined with increasing systemic therapy options may explain the rising trends in the diagnoses of brain metastases. The treatment options range from surgical resection, stereotactic radiosurgery (SRS) and WBRT or steroids with best supportive care alone. The diagnosis of brain metastases carries a poor prognosis. In the two landmark studies for patients with single brain metastases by Patchell *et al*., nearly 50% of the patients had a local recurrence with either surgery alone or WBRT alone, while the combination of two modalities resulted in a local recurrence of 10-20% [4, 5]. The median survival with WBRT alone was 15 weeks, while with surgery ± WBRT ranged from 40-48 weeks. In addition to the mortality risks, occurrence of brain metastases is associated with a significant impact on quality of life. In a phase III trial, the baseline Spitzer Quality of Life Index (SQLI) score was nearly 30-40% reduced in patients diagnosed to have brain metastases [6]. In addition, more than 90% patients may have changes in one or more neurocognitive domains, with up to 40% patients having

changes in more than three domains [7].

With nearly 80% of patients with brain metastases presenting with multiple identifiable lesions in the brain, WBRT continues to be the backbone of therapy with surgery and radiosurgery reserved for patients with limited metastatic disease [8]. The use of adjuvant WBRT in these patients continues to be an area of debate. In a randomized European study, while no overall survival (OS) difference was noted with the addition of WBRT to surgery or SRS in patients with one to three cerebral metastases, WBRT did result in a reduction of 2-year recurrences at the sites of initial disease and at distant sites, reducing the need for salvage treatments. In this study, 28% of the patients in WBRT arm had death due to intracranial progression as against 44% in patients who did not receive adjuvant WBRT. More recently, in a cooperative group trial from the U.S. intracranial tumor control at 12 months was better with the addition of WBRT (85% vs 51%, $p < 0.001$) though this did not translate into any benefit in OS (median 7.5 m vs 10.7 m, $p = 0.93$). These results were presented at the 2015 annual meeting of American Society of Clinical Oncology (ASCO) [9]. The detailed results from the study are awaited to further understand the reasons for an apparent, non-significant, reduction in OS with WBRT. In routine clinical practice, deaths from toxicity of WBRT are unusual and the likely difference in OS may be reflective of disparities in patient population between the two cohorts. Further, intracranial control has been shown to impact neurocognitive function and survival [10]. As such, WBRT continues to play a central role in the palliative therapy of brain metastases with selective use of surgical or SRS approaches for patients with good performance status, limited extra cranial disease and young age [8]. The parameters defining the choice between WBRT and SRS are practice dependent. The intent of this protocol is to not define the parameters that define this choice, but to evaluate use of concurrent systemic therapy in patient whom WBRT is clinically indicated.

Approximately 50-60% of patients with NSCLC develop brain metastases with a poor survival post-development of brain metastases (1-year survival < 20%, median survival of 4-6 months) [11]. In a retrospective multi-institutional database from 11 institutions that lead to the identification of disease-specific graded prognostic assessment index (DS-GPA), the median survival for the entire cohort of nearly 1900 NSCLC patients was 7 months (95% CI 6.5-7.5). Even for patients with > 3 metastases, if the DS-GPA index was 3 or 1.5-2.5, the median survival was 11.3 and 6.5 months respectively [12]. However, unlike non-metastatic but loco-regionally advanced presentations where concurrent chemoradiotherapy has shown survival benefit, role of concurrent chemotherapy with WBRT is limited by toxicity and restricted penetration through the blood-brain-barrier. At this point, there are no approved drugs to be delivered concurrently with WBRT for the management of brain metastases in NSCLC. In a recently published meta-analysis of 6 trials evaluating use of concurrent systemic therapy with WBRT for patients with brain metastases from NSCLC, improvement in response rate was noted with the addition of chemotherapy [13]. The agents evaluated in these trials included motexafin gadolinium, temozolomide, carboplatin and multi agent CCNU based chemotherapy. No differences in survival or time to neurological progression were

seen, yet, there was an increase in the incidence of ≥ Grade 3 adverse events. Hence, the choice of appropriate concurrent radio sensitizer with WBRT that improves outcome without adding to toxicity continues to be an area of unmet need with immense clinical significance. In view of these concerns, ongoing clinical studies are looking at targeted therapy options for brain metastases from NSCLC. Erlotinib was evaluated in a phase 3 trial assessing its combination with WBRT [14]. No significant differences were seen in the neurological PFS with the addition of erlotinib to WBRT. In a phase 1/2 study for patients with crizotinib resistant ALK-rearranged NSCLC, alectinib, a novel, highly selective and potent ALK inhibitor, was well tolerated by patients with active brain metastases and with 55% objective radiological responses [15]. Additional studies are needed to look at newer targeted therapies which could be safely combined with WBRT for the management of patients with brain metastases.

With this background, the Cancer Therapy Evaluation Program (CTEP) led a Project Team to help direct the development of M6620 (VX-970, berzosertib), a potent inhibitor of ataxia telangiectasia mutated and Rad3-related (ATR) kinase, as an anticancer agent in collaboration with Vertex Pharmaceuticals Incorporated (Vertex), Boston, MA. The details of the agent M6620 (VX-970, berzosertib) are described below. Between the months of December 2014 and February 2015, a series of weekly teleconferences with multiple additional correspondences were completed between the Project Team members to guide the development of a clinical plan for M6620 (VX-970, berzosertib). One of the recommended ideas was to test the combination of M6620 (VX-970, berzosertib) and WBRT in the management of brain metastases. A preliminary outline of the protocol concept was presented at the IDSC meeting on February 13, 2015 followed by a detailed review of the Letter of Intent (LOI) leading to the development of this clinical trial proposal.

2.2 ATR and DNA Damage response

The DNA-damage response (DDR) is a multi-complex network of signaling pathways involved in surveillance and repair of DNA damage and transient cell cycle arrest to ensure genomic stability and cell viability [16-18]. 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 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 [16, 19, 20]. 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 [18]. 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 [16, 19]. 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 [19,21]. 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 [16]. 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 [16, 22]. 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 [16, 17]. However, the effectiveness of such DNA damage-inducing therapies in cancer treatment is attenuated by cells developing drug resistance, leading to tumor recurrence. Acquired resistance to cytotoxic therapies in tumors has been linked to the activation of DDR. There is accumulating preclinical evidence that ATR inhibition can sensitize tumor cells to the effects of radiation or chemotherapy.

2.3 **M6620 (VX-970, berzosertib)**

2.3.1 Mechanism of Action

M6620 (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) [23]. In comparison, M6620 (VX-970, berzosertib) was > 100-fold weaker inhibitor of ATM (Ki = 34 nM) and >1000-fold less effective against other closely related kinases, such as DNA-dependent protein kinase (DNA-PK) (Ki > 4 mcM), mTOR (Ki > 1mcM), and PI3K-gamma (Ki = 0.22 mcM) (Fokas *et al*., 2012). Overall, among 291 kinases tested, M6620 (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. A cellular 50% inhibition of ATR was attained at a M6620 (VX-970, berzosertib) concentration (IC_{50}) of 0.019 mcM, demonstrating >100-fold greater selectivity against ATR compared to ATM or DNA-PK (IC_{50} of 2.6 mcM or 18.1 mcM, respectively) [23].

Effect of M6620 (VX-970, berzosertib) on DDR Signaling and DNA Damage

Concurrent treatment of cancer cell lines with M6620 (VX-970, berzosertib) and various

DNA-damaging agents led to sustained M6620 (VX-970, berzosertib)-dose-dependent decreases in levels of chemotherapy-induced CHK1pS^{345}, a major substrate of ATR [23, 24]. 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*.) [25]. 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 [26]. Exposure of lung cancer cell lines as well as primary tumors to M6620 (VX-970, berzosertib) in combination with DNA-damaging agents enhanced levels of the DNA-damage markers, *i.e*., γH2AX and KAP1pS^{824}, as compared to DNA-damaging agent alone [24]. Sequential treatment of cells with DNA-damaging agent followed 15 h later by M6620 (VX-970, berzosertib) resulted in an initial inhibition of phospho-CHK1 (for 1 to 2 h). However, over time, phospho-CHK1 reappeared despite continued exposure to M6620 (VX-970, berzosertib). The rebound of phospho-CHK1 has been attributed to non-specific phosphorylation by an undefined kinase. However, despite the transient inhibition of phospho-CHK1, the sustained accumulation of γH2AX and KAP1pS^{824} was observed. Together these data suggest that disruption of ATR-mediated DDR signaling by M6620 (VX-970, berzosertib) leads to sustained accumulation of DNA damage in cancer cells exposed to DNA-damaging agents. Failure to repair chemotherapy-induced DNA damage in the presence of M6620 (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) activity.

M6620 (VX-970, berzosertib)-mediated radiosensitivity of pancreatic ductal adenocarcinoma cells was associated with inhibition of HR repair [23]. M6620 (VX-970, berzosertib) caused increased persistence of γH2AX levels both *in vitro* and *in vivo*. Adding M6620 (VX-970, berzosertib) to gemcitabine and ionizing radiation (IR) dramatically enhanced antitumor effects, with early and late apoptosis and abrogation of IR-induced G2 checkpoint in cell culture experiments. It has been suggested that by promoting strong S-phase arrest, chemoradiation may further increase dependence of tumor cells on ATR-mediated homologous recombination (HR) repair of DNA double strand breaks (DSBs) and for survival.

2.3.2 Nonclinical Studies

In vitro Antitumor Activity

In the absence of exogenous DNA-damaging agents, M6620 (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). However, among the

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

The impact of M6620 (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. Most lung cancer cell lines responded well to M6620 (VX-970, berzosertib) in combination with cisplatin (84% of cell lines) or gemcitabine (76% of cell lines), demonstrating ≥ 3-fold reduction in the IC_{50} compared to IC_{50} of the cytotoxic agent alone [24]. 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). Marked synergy between the two agents was also seen against four of seven human NSCLC primary tumors tested *in vitro* [24]. The greatest antitumor synergistic effect was demonstrated by tumors with poor response to cisplatin alone. Similarly, most pancreatic cancer lines responded well to combination of M6620 (VX-970, berzosertib) with cisplatin or gemcitabine: antitumor IC_{50} was ≥ 3-fold lower for the M6620 (VX-970, berzosertib) + cytotoxic agent in >70% of cell lines as compared to IC_{50} of cytotoxic agent alone.

In addition, significant radio sensitization effects by M6620 (VX-970, berzosertib) were observed against two human pancreatic cancer cell lines with mutant KRAS and mutant p53 (MiaPaCa-2 and PSN1) ($P < 0.05$), but not against non-cancerous fibroblast cell lines [23]. In addition, M6620 (VX-970, berzosertib) profoundly sensitized pancreatic tumor cells to gemcitabine-based chemoradiation.

Impact of defective ATM signaling on sensitivity of cells to M6620 (VX-970, berzosertib) in combination with a cytotoxic agent (cisplatin, gemcitabine, irinotecan, oxaliplatin, or etoposide) was examined in isogenic matched lung cancer cells (wild-type p53 A549 versus A549 transfected with p53 shRNA), using a cell viability assay [24]. 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) also synergized with cisplatin resulting in cytotoxicity in ATM-null primary skin fibroblasts,

but no cytotoxicity was observed against wild-type fibroblasts. This suggests that the functional status of the ATM pathway is a contributing factor in the cellular response to the inhibition of ATR.

Of note, the response/p53 status relationship was unclear in the panel of heterogeneous cancer cell lines exposed to M6620 (VX-970, berzosertib) + chemotherapy [24]. Although not significant, there was a trend of causality between response and p53 status ($p = 0.08$) for M6620 (VX-970, berzosertib) combined with cisplatin. Furthermore, no clear relationship between cellular response to M6620 (VX-970, berzosertib) + cisplatin and p53 status was observed in seven primary lung tumors.

In vivo Antitumor Activity

The *in vivo* activity of M6620 (VX-970, berzosertib) was tested in multiple mouse xenograft models derived from human hung cancer cell lines and primary human tumor cells [24]. M6620 (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). Single-agent M6620 (VX-970, berzosertib) had no significant effect on tumor growth in the experimental models. M6620 (VX-970, berzosertib) was generally well tolerated at efficacious doses in combination with DNA-damaging agents. Some body weight loss and enhanced changes in specific peripheral blood cell populations were observed with intensive and sustained dosing of M6620 (VX-970, berzosertib) in combination with cisplatin. This effect could be attributed to an increased growth arrest, which was observed *in vitro* in normal cells for combinations of M6620 (VX-970, berzosertib) with DNA-damaging agents. This effect was reversed when ATR activity was restored. M6620 (VX-970, berzosertib) sensitized pancreatic tumor xenografts to the cytotoxic effects of gemcitabine-based chemoradiation [23]. The combination treatment was effective even at gemcitabine doses with no single-agent activity. M6620 (VX-970, berzosertib) administered in combination with gemcitabine + IR was well tolerated.

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

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

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

Nonclinical Pharmacokinetics

In all non-clinical species (the mouse, rat, dog, and monkey), M6620 (VX-970, berzosertib) exhibited a high volume of distribution (V_d); tissue exposure, including tumor, was high. 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) was extensively bound to plasma proteins; the free fraction of M6620 (VX-970, berzosertib) was only 2.1% in human blood.

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

Nonclinical Safety Pharmacology

An in-house manual patch-clamp human ether-a-go-go-related gene (hERG) assay demonstrated moderate inhibition of the hERG channel. 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, VX 970 inhibits DNA-damage repair and will be administered in conjunction with cytotoxic chemotherapy, thus the potential for teratogenicity should be considered high.

2.3.3 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). 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 withM6620 (VX-970, berzosertib) being administered in combination with DNA-damaging agents to patients with advanced solid malignancies (Study 001); the study is ongoing. 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 or 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 1.36 times greater and $AUC_{0-\infty}$ 1.43 times 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). 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%) 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 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).

2.4 Rationale

Tumor type: By virtue of the mechanism of action of the M6620 (VX-970, berzosertib), the histology spectrum which may manifest response to treatment may be broad. Nevertheless, the ultimate outcome of brain metastases is highly dependent on the histology of primary tumor. Prior experiences have shown that brain metastases from NSCLC and from breast cancer need independent studies due to the inherent differences in the biology [11, 14, 27]. NSCLC continues to be one of the most common causes of brain metastases accounting for 25-45% of all brain metastases [3]. Further, 30-40% of patients with NSCLC may develop brain metastases as the only site of metastatic disease, justifying the need to develop therapeutic approaches targeting brain metastases from NSCLC. Hence, to initially test the agent, M6620 (VX-970, berzosertib), we have elected to restrict the trial to patients with NSCLC primary. There is extensive published phase III data on outcomes with this histology, and the results obtained from the current

phase1 trial with a modern adaptive trial design, would provide initial data on outcomes which can then be used to power the future phase 2/3 study.

Justification for a phase 1 trial: There is no clinical data regarding the efficacy of M6620 (VX-970, berzosertib) in combination with radiation. Pre-clinical data has demonstrated enhanced efficacy of M6620 (VX-970, berzosertib) + radiation, justifying its evaluation in clinic. However, in absence of any safety data of the combination with radiation in humans, and due to concerns that there may be some overlap between the downstream effects of ATR inhibition and ATM pathways, which is a known factor, predisposing to extreme radiosensitivity, an initial phase 1 trial is imperative before embarking on a large scale randomized phase 2 design. Further, patients with NSCLC are more likely to have pre-existing smoking history with resulting microvascular changes that put them at higher risk of delayed toxicity. Hence, the NSCLC-specific clinical trial platform provides a higher bar of safety which can then be used to guide trials in other histologies like breast cancer with brain metastases, where the survival is expected to be longer and hence, delayed toxicities may have high clinical relevance. Finally, while the initial phase 1 studies with M6620 (VX-970, berzosertib) monotherapy in extra-cranial malignancies have demonstrated the relative tolerance of this drug, the data regarding penetration of M6620 (VX-970, berzosertib) across the blood-brain barrier and blood-CSF barrier in humans is unavailable. Hence, a formal dose-escalation trial is necessary to define the optimal dose with maximal therapeutic ratio. This proposal was extensively discussed in the preliminary teleconferences by the M6620 (VX-970, berzosertib) project team members and received full support. Further, due to the relative commonness of brain metastases in NSCLC, we don't expect any hurdles in accrual, especially with support from the participating UM1 sites.

With regards to timing of administration of M6620 (VX-970, berzosertib) and WBRT, in vitro cell culture experiments and animal models have shown that maximal cytotoxicity was noted when VX-970 was given 24 hours after administration of a DNA-damaging agent. Radiation being the DNA-damaging agent in this trial, M6620 (VX-970, berzosertib) will be administered starting 18-30 hours after the first fraction of WBRT since. A broad range of 18-30 hours will allow for the logistics of delivering treatments in two different departments (radiation and medical oncology) and due to the inherent variability in timing of radiation on a given day as per the clinic schedule. This will be especially important in a multi-institutional setting where there may be a wide variation in clinic schedules.

2.5 **Hypotheses**

2.5.1 Primary Objective

The combination of concurrent M6620 (VX-970, berzosertib) administered as twice weekly infusion at the identified RP2D can be safely administered with whole brain radiotherapy in patients with brain metastases from NSCLC. The recommended phase 2

dose (RP2D) using this dosing schedule will be established as the primary objective.

2.5.2 Secondary Objective

When compared to whole brain radiotherapy alone, the combination of concurrent M6620 (VX-970, berzosertib) administered as twice weekly infusion at the identified RP2D along with whole brain radiotherapy in patients with brain metastases from NSCLC will result in:

- ≤ 10% incidence of Grade 3 or higher, 6-month neurological toxicity in absence of intracranial progression. In the RTOG 9508 trial, the incidence of Grade 1/2 or Grade 3/4 late toxicities (> 90-days after treatment) were approximately 20% and < 5% respectively [28]. The corresponding incidences with the addition of SRS were comparable with only a marginal increase in Grade 3/4 toxicities (6%). When specifically evaluating cognitive function, in the WBRT-alone arm of the PCI-P-120-9801 clinical trial (motexafin gadolinium), the mean relative loss in HVLT-R delayed recall score at 4 months was 30% [11].

- ≥ 50% radiological response rates (complete response/CR + partial response/PR). In recent phase-III trials looking at WBRT ± radio sensitizers, the rates of radiological responses (CR + PR) range from approximately 25-65% [29]. In the RTOG 9508 study, the response rates were 35-40% in WBRT ± SRS [28].

- ≥ 70% intra-cranial PFS at 6-months. In the NSCLC sub-set, 6-month neurological PFS (clinical or radiological progression) has ranged from 15% in the recently reported phase-III trial evaluating WBRT ± erlotinib to 70% proportion of progression free (non-neurological deaths censored) in the WBRT ± Motexafin trial [11,14]. The corresponding median neurological PFS in the former trial was 1.6 months, while the median time to neurological progression in the latter trial was 10 months.

2.5.3 Impact and Future Directions

The current proposed study with a first-in-class ATR inhibitor is a novel and untested combination with WBRT for brain metastases. Data from this study will lay the platform for testing of this drug using a phase 2 randomized design of WBRT ± M6620 (VX-970, berzosertib) for brain metastases from NSCLC. Due to relative histology non-specific mechanism of action at the DNA repair level, responses seen in this study can be extrapolated to other tumor histologies. Hence, if a positive response is seen, the concept could be extended to selected patient population with brain metastases from breast primary. Further, if an intracranial response is seen, we would recommend proceeding with evaluation of M6620 (VX-970, berzosertib) in combination with standard chemoradiotherapy for loco-regionally advanced NSCLC through the platform of a phase 1 study. ATR mediated DNA damage repair pathways have also been reported to mediate resistance of glioblastoma and melanoma cells to temozolomide suggesting that

the drug may merit evaluation in setting of high-grade gliomas [30]. Data from this trial, including the translational cohort exploring evidence of CSF and tumor penetration, can help guide future efforts towards glioma management.

2.6 **Correlative Studies Background**

Please refer to section 3.2 for information on DNA damage response and ATR pathway and section 3.3.1 for a detailed description of the relevant pre-clinical data and the description of mechanism of action of M6620 (VX-970, berzosertib) which lays the pretext for the following correlative studies.

Based on the extensive discussions during the preliminary teleconferences of the experts within the M6620 (VX-970, berzosertib) Project Team, induction of γH2AX was proposed as an integrated marker to assess increased double-strand DNA damage with the combination of M6620 (VX-970, berzosertib) with another DNA damaging agent. This requires assessment of baseline and post-treatment tumor samples. However, in the current phase 1 clinical trial, intra-cranial location of the tumor sample precludes obtaining multiple/ serial pre- and post-treatment biopsies, which limits the utility of γH2AX as a biomarker of response. Some patients with active extra-cranial disease may provide tumor tissue amenable to serial sampling. However, use of WBRT alone without any planned radiation targeting the extra-cranial tissue, the effect of increased DNA damage with M6620 (VX-970, berzosertib) + radiation combination cannot be tested in these extra-cranial samples. While some genomic alterations might correlate with sensitivity to an ATR inhibitor (cyclin E or ATR amplification, ATM mutation, p53 mutation), this is a phase 1 study with most of the patients on dose escalation cohorts of M6620 (VX-970, berzosertib) the scope of pharmacodynamic/correlative biomarkers is limited. Further, the effect of the genomic alterations on response or survival would be difficult to assess in a small study due to the effects of the systemic NSCLC disease on survival, which is not impacted by the M6620 (VX-970, berzosertib) + WBRT combination. Also discussed during initial Project Team discussions was use of markers such as pATR, pCHK1 and pDNA-PK. However, measurement of these labile markers in archived specimens, which would be the only available specimens in the group 1 patients, is subject to limited test sensitivities and confounding effects. As such, no PD biomarker testing will be done in group 1 patients.

2.6.1 Intra-Operative Blood, CSF and Tumor Specimen Collection

Based on animal pharmacokinetic studies, while excellent distribution into tissues was seen the peak brain tissue to plasma ratio was 0.71. This suggests limited penetration of the blood-brain barrier. However, in the setting of parenchymal metastases causing damaged blood-brain-barrier, the degree of drug-tumor penetration is expected to be higher. Innovation: To get a better estimate of the tumor drug penetration in setting of clinical brain metastases in human, the current study proposal includes Group 2, a novel design with a translational cohort of 6 patients in whom M6620 (VX-970, berzosertib) will be administered 2-4 hours prior to the craniotomy followed by intra-operative CSF

and tumor specimen collection. This will provide a direct estimation of intra-cranial and intra-lesional drug penetration in humans, which may be used to establish a PD-PK relationship. A signal of drug effect will be measured through measurement of pATR-Thr1989, pCHK1 S345 and RAD51 multiplex levels in the intra-cranial tumor specimen. Rad51, which plays a key role in the homologous recombination repair pathway and pATR-Thr1989, which is an autophosphorylation site critical for ATR function will be assessed through the multiplex assay. Depending on the evolving understanding of drug effects in combination with other chemotherapy agents or radiation, additional biomarkers may be added in future, pending approval and funding. Even if a definite PD-PK relationship is difficult to discern due to small patient number and the challenges as noted above, the mere observation of CSF and tumor penetration could also help direct efforts in other intra-cranial histologies including high-grade gliomas. By virtue of the design, this data will be obtained without any added risks to the patient who will be scheduled to undergo a craniotomy to surgical de-bulk an intracranial mass per clinical indications.

As noted above, due to the extreme and unjustifiable risk of obtaining intra-cranial tumor biopsy prior to M6620 (VX-970, berzosertib) administration, a definite PD relationship through the measurement of pATR and RAD51 foci is difficult to establish. As an alternate, a parallel study at the PI's institution would be conducted wherein fresh tumor biopsies from 12 matched control patients who are scheduled to undergo a craniotomy but not accrued to the proposed study will be collected as a separate IRB approved study for assessments of pATR T1989, pCHK1 S345 and RAD51 multiplex foci. Expression of these markers will be compared with the data from 6 patients in the group 2 of the proposed study. The samples will be forwarded to the same central laboratories that will be performing study on the current protocol.

2.7 **Role of Magnetic Resonance Imaging for Response Assessment in Brain Metastases**

Response assessment of brain metastasis after radiotherapy may be performed by a combination of morphologic and functional MR methods.

2.7.1 Morphological Assessment

Manual measurements of metastatic foci on contrast enhanced MR imaging remains the standard for assessment of treatment response. Although a number of guidelines for such measurement exist, a standard approach is to obtain a maximal dimension on an axial image and a second dimension orthogonal to this (bidirectional assessment). However, concerns about the reliability and reproducibility of such measurements are addressed in a recent reevaluation of the RANO-BM criteria (which propose obtaining such measurements on axial 5 mm thick non-overlapping MR slices and restrict such measurements to lesions that are greater than or equal to 10 mm in maximal dimension) [31-33]. Although such measurements will be obtained as a part of the study, the addition of a widely available standard volumetric T1 weighted contrast enhanced

sequence will permit both manual and automated measurements of smaller (less than 5 mm) lesions. It must however be acknowledged that the utility of routine volumetric assessment and the threshold of volume reduction necessary for treatment response have yet to be established. For specific details of a standard volumetric T1 weighted post-contrast MR imaging protocol please refer to Appendix E.

2.7.2 Perfusion MRI

A vast body of the literature exists describing the use of MR perfusion imaging in the diagnosis and grading of primary and secondary brain neoplasms and in monitoring their response to treatment [34]. MR perfusion imaging allows qualitative and quantitative estimation of cerebral perfusion parameters using intravenously administered gadolinium based contrast agents (GBCA). Measurement of alterations in magnetic susceptibility (T2-Dynamic Susceptibility Contrast Enhanced MRI, DSC-MRI) or T1 relaxation (Dynamic Contrast-Enhanced MRI, DCE-MRI) provide information about the perfusion and vascular permeability characteristics of the tumoral micro-environment (indirectly related to intra-tumoral interstitial pressure), which is known to influence response and outcome to radiation therapy [35]. DSC-MRI involves monitoring of the first pass of intravenously administered GBCA through the brain using a rapidly acquired dynamic T2 sequences. The most robust and widely used parameter derived from DSC-MRI is rCBV (relative Cerebral Blood Volume). Although the bulk of the perfusion MRI literature is focused on the evaluation of primary glial neoplasms, recent studies have demonstrated the use of this technique in patients with metastatic brain disease undergoing radiotherapy, both in the assessment of response to treatment and in the differentiation of recurrent metastatic tumor from radiation induced changes [36-40]. A decrease of the regional CBV value has been demonstrated to help predict response in radiosurgically treated metastatic disease with a sensitivity of greater than 80% [41]. The same group has also shown utility of non-tumor perfusion changes as a function of radiation dose, which may have role to play in assessment of toxicity from WBRT [42]. DSC-MRI is a part of routine brain tumor MR imaging protocols in many institutions. For specific details of a standard protocol DSC-MRI lease refer to Appendix E.

2.7.3 Diffusion MRI

Measurement of the Apparent Diffusion Coefficient (ADC) of water molecules provides information about tumor characteristics such as cellularity, which may not be readily estimated by conventional MR imaging methods [43, 44]. Variations in ADC values based on histology have also been described with a value of 1.17 ± 0.49 for NSCLC [45]. Diffusion-weighted magnetic resonance imaging (DWI) of metastatic brain tumors has been employed to assess response to radiation and chemotherapy [46-48]. Most studies describe increased ADC values with treatment response, perhaps reflecting decreased tumor cellularity and increased necrosis. Increased ADC may be a marker, even at earlier time points, as a predictor of response to radiotherapy. Specific details of a standard diffusion weighted imaging protocol may be found in Appendix E.

Response assessment criteria on DWI and DSC-MRI are still unclear with no published consensus recommendations. Even the choice of fitting model to obtain an ADC value may impact the measurement though the definition of region of interest may not be that significant [49]. There is also suggestion that the changes in ADC values at the junction of tumor and peri-tumoral brain tissue may have prognostic significance [50]. Based on limited available literature, we anticipate treatment response to correspond to a decrease in rCBV (perhaps of the order of 25- 33%) and an increase in ADC value [51, 52]. Further, the precise degree of change in rCBV and ADC on DSC-MRI and DWI respectively cannot be predicted for the study drug due to lack of efficacy data. As such, these end-points will be exploratory. Information from the proposed phase-I study will provide data to help design the end-point in the future phase-II/III study.

2.8 Relevance of Neurocognitive Testing for Whole Brain Radiotherapy Clinical Trials

Historically, patients with brain metastases had very limited survival [4, 5]. However, subgroups of patients exist in which prolonged survival is possible. Based on graded prognostic assessment (GPA), the median survival of patients with brain metastases ranges from 3.1-13.5 months based on the risk score [53]. Specifically in patients with NSCLC, the factors favoring longer survival include age < 50 years, Karnofsky Performance Status (KPS) of 90-100, absent extra-cranial disease and solitary brain metastases. Because of advances in the diagnosis and management of this condition, most patients receive effective palliation and many do not die from the metastases, which increases the relevance of delayed toxicity from WBRT.

Neurocognitive impairment has received significant importance in recent clinical trials evaluating WBRT, though the occurrence of this toxicity was noted even in older series. In a retrospective review of 70 patients treated with WBRT in daily fractions of 3-6 Gy treated to a dose of 25-39 Gy, 11 percent showed evidence of progressive, debilitating dementia within 5 to 36 months of treatment [54]. RTOG 0018, a cooperative group Phase 2 trial, evaluated feasibility of cognitive testing of brain metastasis patients receiving WBRT. With > 90% pre-WBRT and > 84% post-WBT compliance, this study established the feasibility of using multi-pronged and comprehensive neurocognitive testing in a multi-institution cooperative group setting, while also establishing the certification process to conduct these studies [55]. The first, large, international phase 3 randomized study to evaluate cognitive function for patients with brain metastasis using a battery of cognitive tests showed that the majority of patients experienced cognitive decline after WBRT, with 59% experiencing a greater than 2 SD decline in their performance in one or more tests at 6 months [7]. In a phase 3 trial of SRS plus WBRT compared to radiosurgery alone, Chang and colleagues demonstrated a higher rate of 4-month decline in list-learning recall, assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R), with the addition of upfront WBRT [56]. Similar findings were reported by Welzel *et al*., who observed a decline in verbal memory function, as assessed by the Auditory Verbal Learning Test (AVLT) 6 to 8 weeks after the completion of WBRT for brain metastases [57]. Results from a recent U.S. cooperative group trial

presented at the 2015 annual meeting of ASCO, the rates of cognitive decline (> 1 standard deviation decline from baseline in any of the 6 cognitive tests at 3 months) were higher in the patients randomized to WBRT + SRS arm (88%) vs SRS alone arm (61.9%) [9]. These and many other institutional series provide the rationale for close monitoring of neuro-cognitive toxicity in this phase-I clinical trial.

We will use Hopkins Verbal Learning Test-Revised for delayed recall (HVLT-R DR) and Functional Assessment of Cancer Therapy- Brain subscale (FACT-BR) to assess neurocognitive toxicity and impact on quality of life as was performed in the RTOG 0933 evaluating the feasibility of hippocampal avoidance WBRT techniques [58]. Participating institutions were all credentialed for these tests, which would allow standardized collection of data in the current protocol.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with a histologically confirmed diagnosis of non-small cell lung cancer (NSCLC), including neuroendocrine tumors or small cell lung cancer (SCLC) who are being evaluated for palliative WBRT (with or without neurosurgical resection or SRS) for radiologically or histologically diagnosed brain metastases presumed to be from the lung cancer are eligible for this Phase I study. Group 2 will only include NSCLC patients.

3.1.2 Life expectance of greater than two months to allow completion of study treatment and assessment of dose-limiting toxicity.

3.1.3 Group 2 patients should have archived or fresh tumor tissue available from the non-craniotomy site and will have fresh tumor tissue available from the planned craniotomy.

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 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). Note: though patients with ECOG performance status of 3 due to neurological deficits who are otherwise fit to receive systemic therapy per clinician assessments will be allowed.

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

- Leukocytes ≥ 3,000/mcL
- Absolute Neutrophil Count (ANC) ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL

- Total bilirubin, AST (SGOT) and ALT (SGPT):

If no known liver metastases:
Total bilirubin < 1.5 x institutional upper limit of normal (ULN), AST/SGOT or ALT/SGPT < 2 x ULN.

If known liver metastases, then:
Total bilirubin < 2.5 x ULN, AST/SGOT or ALT/SGPT < 5 x ULN.

- Creatinine within normal institutional limits for age

OR

Calculated creatinine clearance ≥ 45 mL/min/1.73 m^2 for patients with creatinine levels above ULN.

3.1.7 Negative serum or urine pregnancy test result for females of child bearing potential

Note: The effects of M6620 (VX-970, berzosertib) on the developing human fetus are unknown. For this reason and because radiation therapy is known to have teratogenic potential, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of M6620 (VX-970, berzosertib) administration.

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

3.2 Exclusion Criteria

3.2.1 Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, with stable systemic disease and ECOG score of 0-2, who would otherwise be eligible for SRS/SRT alone should not be enrolled into this study unless WBRT is recommended due to any medical reasons or logistic limitations as determined by the treating physician. Patients who develop recurrence post-SRS/SRT or surgery alone and are recommended WBRT will be eligible for the protocol.

3.2.2 Greater than 1 cm mid-line shift, severe uncal herniation or significant hemorrhage/hydrocephalous (intra-lesional hemorrhage is acceptable). Patients with seizure at presentation who have been started on Levetiracetam and have been stable for 48 hours prior to study registration are eligible at the discretion of treating physician.

3.2.3 Patients who have received systemic cytotoxic chemotherapy and/or, immunotherapy or other intraveneous standard therapy for 2 weeks before initiation of planned WBRT, for oral targeted agents 3-7 days per clinician discretion or patients who have not recovered to CTCAE grade 2 or less from serious (CTCAE grade 3 or more) adverse events form the previously received agents. For any other investigational agents, at least 4 half-lives of the agent (6 weeks for nitrosoureas or mitomycin C) should have elapsed prior to starting study treatment.

3.2.4 Patients must not have received prior WBRT (previous SRS/SRT done at least 2 weeks from the planned start of WBRT is acceptable). Patients planned upfront to undergo SRS/SRT/fractionated boosts or neurosurgery after WBRT are not eligible; however, these treatments/procedures can be performed once the DLT assessment has been completed, if felt clinically necessary.

3.2.5 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. Further, radiation therapy is known to 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).

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

3.2.7 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 C (Patient Drug Information Handout and Wallet Card) should be provided to patients. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Ongoing phenytoin should be either discontinued if clinically safe or transitioned to non-enzyme-inducing antiepileptics like Levetiracetam with a 8-day washout period (half-life 18-22 hours, time to steady-state 4-8 days) prior to first dose of M6620 (VX-970, berzosertib) (7-days prior to WBRT).

3.2.8 Patients needing more than 8 mg dexamethasone per day at the time of start of WBRT will not be eligible to participate in the study. However, patients will be allowed entry into the study if it is medically safe to reduce the daily dose of dexamethasone to 8 mg or less from the day of the start of WBRT. The dexamethasone dose for such patients may be increased beyond 8 mg per day during the course of treatment if medically necessary. This increased need for dose should be communicated to the study's Principal Investigator, Dr Mohindra, at the University of Maryland.

3.2.9 Uncontrolled intercurrent illness that would increase the risk of toxicity or limit compliance with study requirements. This includes but is not limited to, ongoing uncontrolled serious infection requiring i.v. antibiotics at the time of registration, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with M6620 (VX-970, berzosertib) and the uncertainties of any impact thereof on the radiation toxicities. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.11 Patients with known diagnoses that are associated with germline DDR defects such as Li Fraumeni syndrome and ataxia telangiectasia are excluded from the study as M6620 (VX-970, berzosertib) is a DDR inhibitor.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
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 act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

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

4.2 Site Registration

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

IRB Approval

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

For trials that will include sites using their local IRB or REB as well as for a trial with non-U.S.-based NCTN and NCORP sites, include the following paragraph and the three associated bullet points:

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

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

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

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,

- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

4.2.1 Downloading Regulatory Documents

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

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP IAM username and password.
- Click on *Protocols* in the upper left of your screen.
  - Enter the protocol # in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select LAO-MN026 and protocol # 9952.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Protocol Specific Requirements for 9952 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. A primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, please view the Person Roster Browser under the RUMS link on the CTSU website.

- Site Initiation Teleconference (SIV TC with lead site)
- Credentials showing proficiency in neurocognitive testing from a prior NRG or Alliance study

4.2.3 Submitting Regulatory Documents

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

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

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

4.2.4 Checking Site Registration Status

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

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

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

4.3 **Patient Registration**

4.3.1 OPEN / IWRS

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

Requirements for OPEN access:

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

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

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

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

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

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

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 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.

Prior to receiving ability to enroll a patient to this study, Registrar will have to have completed neurocognitive certification protocol-specific requirement.

4.3.3 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 14 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.

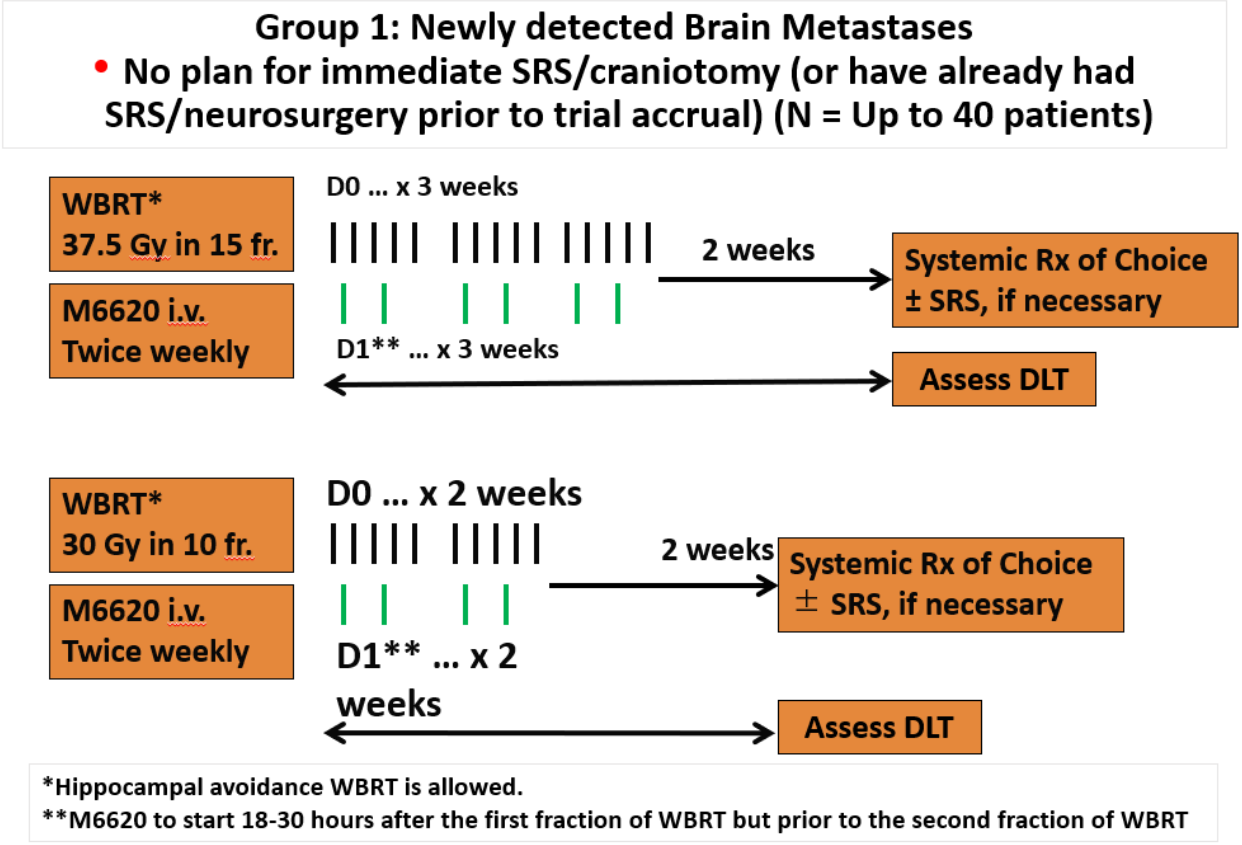
5. TREATMENT PLAN

The current proposed study will be completed through the accrual of two sequential groups as below:

Group 1: The study design is a dose-finding phase 1 trial in the relevant patient population with the aim of characterizing the safety profile and deriving the Recommended Phase 2 Dose (RP2D) of M6620 (VX-970, berzosertib) combined with WBRT for treatment of brain metastases. This will include patients that are not being considered for an immediate SRS or craniotomy. Patients may have already undergone craniotomy or SRS prior to being screened for the study. This group of patients will be allowed to accrue into the dose-escalation phase 1 study with increasing doses of M6620 (VX-970, berzosertib) combined with fixed dose radiotherapy. The data from this group will be used in achieving the primary and the secondary objectives of the phase 1 study.

It is noted that the ideal schedule and sequence of M6620 (VX-970, berzosertib) and radiation has not been determined with *in vivo* studies, which is being currently planned and coordinated through NCI. Since the current study is a safety study to rule out toxicity, we will proceed with the current protocol guided by the studies described in the Investigator's Brochure (IB), wherein it is noted through *in vitro* cell culture experiments and animal models that maximal cytotoxicity is noted when VX-970 is given 24 hours after administration of a DNA-damaging agent. Radiation being the DNA-damaging agent in this trial, M6620 (VX-970, berzosertib) will be administered starting 18-30 hours after the first fraction of WBRT since (but prior to the second fraction of WBRT). A broad range of 18-30 hours will allow for the logistics of delivering treatments in two different departments (radiation and medical oncology) and due to the inherent variability

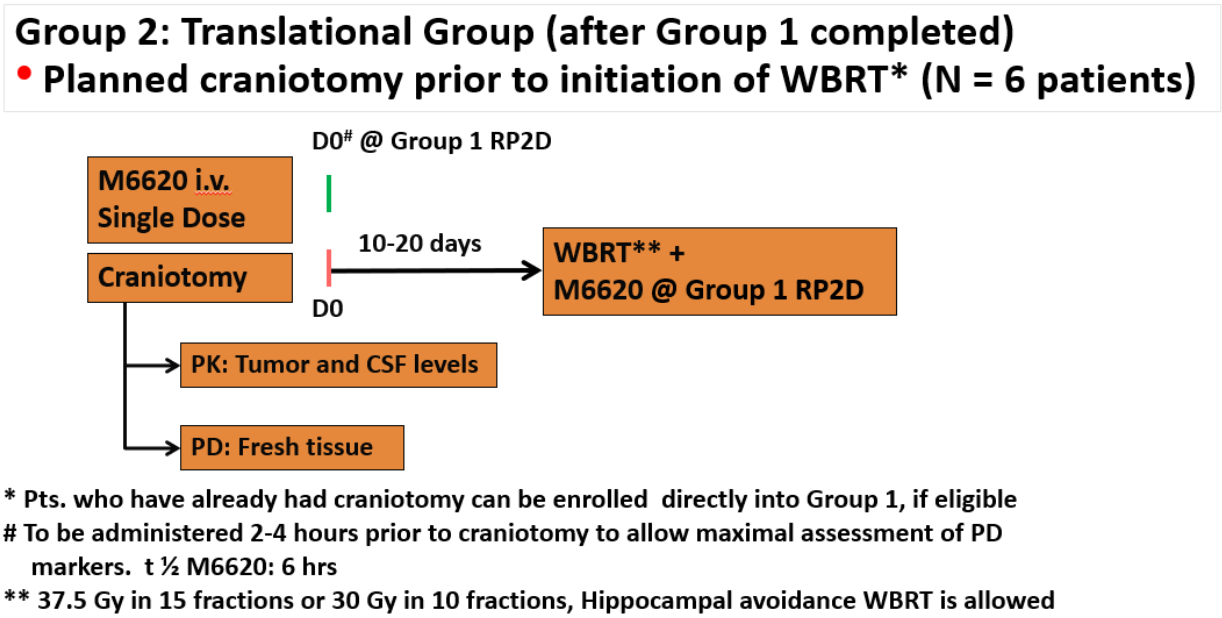
in timing of radiation on a given day as per the clinic schedule. This will be especially important in a multi-institutional setting where there may be a wide variation in clinic schedules. It will be recommended to keep as close to 24 hours gap as possible between the first fraction of radiation and the first dose of M6620 (VX-970, berzosertib). The timing of radiation and M6620 (VX-970, berzosertib) will be strictly recorded and monitored by the data monitoring committee. Once new data regarding sequencing of M6620 (VX-970, berzosertib) and irradiation is available from the currently planned *in vivo* studies, we will appropriately modify the sequencing in the current protocol.



Group 2: Restricted to the University of Maryland only

This will include patients that are being considered for craniotomy prior to the initiation of WBRT. If found eligible and study registration is completed after an informed consent, patients will receive a single dose of M6620 (VX-970, berzosertib) at the RP2D derived from the group 1. This dose will be administered 2 to 4 hours prior to the planned craniotomy. Subsequent to craniotomy, patients will initiate WBRT preferably 10-20 days post-operatively or as clinically appropriate. WBRT (37.5 Gy in 15 fractions or 30 Gy in 10 fractions) will be delivered concurrently with M6620 (VX-970, berzosertib) administered at the Group 1 identified RP2D. As such, this group of patients will be enrolled after the identification of RP2D from group 1. The scheduling of M6620

(VX-970, berzosertib) during WBRT will be identical to the group 1 patients, as detailed in section 5.1.1 below.



5.1 Agent Administration

5.1.1 M6620 (VX-970, berzosertib)

Group 1: Treatment will be administered on an outpatient basis. The drug will be administered on a twice weekly schedule M6620 (VX-970, berzosertib) will be administered starting 18-30 hours after the first fraction of WBRT but prior to the second fraction of WBRT. It will be recommended to keep as close to 24 hours gap as possible between the first fraction of radiation and the first dose of M6620 (VX-970, berzosertib). The timing of radiation and M6620 (VX-970, berzosertib) will be strictly recorded and monitored by the data monitoring committee.
Since in routine clinical practice WBRT may start any day of the week and not necessarily on Mondays (like most curative intent chemo-radiations), for the protocol purpose the study protocol will allow a Monday through Thursday start of WBRT, with M6620 (VX-970, berzosertib) administered as follows:

- Monday or Thursday WBRT start: M6620 (VX-970, berzosertib) administered Tuesday and Friday
- Tuesday WBRT start: M6620 (VX-970, berzosertib) administered Wednesday and Friday in week 1 followed by Tuesday and Friday from week 2 onwards
- Wednesday WBRT start: M6620 (VX-970, berzosertib) administered Thursday in week 1 and then Monday and Thursday from week 2 onwards.

This will allow all patients to get 6 doses of M6620 (VX-970, berzosertib) over 3 weeks

course of WBRT (37.5 Gy in 15 fractions) or 4 doses of M6620 (VX-970, berzosertib) over 2 weeks course of WBRT (30 Gy in 10 fractions).

For the protocol purpose and due to the logistic difficulties of M6620 (VX-970, berzosertib) administration on Saturdays, the study calendar will include a comment to avoid a Friday start of WBRT, when clinically appropriate.

Patients can receive WBRT at a community site/satellite location within the health system where the study is approved as long as the study agent is received at the site approved to dispense/administer the study drug, and patient can be monitored closely for toxicities and undergo necessary HVLT-R and FACT-BR testing.

For the second and subsequent doses of M6620 (VX-970, berzosertib), the drug will be administered after the day's administration of radiation treatment. This schedule will allow maximum overlap of drug during the active days of radiation treatment.

M6620 (VX-970, berzosertib) Administration				
Premedication/ Precautions	**Dose***	**Route**	**Schedule**	**Duration**
Premedicate with dexamethasone as per institutional guidelines	[redacted]	IV over 60 minutes	Twice weekly	Three weeks

Group 2: **Restricted to the University of Maryland only**
Patients will first receive a single dose of M6620 (VX-970, berzosertib) (per above administration guidelines) at the RP2D derived from the group 1. This dose will be administered 2 to 4 hours prior to the planned craniotomy. The time of M6620 (VX-970, berzosertib) administration and time of blood, CSF and tissue collection will be recorded.

M6620 (VX-970, berzosertib) will also be administered concurrently with WBRT at the RP2D derived from group 1. The scheduling of M6620 (VX-970, berzosertib) during

WBRT will be identical to the group 1 patients, as detailed above.

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

5.1.1.1 Group 1 Dose Escalation

Several statistical designs have been studied for dose-finding phase 1 trials. We will employ a Bayesian adaptive design, Escalation With Overdose Control (EWOC), originally proposed by Babb, Rogatko and Zacks [59]. EWOC is coherent and utilizes all the toxicity data available at the time of each dose assignment and controls the probability of overdosing patients at each stage. Compared to alternative, non-parametric designs, EWOC treats fewer patients at either sub-therapeutic or severely toxic dose levels, treats more patients at optimal dose levels and estimates the maximum tolerated dose with smaller average bias and mean squared error. Toxicities are treated as binary (yes-no) in the EWOC modeling. Note, that with this type of design a discrete set of dose levels is not defined a priori. The algorithm will estimate the next dose level where the expected incidence of toxicity is equal to the pre-defined target for maximum acceptable toxicity.

EWOC requires definition of a range of doses to be studied. Per the algorithm, the first dose level chosen will be the presumed “very-safe” dose based on available clinical data. In the ongoing phase 1 clinical study (002) using M6620 (VX-970, berzosertib) as monotherapy, the currently open dose level is at 480 mg/m^2. No dose-limiting toxicity was seen at lower dose levels. Note, however, that there are mechanistic reasons to expect interactions between M6620 (VX-970, berzosertib) and ionizing radiation and that the level of grade 3+ toxicity after WBRT alone is about 10%. Since the drug was administered on a weekly schedule, while the current proposal is at a twice weekly schedule, a weekly dose of 60 mg/m^2 (1/8th of the current dose level on the 002 study) was felt to be a “very-safe” dose at which the likelihood of toxicity is very low. Assuming a BSA of 1.7, this translates into an absolute dose of 100 mg per week (50 mg twice weekly dose) approximately. As a safeguard against putting patient’s safety at risk due to too rapid dose escalation in the EWOC design in case of no toxicities at the initial dose level(s), we will cap the dose at level n to be no more than a factor of two larger than the dose at level n-1. At each step, the next dose level will be guided by the EWOC algorithm, with all DLT data from the run-in being part of the data set for defining dose levels for new trial participants, but applying the cap on dose escalation if required.

The maximum single dose is chosen to be 480 mg/m^2 (800 mg), although this may be increased if the MTD in the single agent 002 study turns out to be higher before the commencement of our phase 1 trial.

Dose Escalation Schedule [1]	
Dose Level	**Dose of M6620 (VX-970, berzosertib) (mg)**
Level 1	50 mg twice weekly
Level 2	100 mg twice weekly
Level n	estimated using the EWOC algorithm, ≤ 2 times the dose level (n-1) [3]
Highest level	800 mg twice weekly [4]

1. Once enrollment at level one has been completed, the subsequent dose escalation will be based on the Bayesian adaptive design, Escalation With Overdose Control (EWOC) algorithm, with all DLT data from all tested dose levels being part of the data set for defining dose levels for new trial participants.
2. See Section 13.2.2 for special early stoppage and slow convergence scenarios.
3. In case of no toxicities at prior levels the EWOC may escalate the dose quite rapidly. As an added precaution, dose level n will not exceed the dose at level n-1 by more than a factor of 2, see section 13.2.2 for further details.
4. Highest dose-level may be increased if the MTD in the single agent 002 study turns out to be higher before the commencement of our phase I trial.

Three patients will be accrued into an open dose-level to allow accrual at more than one participating site, without significant delay in accrual. After accrual of the three patients to an open dose level, the next cohort will be opened once DLT assessment has been completed for all the three patients. The next dose level will be computed by the statisticians, see statistics section below. The dose level computation will rely on a real-time maintained log of DLT for the accrued patients. If three patients have been accrued at the current dose level but one or more of these have not been followed for the planned duration required to evaluate DLTs (three weeks of WBRT and 3 weeks after the completion of WBRT), we will allow accrual of up to 3 patients to the next *lower* dose level that has been tested before the current dose level. By virtue of the statistical approach, these additional 3 patients will contribute to the EWOC modeling and provide robustness in estimation of the ultimate RP2D. If with newer patients in the lower dose, the estimated toxicity at the current dose is above the target 25%, the enrollment will be suspended immediately until the current dose level is evaluable for the DLT rate. Accrual will open once the next dose level is estimate per the EWOC algorithm. Further, based on the EWOC modeling, since the model allows dose escalation to the likely RP2D fairly quickly, most patients are expected to be treated at a dose very close to the final RP2D, thereby limiting use of sub-therapeutic treatment exposure. As soon as the cases enrolled at the current dose level have complete follow-up for DLT assessments, we will revert to the standard EWOC algorithm.

Accrual will open once the next dose level is estimated as per the EWOC algorithm.

Figure 3 shows a single simulated trial, starting at a dose level of 50 mg twice weekly and with a maximum dose of 800 mg twice weekly. Three patients were enrolled at each dose level. The simulation was performed with a logistic dose response model with 10% toxicity at the minimum dose and 25% toxicity at a dose of 250 mg. The simulated responses are shown for each patient, with 1/0 indicating that the patient did or did not experience a DLT, respectively. Level 2 is capped at 100 mg and level 3 at 200 mg as no toxicities have occurred at levels 1 and 2 in this particular simulated trial. As toxicities start to occur, the rate of dose escalation/de-escalation is reduced. In this particular case only 20% of the 40 patients overall experienced a DLT and 85% were treated at doses within ± 15% of the (in this case known) MTD of 250 mg. The final estimated MTD is 260 mg with the 90% highest posterior density credible interval estimate from 157 mg to 634 mg.

Sample simulation of dose-escalation using a Bayesian adaptive design, Escalation With Overdose Control (EWOC)

Pt. #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Dose	50	50	50	300	300	300	430	430	430	420	420	420	480	480	480	530	530	530	570	570	570
Tox	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

Pt. #	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Dose	580	580	580	580	580	580	580	580	580	570	570	570	570	570	570	580	580	580
Tox	1	0	0	0	1	0	1	0	0	0	0	0	0	0	1	1	0	0

When a patient at any site is undergoing the study treatment, the PI of the study (or representative) will meet (in person, by teleconference or by email) with the participating site's study team member(s) regularly to review any updates regarding potential adverse events being experienced by the study subject. If necessary, clinical inputs from the treating physician and the participating site PI will be obtained to assist in the decision regarding the adverse event being labeled as a DLT.

Unexpected severe late radiation toxicity will be recorded as a secondary end-point. These events will be reviewed by the study PI, CTEP and CIRB who will be charged with considering cessation of the trial if the long term/delayed (at 6 months) ≥ grade 3 symptomatic neurotoxicity is > 20%. Use of other therapies post-DLT assessments which might impact neurological functioning (including, but not limited to, immunotherapy, for which safety data of immune-related neurological adverse events after WBRT is relatively limited) will be considered for this decision.

We will use the IWRS web-based registration system, the CTSU website and all appropriate web-based electronic portals to provide information regarding the open dose level and availability of slot for accrual (section 4.3).

5.1.1.2 Determination of Recommended Phase 2Dose (RP2D)

The stopping rule for the dose-escalation trial will be pre-defined and guided by the accepted level of ≥ Grade 3 acute dose limiting toxicity seen with the combination of M6620 (VX-970, berzosertib) with WBRT. In the phase 3 randomized trial of WBRT plus motexafin gadolinium for patients with brain metastases from non-small cell lung cancer or with WBRT + efaproxiral for breast cancer, the incidence of ≥ Grade 3 toxicity with WBRT alone was approximately 10%, while with WBRT + drug combination was approximately 25-30%. Hence, for the purpose of this trial, an incidence of 25% ≥ Grade 3 toxicity from the combination therapy will be considered an acceptable upper limit. In addition to the acute toxicity, severe late radiation toxicity will be recorded as a secondary end-point. The RP2D will be defined as the dose level estimated to be associated with an incidence of dose-limiting toxicity (DLT) of 25%, see statistics section below.

5.1.2 Whole Brain Radiotherapy (WBRT)

5.1.2.1 Dose Specifications

Protocol whole brain radiotherapy (WBRT) must begin within 14 days following registration; if day fourteen falls on a holiday or weekend, it is acceptable to begin treatment the next business day. Two dose fractions for WBRT are allowed: One treatment of 2.5 Gy will be given daily for not more than 5 days per week (15 fractions), once daily fractionation, without any planned interruptions for a total of 37.5 Gy over three weeks or One treatment of 3 Gy will be given daily for not more than 5 days per week (10 fractions), once daily fractionation, without any planned interruptions for a total of 30 Gy over two weeks. All portals shall be planned to be treated during each treatment session. Doses are specified as the target dose which shall be the dose on the central ray at mid-separation for two opposed coaxial equally weighted beams (or as mean dose to a specified target volume, in this case, whole brain). “Compensating beams” that block hot spots (these hot spots are typically present along the midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity.

5.1.2.2 Technical Factors

Treatment shall be delivered with megavoltage machines of energy ranging from 4MV to 6 MV photons. Patients will be planned and treated using three-dimensional conformal radiation technique (3D-CRT). Intensity Modulated Radiotherapy (IMRT) with or without hippocampal avoidance (Fixed-gantry IMRT, helical tomotherapy or VMAT) will be allowed per institutional protocols. Partial brain cone down, stereotactic, electron, particle or implant boost are not permissible during the course of

the study treatment and until the DLT assessments are complete. However, patients will be eligible to undergo SRS/SRT/fractionated boosts or neurosurgery, once the DLT assessment has been completed, if felt clinically necessary.

5.1.2.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position to allow planning and delivery of WBRT. A head-holding device must ensure adequate immobilization during therapy and ensure reproducibility. A non-contrast treatment-planning CT scan of the entire head region extending into neck should be obtained. When using hippocampal avoidance WBRT, it is recommended he axial slice thickness should match the MRI axial slice thickness as much as possible (preferred 1.5 mm). The treatment-planning CT scan must be acquired with the patient in the same position and immobilization device as for treatment. For 3D-CRT, the target volume shall include the entire cranial contents, with flashing beyond skin and adequate margin on the skull base as visualized on the simulator or portal films to account for beam penumbra and day-to-day set-up variation. Treatments must be delivered through parallel opposed fields. The lenses and the anterior globe will be excluded from the beam either by field arrangement or shielding. 'Helmet' portals with customized immobilization and shielding are permitted.

5.1.2.4 Critical Structures

Care should be taken to minimize the dose to the lens. For patients post-cataract surgery, a surrogate lens structure should be created.

5.1.2.5 Hippocampal avoidance WBRT:

Hippocampal avoidance WBRT should be planned in accordance with the ongoing (or most recently completed, if no ongoing study) cooperative group protocol. The target volume will include the entire cranial contents to the foramen magnum (labeled as CTV). Care should be taken to delineate cribriform plate in the CTV. The PTV is equal to CTV without the hippocampal avoidance region.

When prescribing 37.5 Gy in 15 fractions, the IMRT plan should be normalized such that 95% of the PTV volume receives prescription dose of 37.5 Gy (V37.5 Gy ≥ 95%), D2% (Dose to hottest 2% of PTV) is ≤ 40 Gy, D98% (Dose to 2% of PTV) is ≥ 32.5 Gy. Variation Acceptable include, V37.5 Gy ≥ 90%, D2% is ≤ 43 Gy and D98% is ≥ 30 Gy.

When prescribing 30 Gy in 10 fractions, the IMRT plan should be normalized such that 95% of the PTV volume receives prescription dose of 30 Gy (V30 Gy ≥ 95%), D2% (Dose to hottest 2% of PTV) is ≤ 37.5 Gy, D98% (Dose to 2% of PTV) is ≥ 25 Gy. Variation Acceptable include, V30 Gy ≥ 90%, D2% is ≤ 40 Gy and D98% is ≥ 22.5 Gy.

QA for the physician-approved plan should be performed per institutional policies.

For hippocampal avoidance WBRT, bilateral hippocampal contours (Hippocampi) will be manually generated on the fused planning MRI/CT image set by the treating physician according to contouring instructions specified on http://www.rtog.org//corelab/contouringatlases/hippocampalsparing.aspx . Hippocampal avoidance region (Hippocampi_05) will be generated by three-dimensionally expanding the hippocampal contours by 5 mm. Bilateral hippocampal contours will be subdivided into Left (Hippo_L) and Right (Hippo_R) hippocampi. Due to variance in eye position between the CT and MRI, if possible, the left (OpticNerve_L) and right (OpticNerve_R) optic nerve should be contoured using the CT dataset only. Located above the pituitary fossa, the optic chiasm (OpticChiasm) includes both anterior and posterior limbs. It is best visualized on SPGR/MPR/TFE T1 MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.

OAR constraints for hippocampal avoidance WBRT (37.5 Gy in 15 fractions) are shown below:

Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Variation Acceptable**	**Notes**
	D100%(Gy)	≤ 11	11 to 13	Dose to 100% of Hippocampus
	D_{max}(Gy)	≤ 16	16 to 20	Dose to hottest 0.03 cc volume of

				Hippocampus
OpticNerve_L	D_{max}(Gy)	≤ 39	39 to 42 Gy	Dose to hottest 0.03 cc volume of OpticNerve_L
OpticNerve_R	D_{max}(Gy)	≤ 39	39 to 42 Gy	Dose to hottest 0.03 cc volume of OpticNerve_R
OpticChiasm	D_{max}(Gy)	≤ 39	39 to 42 Gy	Dose to hottest 0.03 cc volume of OpticChiasm

OAR constraints for hippocampal avoidance WBRT (30 Gy in 10 fractions) are shown below:

Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Variation Acceptable**	**Notes**
	D100%(Gy)	≤ 9	9-10 Gy	Dose to 100% of Hippocampus
	D_{max}(Gy)	≤ 16	16 to 17 Gy	Dose to hottest 0.03 cc volume of Hippocampus
OpticNerve_L	D_{max}(Gy)	≤ 33	33 to 37.5 Gy	Dose to hottest 0.03 cc volume of OpticNerve_L
OpticNerve_R	D_{max}(Gy)	≤ 33	33 to 37.5 Gy	Dose to hottest 0.03 cc volume of OpticNerve_R
OpticChiasm	D_{max}(Gy)	≤ 33	33 to 37.5 Gy	Dose to hottest 0.03 cc volume of OpticChiasm

In optimizing planning, the following treatment-planning priorities should be followed:
1. OpticChiasm
2. OpticNerve_L or OpticNerve_R
3. Hippocampus
4. PTV_3000
5. Lens_L or Lens_R

In the event that an OAR with higher priority than PTV cannot be constrained within Unacceptable Deviation limits, then D98% and/or V30Gy for PTV should be lowered to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits. Please contact the study PI (or representative) if there are challenges meeting above.

5.1.2.6 Documentation Requirements

The following documents should be submitted to the PI at the University of Maryland
- Radiation Total Dose
- Radiation Dose per Fraction
- Radiation Number of fractions
- Radiation Technique: 3D-CRT or IMRT/VMAT/Tomotherapy
- Use of Hippocampal avoidance: Yes or No
- Radiation Start Date
- Radiation Completion Date
- Treatment Interruptions/Delays
- Acute on-treatment toxicity with grades
- RT plan report with dose to organs at risk, if applicable.
- Dexamethasone pill diary during WBRT and for three weeks post-WBRT (DLT assessment period)

5.1.2.7 Compliance Criteria

The planned protocol treatment should be completed without any unplanned breaks/ interruptions. Dose delay/modification table has been noted in section 7.

5.1.2.8 Radiation Adverse Events

Acute (≤ 90 days from treatment start): Expected adverse events include hair loss, erythema of the scalp, headache, nausea and vomiting, eye/ear irritation, mucositis, taste/salivary changes, loss of appetite, fatigue, lethargy, and transient worsening of neurological deficits.

Late (> 90 days from treatment start): Possible adverse events include radiation necrosis, cognitive dysfunction, visual difficulties, accelerated atherosclerosis, and radiation-induced neoplasms.

5.1.2.9 Radiation Adverse Event Reporting
See Section 8 for Adverse Event Reporting

5.2 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as any grade 3 or more non-hematological toxicity requiring more than 5-day interruption in therapy or any grade 4 or higher hematological toxicity that is attributable to the M6620 (VX-970, berzosertib) and/or whole brain radiotherapy.

DLTs will be assessed from the day of the start of WBRT until 3 weeks post completion

of WBRT.

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 C (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.

Ongoing phenytoin should be either discontinued if clinically safe or transitioned to non-enzyme-inducing-antiepileptics like Levetiracetam with a 8-day washout period (half-life 18-22 hours, time to steady-state 4-8 days) prior to first dose of M6620 (VX-970, berzosertib) (7-days prior to WBRT).

VX 970 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. 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).

Standard measures (e.g. antihistamines and/or steroids) may be used to manage infusion reactions that may include pruritis, flushing, chills/rigors, urticaria/rash, headache, bronchospasm/dyspnea, and hypotension or hypertension, among others. To prevent

recurrence of these symptoms in subsequent administrations, appropriate desensitizing measures prior to the administration of the study drug may be employed (e.g., premedication with 200 mg hydrocortisone approximately 60 minutes before infusion and 4 mg of chlorphenamine approximately 30 minutes before infusion; alternative anti-histamine and steroid combinations may be considered). If standard procedures to limit symptoms of an infusion reaction are insufficient, then the infusion time may be extended beyond 60 minutes but no more than 90 minutes.

Serious acute hypersensitivity reactions can occur within minutes of re-exposure of M6620 (VX-970, berzosertib). This may include hypotension and mental status changes. These require immediate discontinuation of the inciting infusion and administration of IV corticosteroid and anti-histamine with IV fluids and oxygen as needed.

Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) and documented on each site's source documents as concomitant medication.

Patients with symptoms, neurologic signs or imaging evidence of edema or mass effect should be placed on dexamethasone at the time of brain metastasis diagnosis. The recommended starting dose should be 8-16 mg per day of dexamethasone in four divided doses or equivalent doses of other types of glucocorticoids. For this patient population, variations in the amount and frequency of steroid usage are anticipated. Per standard of care, the least amount of steroid necessary is used. Hence, it is not appropriate to define a uniform stable dose of steroid for all patients accrued to the clinical study. It is also noted that M6620 (VX-970, berzosertib) pre-medication is with dexamethasone. Patients will record the use of steroid medications using the steroid medication diary in Appendix D from time of consent through the DLT assessment period (week 6 for Group 1 patients, week 8 for Group 2 patients).

Nevertheless, to reduce/limit any potential PK impact of the concurrent use of dexamethasone, the maximum dose of dexamethasone for the patients at the time of the start of WBRT will be restricted to 8 mg per day or lower (2 mg qid, 4 mg bid or 8 mg once a day). Patients needing more than 8 mg dexamethasone on the day of the start of WBRT will not be eligible to participate in the study. Patients already accrued in the study at a dose of 8 mg or less who subsequently need more than 8 mg of dexamethasone per day while undergoing study treatment should be reported to the study PI. This will be recorded as an AE. Steroids will be continued without taper until the whole brain radiation therapy is completed.

At the completion of WBRT, a steroid taper should be initiated provide that the patient does not have persistent symptoms related to edema or mass effect from brain metastases. Every four days, the dose should be lowered as follows:

8 mg starting dose*		Duration
2 mg four times a day	4 mg two times a day	Throughout the course of WBRT
2 mg twice daily	2 mg twice daily	4 days
1 mg twice daily	1 mg twice daily	4 days
1 mg once daily	1 mg once daily	4 days
1 mg every other day	1 mg every other day	4 days
Discontinue		

*If the daily dose is < 8 mg per day, then maintain the same dose during WBRT and thereafter reduce the dose by half every 4 days until 1 mg every other day times 4 days and then stop.

In patients who cannot tolerate taper and/or cessation of steroids, the steroid dose will be maintained at the lowest dose consistent with good medical practice. Patients on steroids are recommended to receive gastritis prophylaxis and monitoring/treatment for oropharyngeal candidiasis.

Anticonvulsant usage and dosage should be noted at the time of study entry, at each follow-up evaluation and at any changes in medication use. Please refer to section 6.4 for choice of anticonvulsant therapy.

Patients will be allowed to initiate systemic therapy per clinician preference 3 weeks after the last fraction of WBRT.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment (WBRT + M6620 (VX-970, berzosertib)) will be planned for 2-3 weeks followed by 2 weeks for observation of acute toxicity and 6-months from the completion of WBRT for delayed toxicity or until one of the following criteria apply:

- Inter-current 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.

- Patients already accrued in the study at a daily dose of 8 mg or less of dexamethasone who subsequently need more than 8 mg of dexamethasone per day while undergoing study treatment should be reported to the study PI. This will be recorded as an AE.

5.5 Duration of Follow Up

Patients will be followed for up to two years from the study registration or until death, whichever occurs first. From the date of completion of WBRT, follow-ups would be done through clinic visits every 2 months (± 1 week) for the first 6 months, every 3-4 months (± 2 weeks) for the next 6 months and every 6 months (± 3 weeks) for the next one year. After the first DLT assessment visit (the primary endpoint), the clinic visits can be performed at an outside institution if appropriate clinical staff is available to complete adverse event, neurocognitive testing and QOL assessments. Neurocognitive testing may also be performed by the study team through videoconferencing, if feasible. , After 6 months, the clinic visits may be replaced by phone calls or videoconference or visits at an outside institution. Follow up notes or documentation of phone calls must be included in the study chart. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Follow-up MRI at 6 months (± 2 weeks) from the completion of WBRT is required to assess intracranial treatment response and disease control. As guided by institutional practices, MRIs performed are also recommended during follow-up visits every 2 months (± 1 week) for the first 6 months and every 3-4 months (± 2 weeks) for the next 6 months from the completion of WBRT. If progressive disease is found in the brain by MRI, then subsequent MRI scans of the brain will be done off study as per clinical standard of care.

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.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose de-escalation will be pursued if patients develop a significant related AE as below.

No intra-patient dose-escalation will be performed

Dose delays (for M6620 (VX-970, berzosertib) with or without WBRT) are allowed for a maximum of two weeks if patient develops any grade 3 or higher toxicity.

Any Adverse Event	Management/ Next Dose for M6620 (VX-970, berzosertib)	Management/ Next Dose for WBRT
≤ Grade 1 (any toxicity)	No change in dose	No change in dose
Grade 2 (any toxicity)	No change in dose	No change in dose
Grade 3 (hematological toxicity)	Hold* until Grade 2 or less hematological toxicity. Resume at a previous dose level that is a lower dose than the current level, if indicated. **‡	No change in dose
Grade 3 (non-hematological toxicity)	Hold* until Grade 2 or less non-hematological toxicity. Resume at a previous dose level that is a lower dose than the current level, if indicated. **‡	Hold* until Grade 2 or less. Resume treatment as originally planned
Grade 4 (any toxicity)	Off protocol therapy	Off protocol therapy. Once grade 2 or less, then may consider re-start of whole brain radiation alone at the discretion of treating physician.
*Patients requiring a delay of > 2 weeks should go off M6620 (VX-970, berzosertib). **Patients requiring > two dose reductions should go off M6620 (VX-970, berzosertib). ‡ See Section 13.2.2 regarding the situation if Grade ≥ 3 DLT occurs at dose level 1.		
Adverse events to be managed per standard of care clinical recommendations. Please contact the PI and Study Statistician by email or phone to get information on the previous dose level that is a lower dose than the current level. The study team will also regularly update information on the accrued dose level on the cancer.gov website (and/or institutional web portal, information on which will be provided to each participating institution).		

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 (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting.

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

7.1.1 CAEPR for M6620 (VX-970, berzosertib)

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)***

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

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

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

CARDIAC DISORDERS - Palpitations
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Colonic obstruction; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (lower respiratory

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

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

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized 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 <u>both</u> 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.

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

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

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

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

CTCAE SOC	Adverse Event	CTCAE Grade at which the event will not require expedited reporting[1]
Gastrointestinal disorders	Abdominal pain or diarrhea or gastroesophageal reflux disease or dry mouth	Grade 1 or 2
General Disorders and administration site conditions	Fatigue	Grade 1 or 2
General Disorders and administration site conditions	Flu-like symptoms	Grade 1
Investigations	Weight loss	Grade 1 or 2
Metabolism and Nutrition Disorders	Anorexia	Grade 1 or 2
Musculoskeletal and connective tissue disorders	Arthralgia	Grade 1 or 2
Injury, Poisoning and Procedural Complications	Radiation Dermatitis	Grade 1 or 2
Skin and Subcutaneous Connective Tissue Disorder	Scalp Alopecia or dry skin	Grade 1 or 2
Skin and Subcutaneous Connective Tissue Disorder	Hyperhidrosis	Grade 1

Respiratory, Thoracic and Mediastinal Disorders	Pharyngeal mucositis	Grade 1 or 2
Ear and Labyrinth Disorder	External or middle ear inflammation	Grade 1 or 2
	Hearing Loss	Grade 1
	Tinnitus	
Eye Disorder	Conjunctivitis	Grade 1 or 2
	Blurred vision	Grade 1
Nervous System Disorder	Dysgeusia or Headache or Lethargy	Grade 1 or 2
Nervous System Disorder	Dizziness	Grade 1
Vascular disorders	Hypotension	Grade 1 or 2

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes, for signs and symptoms of progression of the cancer.

7.4 Routine Adverse Event Reporting

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

PMBAfterHours@mail.nih.gov

[redacted]

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 low risk of drug-drug interaction with OATP1B3 and BCRP. Use caution when administered with sensitive substrates of OATP1B3 and BCRP transporters.

Availability

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

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (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 any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all oral agents received from DCTD using the NCI Drug Accountability Record Form (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

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

8.1.2.4 Useful links and Contacts

- **CTEP Forms, Templates, Documents:** http://ctep.cancer.gov/forms/
- **NCI CTEP Investigator Registration:** PMBRegPend@ctep.nci.nih.gov
- **PMB policies and guidelines:** http://ctep.cancer.gov/branches/pmb/agent_management.htm
- **PMB Online Agent Order Processing (OAOP) application:** https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- **CTEP Identity and Access Management (IAM) account:** https://eapps-ctep.nci.nih.gov/iam/
- **CTEP IAM account help:** ctepreghelp@ctep.nci.nih.gov

- **IB Coordinator:** IBCoordinator@mail.nih.gov
- **PMB email:** PMBAfterHours@mail.nih.gov
- **PMB phone and hours of service:** (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Exploratory Biomarker Studies - *Performed for Group 2 at the University of Maryland Only*

9.1.1 Plasma Pharmacokinetics

The PK of M6620 (VX-970, berzosertib) administered as a single agent or in combination with other chemotherapeutic agents has been tested and described in the Study 001 and 002. Exposure (Cmax and AUC) tended to be approximately linear across the studied doses with no accumulation noted during the once weekly scheduling. Mean whole blood AUC were similar with low to moderate inter-subject variability in each dose group.

We do not anticipate any changes in PK with the addition of WBRT. Hence, extensive blood PK studies are not needed in Group 1.

Per the Investigator Brochure 2013, due to minimal inhibition or induction of cytochrome (CYP) 450 isozymes by M6620 (VX-970, berzosertib) a low potential for drug-drug interactions was predicted. However, since strong inducers or inhibitors of CYP3A4 may alter M6620 (VX-970, berzosertib) kinetics and blood levels, all patients on phenytoin based anti-seizure medications will be transitioned to non-enzyme-inducing-antiepileptics like Keppra (Levetiracetam) with a 8-day washout period (half -life 18-22 hours, time to steady-state 4-8 days) prior to first dose of M6620 (VX-970, berzosertib) (7-days prior to WBRT).

Please see section 5.3 pertaining to the use of dexamethasone for patients accrued into the study.

Group 2, on the other hand, is a novel translational cohort, where patients will undergo craniotomy 2-4 hours after M6620 (VX-970, berzosertib) administration. This provides a unique opportunity to test the drug PK/PD effects intracranially. Additionally, for this small cohort, limited PK testing will be performed in week 1 of WBRT + M6620 (VX-970, berzosertib).

9.1.1.1 Hypothesis and Rationale:

Hypothesis: The ratio of CSF: plasma M6620 (VX-970, berzosertib) levels and craniotomy tumor tissue: plasma M6620 (VX-970, berzosertib) levels will be

correlated with the radiological response and intracranial disease control.

Rationale: This cohort was specifically designed to test intra-cranial tumor and CSF penetration in setting of known brain metastases, which may impair the blood-brain barrier. In this cohort, intra-operative plasma, CSF and tumor tissue samples will be tested for drug concentration. This will provide a direct estimation of intra-cranial and intra-lesional drug penetration in humans, which may be used to establish a PD-PK relationship and also guide the appropriate choice of systemic dose. The CSF and tumor penetration data will be obtained without any added risk to the patient since the patients will be scheduled to undergo a craniotomy to surgical de-bulk an intracranial mass per clinical indications.

Even if a definite PD-PK relationship is difficult to discern due to small patient number and the challenges as noted above, the mere observation of CSF and tumor penetration could also help direct efforts in other intra-cranial histologies including high-grade gliomas.

M6620 (VX-970, berzosertib) plasma PK will be performed to add to the present knowledge base of M6620 (VX-970, berzosertib) PK, to correlate exposure to PD metrics and to document any accumulation due to the more frequent administration of M6620 (VX-970, berzosertib) (twice weekly).

9.1.1.2 Assay Validity and Appropriateness for Study

Plasma, CSF and tissue concentrations of M6620 (VX-970, berzosertib) will be measured with a method developed by Vertex and currently being implemented in the University of Pittsburgh cancer Institute (UPCI) PK core by Dr. Jan Beumer. SOPs for the methods will be included as an appendix to this protocol document, once available.

9.1.1.3 Performance Site

The pk assay will be performed at the UPCI PK core by Dr. Jan Beumer. Per the facts noted at the facility's website, the UPCI Cancer Pharmacokinetics and Pharmacodynamics Facility (CPPF) provides accessible, economical, comprehensive, and state-of-the-art pharmacology research services that support preclinical and clinical research programs at UPCI and medical institutions nationwide. The CPPF has developed, validated and implemented assays for (but not limited to): abiraterone, alisertib, ATRA, belinostat, bortezomib, busulfan, cabozantinib, celecoxib, DMS612, docetaxel, erlotinib, fluorouracil, imatinib, indenoisoquinoline 400, 776, 744, iso-fludelone, ixabepilone, lapatinib, nilotinib, paclitaxel, phenyl-isothiocyanate, platinating agents carboplatin, cisplatin and oxaliplatin, temozolomide, tetrahydrouridine, vitamin D3, veliparib, vincristine, vorinostat, zebularine, and zileuton. The CPPF supports clinical research through multiple programs at UPCI, including studies within the Cancer Therapeutics Program, Melanoma Program and

Lung Cancer Program. Most prominent is the role of the CPPF in the successful re-competition of the CTEP phase I grant (NCI ET-CTN with Phase I Emphasis at UPCI; UM1-CA186690).Outside of UPCI, the facility's quality and capacity has been recognized through its designation as the central reference analytical and pharmacokinetic modeling resource for phase IV clinical studies of imatinib, nilotinib, dasatinib, and ixabepilone, and its continued serving as the pharmacology core laboratory for NRG and Alliance. In addition, the CPPF has served as the NCI reference laboratory to support phase 1 studies involving veliparib and vorinostat, and is currently serving as the reference laboratory for a belinostat hepatic dysfunction study (quantitating belinostat and 5 metabolites), and a veliparib hepatic and renal dysfunction study (quantitation of veliparib and major metabolite M8).

9.1.1.4 Justification of the Number of Patients and Samples

Meaningful conclusions regarding the impact of drug exposure can only be drawn for those patients in whom the assays are performed. Accordingly, the plan is to measure serum pharmacokinetics in all six patients of the group 2. The low number was chosen considering the logistics of arranging for a study screening, consent, registration prior to the craniotomy, which may need to be performed on an urgent/emergent basis limiting the number of potentially eligible patients. This is an exploratory cohort with the primary goal to assess in vivo CSF and tumor penetration of the drug and to measure the proportion of cases with elevated DNA damage repair biomarkers. With a sample size of N=6, we will have 80% power to reject the null hypothesis of a true marker response rate of 40% at the 5% significant level if we observe zero patients with a marker response among the six.

9.1.1.5 Description of Biological Samples Required for Assay

Sample Collection Schedule

Plasma, CSF and tumor samples will be collected 2-4 hours after M6620 (VX-970, berzosertib) administration during the craniotomy procedure. Plasma samples will also be collected on both days of M6620 (VX-970, berzosertib) administration in week 1 of subsequent WBRT only at pre-infusion and 2h 50 min after start of M6620 (VX-970, berzosertib) infusion. Blood samples to be collected through a peripheral blood draw. Samples should be drawn from the opposite arm if infusion is a peripheral infusion.

Handling of Specimens

Blood samples: Collect blood samples in EDTA vacutainer tubes. Invert the tubes several times to mix blood with anticoagulant and place 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.

CSF and Tumor Tissue: CSF and tumor may be collected in cryovials. Document the exact start and stop times of each infusion and exact times of sample draws. CSF and tumor collected in cryovials should be stored at stored at -70 °C.

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

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). 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.

All specimens are to be shipped on Monday, Tuesday or Wednesday to:

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

9.1.2 pATR T1989, pCHK1 S345 and RAD51 multiplex

9.1.2.1 Hypothesis and Rationale

Hypothesis: M6620 (VX-970, berzosertib) is expected to inhibit ATR autophosphorylation which will impact expression of pATR T1989 (autophosphorylation site critical for ATR function), pCHK1 S345 (an additional marker of baseline replication stress and downstream ATR activity) and RAD51

(which plays a key role in the homologous recombination repair pathway) in brain metastases from NSCLC.

Rationale: Due to the extreme and unjustifiable risk of obtaining intra-cranial tumor biopsy prior to M6620 (VX-970, berzosertib) administration, this study will have a novel exploratory cohort (group 2) wherein a single dose of M6620 (VX-970, berzosertib) will be administered 2-4 hours prior to the planned craniotomy followed by obtaining tumor sample at the time of craniotomy. This will allow assessment of assess drug pharmacodynamic (PD) effect in vivo within the tumor and to correlate with the CSF and tumor penetration.

It is noted that a definite PD relationship through the measurement of pATR T1989, pCHK1 S345 and RAD51 foci without baseline estimate of their expression is difficult to establish. As an alternate, a parallel study at the PI's institution would be conducted wherein fresh tumor biopsies from 12 matched control patients who are scheduled to undergo a craniotomy but not accrued to the proposed study will be collected as a separate IRB approved study for assessments of pATR T1989, pCHK1 S345 and RAD51 multiplex foci. Expression of these markers will be compared with the data from 6 patients in the group 2 of the proposed study. The samples will be forwarded to the same central laboratories that will be performing study on the current protocol.. Depending on the evolving understanding of drug effects in combination with other chemotherapy agents or radiation, additional biomarkers may be added in future, pending approval and funding.

9.1.2.2 Assay Validity and Appropriateness for Study

pATR T1989, pCHK1 S345 and RAD51 levels will be measured by multiplex immunofluorescence assay. Details regarding the assay validity and appropriateness for the study will be made available once the sequencing core has been confirmed by the M6620 (VX-970, berzosertib) Project Team leadership.

9.1.2.3 Performance Site

Multiplex immunofluorescence assay will be performed in the laboratory of Dr Deborah Wilsker at PADIS, DCTD/NCI.

9.1.2.4 Justification of the Number of Patients and Specimens

Being an ancillary/exploratory study, meaningful conclusions regarding the impact of drug exposure can only be drawn for those patients in whom the assays are performed. Accordingly, the plan is to measure expression of these PD markers in all the 6 patients from group 2. As noted above in PK measurements for group 2, the low number was chosen considering the logistics of arranging for a study screening, consent, registration prior to the craniotomy, which may need to be performed on an urgent/emergent basis limiting the number of potentially eligible patients. Even if a definite PD-PK relationship is difficult to discern due to small patient number and the challenges as noted above, the mere observation of CSF and tumor penetration could also help direct efforts in other intra-cranial histologies including high-grade gliomas.

9.1.2.5 Description of Biological Samples Required for Assay

Baseline (pre-treatment) tumor tissue samples will be obtained by using archived samples or a fresh biopsy samples that will be obtained only as part of standard of care clinical process. Tumor samples will be collected 2-4 hours after M6620 (VX-970, berzosertib) administration during the craniotomy procedure. This will be performed on formalin-fixed, paraffin-embedded cell pellets. No additional biopsy will be done specifically for the correlative studies; there is no additional risk to the patient.

Information on handling and shipment of specimens will be made available once the sequencing core has been assigned by the M6620 (VX-970, berzosertib) Project Team leadership. Appropriate SOPs will be provided as an appendix.

10. STUDY CALENDAR

Pre-treatment tests and exams must be completed, eligibility confirmed and the patient registered within 6 weeks; baseline imaging evaluations are to be conducted within 4 weeks before the start of the study treatment. Study treatment should begin within 2 weeks after registration. Vital signs including performance status should be obtained 1 week prior to the start of study treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next dose of M6620 (VX-970, berzosertib).

Group 1:

	Pre-study	Week 1	Week 2	Week 3	End of Week 6 [4]	Follow Up Visits [g]	Off-Study [e]
Informed Consent	X						
Radiation Planning [1]	X						
WBRT		X [a]	X	X			
M6620 (VX-970, berzosertib)		V [b]	V	V			
Demographics	X						
Physical Exam [2]	X	X	X	X	X	X	X [e]
CBC with diff, platelets	X		X		X		
Serum chemistry [c]	X		X		X		
Serum or urine pregnancy test [3]	X						
ECG [5]	X						
Neurocognitive Testing [R]	X				X	X [h]	
Quality of Life evaluation [R]	X				X	X [h]	
Adverse event evaluation		X	X	X	X	X	X [e]
MRI [f]	X					X [d]	X [e]
Patient Steroid Diary [i]	X	X	X	X	X		

1. Radiation planning may be performed prior to study registration as per standard of care. Patients can receive WBRT at a community site/satellite location within the health system where the study is approved as long as the study agent is received at the site approved to dispense/administer the study drug, and patient can be monitored closely for toxicities and undergo necessary HVLT-R and FACT-BR testing.
2. Physical exam includes medical history, concurrent medications, vital signs (pulse, blood pressure, temperature), weight, performance status and at pre-treatment only, height.
3. Perform for females of child bearing potential only.
4. The end of week 6 is the DLT assessment period and has a window of ± 3 days.
5. Perform as clinically indicated

a. WBRT schedule as noted in the protocol, to be started on Day 0

b. M6620 (VX-970, berzosertib) dose and administration as assigned in the schedule of the dose-escalation schema. The first dose of M6620 (VX-970, berzosertib) is to start 18-30 hours after first fraction WBRT but before the second fraction of WBRT. It is recommended to keep as close to 24 hours gap as possible between the first fraction of radiation and the first dose of M6620 (VX-970, berzosertib). Record the time of administration of radiation and M6620 (VX-970, berzosertib). The second and subsequent doses of M6620 (VX-970, berzosertib) will be administered after the day's administration of radiation treatment with no specified time interval. The timing of radiation and M6620 (VX-970, berzosertib) will be strictly recorded and monitored by the data monitoring committee.
The study protocol will allow a Monday through Thursday start of WBRT, with M6620 (VX-970, berzosertib) administered as follows:
   - Monday or Thursday WBRT start: M6620 (VX-970, berzosertib) administered Tuesday and Friday
   - Tuesday WBRT start: M6620 (VX-970, berzosertib) administered Wednesday and Friday in week 1 followed by Tuesday and Friday from week 2 onwards
   - Wednesday WBRT start: M6620 (VX-970, berzosertib) administered Thursday in week 1 and then Monday and Thursday from week 2 onwards.

c. Comprehensive metabolic profile (liver function tests including total bilirubin, serum albumin, total protein, AST, ALT, alkaline phosphatase, BUN and serum creatinine) therapy.

d. Follow-up MRI at 6 months (± 2 weeks) from the completion of WBRT is required. As per institutional standard practices, MRIs are also recommended during follow-up visits every 2 months (± 1 week) for the first 6 months and every 3-4 months (± 2 weeks) for the next 6 months from the completion of WBRT.

e. To be performed only if feasible if the patient is removed from the study.

f. For patients accrued to dose level 3 and higher, please send anonymized pre- and post-treatment scans via FTP or hard copy CD to the study PI for central review of response (Section 11.1.7).

g. From the date of completion of WBRT, follow-up visits are performed every 2 months (± 1 week) for the first 6 months and are recommended every 3-4 months (± 2 weeks) for the

next 6 months then every 6 months (± 3 weeks) for the next one year. After the DLT assessment visit at the end of week 6, the clinic visits can be performed at an outside institution if appropriate clinical staff is available to complete adverse event, neurocognitive testing and QOL assessments. Neurocognitive testing may also be performed by the study team through videoconferencing, if feasible. After the first 6 months of follow up, clinic visits may be replaced by phone calls or videoconference or visits at an outside institution. Follow up notes or documentation of phone calls or videoconferences must be included in the study chart.

h. Neurocognitive and quality of life evaluation performed during follow-up visits every 2 months (± 1 week) for the first 6 months from the completion of WBRT (for patients without intracranial progression).

i. Patients must record steroid use from the time informed consent is signed throughout the DLT assessment period at the end of week 6 using the steroid medication dairy in Appendix D.

R. Research funded

Group 2:

	Pre-study	Pre-Cranio-tomy (Day 0)	Cranio-tomy (Day 0)	Week 2 [k]	Week 3	Week 4	Week 5	End of Week 8 [4]	Follow Up Visits [j]	Off-Study [e]
Informed Consent	X									
M6620 (VX-970, berzosertib)		A [a]			A [b]	A	A			
Craniotomy			X							
Radiation Planning [l]				X						
WBRT					X [b]	X	X			
Demographics	X									
Physical Exam [2]	X			X	X	X	X	X	X	X
CBC with diff, platelets	X			X		X		X		
Serum chemistry [c]	X			X		X		X		
Serum or urine pregnancy test [3]	X									
ECG [5]	X									
Neurocognitive Testing [R]	X							X	X [k]	X
Quality of life evaluation [R]	X							X	X [k]	X
Adverse event evaluation				X	X	X	X	X	X	X
MRI [h]	X								X [d]	X
Archived biopsy tissue sample [i]	X									
Fresh biopsy tissue sample			X							
Pk [R]			X [f]		X [g]					
Patient Steroid Diary [l]	X	X	X	X	X	X	X	X		

1. Radiation planning may be performed prior to study registration as per standard of care.
2. Physical exam includes medical history, concurrent medications, vital signs (pulse, blood pressure, temperature), weight, performance status and at pre-treatment only, height.
3. Perform for females of child bearing potential only.
4. The end of week 8 is the DLT assessment period and has a window of ± 3 days.
5. Perform as clinically indicated

a. First dose of M6620 (VX-970, berzosertib) to be administered at the identified RP2D, 2-4 hours prior to the craniotomy

b. WBRT to preferably start 10-20 days after surgery or as clinically indicated. M6620 (VX-970, berzosertib) is to be administered during WBRT at the identified RP2D. The first dose of M6620 (VX-970, berzosertib) is to start18-30 hours after first fraction WBRT but before the second fraction. It will be recommended to keep as close to 24 hours gap as possible between the first fraction of radiation and the first dose of M6620 (VX-970, berzosertib). The timing of radiation and M6620 (VX-970, berzosertib) will be strictly recorded and monitored by the data monitoring committee. See study calendar for group 1 for schedule of M6620 (VX-970, berzosertib) depending on the day of start of WBRT.

c. Comprehensive metabolic profile (liver function tests including total and direct bilirubin, serum albumin, total protein, AST, ALT and alkaline phosphatase; BUN and serum creatinine)

d. Follow up MRI at 6 months (± 2 weeks) from the completion of WBRT is required. As per institutional standard practices, MRIs are also recommended during follow-up visits every 2 months (± 1 week) for the first 6 months then every 3-4 months (± 2 weeks) for the next 6 months from the completion of WBRT.

e. To be performed only if feasible if the patient is removed from the study.

f. During the craniotomy procedure, tumor, plasma and CSF samples will be collected

g. Plasma samples will be collected for the first 2 doses of M6620 (VX-970, berzosertib) administered while on WBRT only. Collect samples at these timepoints: before the start of M6620 (VX-970, berzosertib) infusion and at 2h 50 min after start of M6620 (VX-970, berzosertib) infusion.

h. For patients who have a defined target lesion (other than the lesion surgically resected), please send anonymized pre- and post-treatment scans via FTP or hard copy CD to the study PI for central review of response (Section 11.1.7).

i. Confirm availability of archived/fresh tissue sample available from the non-craniotomy site and will have fresh tumor tissue available from the planned craniotomy.

j. From the date of completion of WBRT, follow-up visits performed every 2 months (± 1 week) for the first 6 months then every 3-4 months (± 2 weeks) for the next 6 months then

every 6 months (± 3 weeks) for the next one year. After DLT assessment visit, the clinic visits can be performed at an outside institution if appropriate clinical staff is available to complete adverse event, neurocognitive testing and QOL assessments. Neurocognitive testing may also be performed by the study team through videoconferencing, if feasible. After the first 6 months of follow-up, clinic visits may be replaced by phone calls or videoconference or visits at an outside institution. Follow up notes or documentation of phone calls or videoconferences must be included in the study chart.

k. Neurocognitive and quality of life evaluation performed during follow-up visits every 2 months (± 1 week) for the first 6 months from the completion of WBRT (for patients without intracranial progression) and M6620 (VX-970, berzosertib).

l. Patients must record steroid use from the time informed consent is signed throughout the DLT assessment period at the end of week 8 using the steroid medication dairy in Appendix D.

R. Research funded

10.1 Neurocognitive Evaluation

10.1.1 Hopkins Verbal Learning Test (HVLT-R)

The HVLT-R incorporates 6 different forms, helping to mitigate practice effects of repeated administrations. Each form includes 12 nouns (targets) for memorization with 4 words drawn from 3 semantic categories, which differ across the 6 forms. Patients will be asked to recall from the list of 12 targets for 3 consecutive trials (immediate recall), identify the 12 targets from a list of semantically related or unrelated items (immediate recognition), and recall the 12 targets after a 20-minute delay (delayed recall). Raw scores will be derived for total recall, delayed recall, retention (percentage retained), and a recognition discrimination index. Each patient will serve as his/her own control, as the difference in scores obtained at baseline and at pre-specified post-treatment intervals will be calculated. The HVLT-R is owned and copyright protected by Psychological Assessment Resources, Inc. (PAR). Electronic distribution of the HVLT is not currently permitted by PAR; please send an email to the study PI, Dr Mohindra, University of Maryland, to request a paper copy of the HVLT prior to enrolling any patients (or to get information regarding procuring institutional copies for the study). Future updates regarding electronic handling of these forms if allowed will be provided directly to the study teams, when available. Based on the copyright agreement with PAR, completed HVLT-R forms can be uploaded to NCI's secure, password protected online portal, iMedidata RAVE ("web portal"). The uploaded forms should contain the original copyright notice on the form. Access to the web portal shall be limited to authorized study personnel at the study site. Completed HVLT-R forms shall not be printed or downloaded from the web portal. Once uploaded to iMedidata RAVE, a hard copy of the completed HVLT-R forms should be mailed to the study PI.

Study personnel administering the HVLT must be previously credentialed in performing neurocognitive testing through existing mechanisms within cooperative groups including but not limited to participation in a prior NRG or Alliance or any other cooperative group/multi-institutional study. The PI may also approve other measures as applicable. Email a copy of the credential to the study PI, Dr Mohindra, at the University of Maryland. This requirement is necessary before any patients can be enrolled into the study at the site, see Site Registration, section 4.2.2. These assessments can be performed at an outside institution if appropriate research staff (credentialed and registered as a study team member prior to the evaluations) is available to complete adverse event and neurocognitive evaluation.

Scoring of HVLT-R

1. HVLT-R Delayed Recall
   Patient scores on the HVLT-R delayed recall section have an integer range from 0 to 12 with lower scores indicating declining cognitive function. The score is the number of words a patient can recall from a list of 12 words. The change in score from baseline to 2-, 4- and 6- months ranges from - 12 to 12. Change scores from 1 to 12 indicate declining cognitive function. A change score of 0 indicates preserved cognitive function. Change scores from -1 to -12 indicate improved

cognitive function and are not expected.

2. HVLT-R Free Recall
   Patient scores on the HVLT-R free recall section have an integer range from 0 to 36 with lower scores indicating declining cognitive function. The score is the number of words a patient can recall from a list of 12 words in three trials.

3. HVLT-R Delayed Recognition
   Patient scores on the HVLT-R delayed recognition section have an integer range from -12 to 12 with lower scores indicating declining cognitive function. The score is the number of correctly identified words from the list of 12 words minus the number of incorrectly identified words from the list of 12 words.

10.2 Functional Assessment of Cancer Therapy with Brain Subscale (FACT-BR) for Quality of Life (QOL)

10.2.1 The FACT-BR

The FACT-BR is a multidimensional, self-report QOL instrument specifically designed and validated for use with brain malignancy patients. It is written at the 4th grade reading level and can be completed in 5 to 10 minutes with little or no assistance in patients who are not neurologically incapacitated. It measures quality of life related to symptoms or problems across 5 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and concerns relevant to patients with brain tumors (23 items). Items are rated on a five-point scale: 0-“not at all”, 1- “a little bit”, 2-“somewhat”, 3-“quite a bit” and 4-“very much”. The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale. Patient scores on the FACT-Br will range from 0 to 92 with lower scores indicating declining quality of life. FACT-BR is self-administered and does not require precertification. It has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at: **http://www.facit.org/facitorg/questionnaires**. The assessments will be scored centrally by a blinded reviewer to avoid potential bias. The self-report of quality of life can be completed by the patient or the examiner and does not require pre-certification.

Scoring of FACT-BR Assessments
The change scores from pretreatment from baseline to 2, 4 and 6 months will be estimated. A mean difference of 5 points represents a clinically meaningful change (CMC). A difference of less than 5 will not be considered meaningful, even if it has statistical significance.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of M6620 (VX-970, berzosertib) 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 noted below. For the purposes of this study, patients should be evaluated at baseline and at 6 months (± 2 week) from the completion of WBRT. As guided by institutional practices, MRIs are also recommended during follow-up visits every 2 months (± 1 week) for the first 6 months and every 3-4 months (± 2 weeks) for the next 6 months from the completion of WBRT.

All patients accrued in group 1 (except the first three dose-levels) will be included in the imaging objective. Based on the EWOC dose algorithm, patients accrued in the cohorts beyond the dose level 3, are anticipated to be treated at a dose very close to the final RP2D. Thus, patients will likely receive effective or near-effective doses and hence, heterogeneity in response due to sub-optimal dose is avoided.

Patients in the group 2 who have defined target lesions (other than the lesion surgically resected) will also be included in the imaging objective.

11.1 Antitumor Effect – Intracranial Metastases

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).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one bi-weekly dose of M6620 (VX-970, berzosertib), 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 1st week of M6620 (VX-970, berzosertib) 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 bi-weekly dose of M6620 (VX-970, berzosertib), 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 ≥ 10 mm (≥ 1

cm) with MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm [< 1 cm] are considered non-measurable disease.

Target lesions. All measurable lesions up to a maximum of 3 lesions will 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 intracranial metastases, 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. Bidimensional product for each of the 1-3 largest brain metastases will be identified at baseline. The bidimensional product is defined as the largest dimension multiplied by the second largest dimension that is perpendicular to it (the largest dimension). This value will be recorded on the baseline form and every subsequent follow-up form. The appearance (yes/no) of any new brain metastases will be recorded on all follow-up forms. A sum of the bidimensional product for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. Volume of the three target lesions will also be estimated by segmentation of the lesions; using auto-segmentation software with appropriate manual editing or manual delineation by the same investigator(s) when auto-segmentation is not feasible. For consistency in measurements, MRI data for all patients (baseline and follow up) from other participating institutions will be collected and analyzed at the PI's institution under the supervision of the Radiology Co-chairs.

Non-target lesions. All other lesions including any measurable lesions over and above the 3 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 target lesion at baseline and during follow-up.

Conventional MRI. MRI-scan based response evaluation is based on the assumption that

MRI slice thickness is 5 mm (0.5 cm) or less. If MRI scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness.

It is recommended that MRI sequences be followed per the consensus recommendations as detailed in the article: "Consensus recommendations for standardized brain tumor imaging protocol in clinical trials. Benjamin M. Ellingson *et al.* Neuro Oncol. 2015 Sep; 17(9):1188-98. doi: 10.1093/neuonc/nov095. Epub 2015 Aug 5."

Please contact the study PI or the radiology co-investigators with any questions.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Patients will undergo gadolinium contrast-enhanced brain MRI prior to the study entry (within 4 weeks of start of therapy), and prior to the start of SRS or systemic therapy or at 2 months post-WBRT (whichever is earlier). Thereafter, MRI will be done every 2 months after WBRT completion for the first 6 months, and every 3 months after WBRT completion for the next 6 months.

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a greater than a 50% decrease in the sum of the bidimensional product of target lesions, taking as reference the baseline measurement.

Progressive Disease (PD): At least a 25% increase in the sum of the bidimensional product of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). For lesions < 1cm in maximum diameter, a minimum increase of 50% of perpendicular bidimensional treatment area will be necessary to score as progression. This caveat is included to account for potential variability in measurement, which will be most susceptible to proportionate errors at smaller sizes. (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.

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

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

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

11.1.4.3 Evaluation of 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
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-CR/Non-PD	No	PR
SD	Non-CR/Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

* 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*
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

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

The date at which CNS progression is identified will be used to calculate the intra-cranial PFS. Survival will be measured from the date of start of treatment to time of progression or death, whichever occurs first. Deaths due to non-neurological causes will be censored.

11.1.7 Response Review

All responses will be reviewed by the radiology investigator of the study at the study's completion to allow simultaneous review of the patients' files and radiological images. Raw data from baseline and follow up MRI will be obtained from the participating institutions for volumetric, perfusion and diffusion-based response assessments. Sites should send anonymized pre- and post-treatment scans via FTP or as a hard copy CD to the study PI, Dr. Mohindra, at the University of Maryland as listed on the title page. The scans and data will be stored in HIPAA compliant secure servers within the Department of Radiology. Each patient will be identified only with the patient number assigned by the study.

11.2 Other Response Parameters (Optional)

In addition to morphological criteria noted above, the current study will also assess changes in magnetic susceptibility (T2-Dynamic Susceptibility Contrast Enhanced MRI, DSC-MRI) that provides information about the perfusion characteristics of the tumoral micro-environment. The most robust and widely used parameter derived from DSC-MRI is rCBV (relative Cerebral Blood Volume). Additionally, measurement of the Apparent Diffusion Coefficient (ADC) of water molecules through Diffusion MRI will provide information about tumor characteristics

such as cellularity, which may not be readily estimated by conventional MR imaging methods [41,42]. Specific details of a standard protocol DSC-MRI and standard diffusion weighted imaging protocol may be found in Appendix E. The published literature regarding these novel end-points is described in section 2.7.

Correlative Objective (Name of Correlate, Lead PI and Site)	Imaging Technique	Organ(s) Scanned and Timing of Scans	M/O
MRI contrast morphological assessment, perfusion and DWI imaging PIs: Prashant Raghavan/Rao Gullapalli	MRI	Brain. See Study Calendar for Timing of scans	Optional MRI protocol attached (Appendix E)

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

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

All decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, during this phase 1 study, 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.

12.2 Data Reporting

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

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

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

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

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

12.1.1 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.

12.1.2 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.

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

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

12.4 Collaborative Agreements Language

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

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

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

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

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial

by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase 1 dose escalation trial in patients with brain metastases NSCLC to determine the recommended phase 2 dose (RP2D) of twice weekly i.v. M6620 (VX-970, berzosertib) administered concurrent with conventionally fractionated WBRT.

13.1.1 Primary Endpoint

Dose-limiting toxicity defined as any grade 3 or more non-hematological toxicity requiring more than 5-day interruption in therapy or any grade 4 or higher hematological toxicity that is attributable to the M6620 (VX-970, berzosertib) and/or WBRT.

Study population. All patients experiencing a DLT will be retained in the study population irrespective of what proportion of the planned dose was actually administered to that patient. Patients who have to stop treatment because of patient withdrawal, disease progression or any other reason unrelated to treatment-related toxicity will be withdrawn from the analysis group and will be replaced by another patient enrolled at the same dose level.

13.1.2 Secondary Endpoints

1. Incidence of delayed neurological toxicity at 2, 4 and 6-months post-completion of WBRT (for patients without intracranial progression) including:
    a. Delayed-recall through HVLT-R
    b. Quality of life as measured by the FACT-BR.

2. Radiological RR at 6 months based on morphological criteria described in section 11.1.4. All patients accrued in group 1 (except the first three dose-levels) will be included in the imaging objective.

3. Intracranial 6-month PFS.

13.1.3 Exploratory Endpoints

Group 1 for patients accrued beyond dose-level 3: Changes in DSC-MRI) perfusion, mean ADC measurements in DWI

Group 2:

a. Pharmacokinetic measurements: Intra-operative blood and CSF M6620 (VX-970, berzosertib) levels and craniotomy tumor specimen M6620 (VX-970, berzosertib) concentration
b. Biomarker (Pharmacodynamic) end-point: Percentage pATR-Thr1989, pCHK1 S345 and RAD51 multiplex in post-M6620 (VX-970, berzosertib) administration intra-cranial tumor tissue specimen
c. MRI end-points (For patients with identifiable target lesion, other than the resected lesion): Changes in DSC-MRI perfusion, mean ADC measurements in

DWI

13.2 Sample Size/Accrual Rate

13.2.1 Group 1 Dose Escalation

Three patients will be accrued at each dose level in this group. Attribution of potential DLTs to the drug/radiation combination will be called through weekly electronic communication or teleconference among the radiation/medical oncology study chairs, participating institutional investigators, study statistician and/or treating physician. The computation of the dose to be administered to each cohort of 3 patients and the 90% highest posterior density credible interval estimate of the RP2D will be carried out by the study statisticians using the EWOC Version 3.1 software [60,61]. The prior distribution of RP2D is selected as a uniform distribution on the interval between the minimum and maximum dose levels and the toxicity-dose (or tolerance) function is chosen as a two parameter logistic dose-response function with $\beta_1>0$ i.e. a positive dose-response relationship, or to put it differently, the probability of a DLT is a monotonically increasing function of dose. The feasibility bound, α, i.e. the expected proportion of patients treated at doses above the maximum tolerated dose (MTD) has been selected at 0.35 based on extensive simulations and discussion with the clinical investigators. The probability of experiencing a DLT at the minimum dose is $\rho_0=0.10$, see section 5.1.1.1. For logistic reasons the minimum dose increment/decrement was selected at 10 mg.

Upon completion of accrual, the RP2D will be estimated as the median of the marginal posterior distribution of the RP2D. A maximum of 40 patients will be enrolled in this protocol. If the convergence toward the RP2D is unexpectedly slow, accrual will be halted and the dose-response data will be analyzed and published once the maximum sample size is reached. Comprehensive simulation studies of the trial design operating characteristics under a broader range of assumptions regarding the true value of the RP2D have been conducted, examples are shown in the table below.

α	MTD	Est. MTD	Bias	RMSE	%DLTs	Trial size	# trials	Rel. RMSE*
0.35	70	69.9	-0.06	6.14	32	40	500	0.09
0.35	100	99.9	-0.09	15.4	30	40	500	0.15
0.35	200	201	0.93	45.1	29	40	500	0.23
0.35	350	350	-0.05	84.4	25	40	500	0.24
0.35	500	446	-54	117.1	22	40	500	0.23
0.35	700	575	-125	148.4	16	40	500	0.21

*All simulations were performed with a minimum dose of 50 mg and a maximum dose of 800 mg. The incidence of DLTs at the minimum dose was $\rho_0=0.1$ and the incidence at the MTD was $\theta=0.25$. α is the feasibility bound, see text for more details. The yellow highlighted fields mark a sample size of n=40. *The relative MSE equals the MSE divided by the MTD.*

With a feasibility bound of α=0.25, bias (defined as the mean estimate of the MTD in the simulated data sets minus the 'true' MTD used in the simulation) becomes an issue even at relatively low MTDs. Increasing α to 0.35 reduces the bias for dose up to 333 mg x2 per week, except for very small sample sizes. At dose levels close to the maximum dose of 800 mg, there is some bias, but this remains a reasonably small proportion of the total MTD. A sample size of 40 patients was chosen as providing good relative precision of the MTD, with relative Root Mean Square Errors (RMSE) in the range from 0.09 to 0.24 depending on the steepness of the dose-response curve. The overall safety of the escalation scheme is mirrored in the %DLT's observed in the total cohort of 40 patients in the simulation studies. This ranges from 16% to 32%, in good concordance with the clinically acceptable level of 25% DLTs at the MTD.

13.2.2 Early Stopping and Slow Convergence

Five scenarios deserve special mention.

i) The EWOC algorithm will not test dose levels below the defined minimum dose 50 mg x 2 per week. If the starting dose turns out to be too toxic, i.e. 2/3 or 3/3 DLTs observed, accrual will continue at a dose level -1 of 25 mg x 2 per week using a Pocock type boundary for continual assessment of toxicity, see table below.

No. of Patients, n	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***
Boundary, b_n	-	-	3	4	4	5	5	5	6

If the number of DLTs is equal to or exceeds b_n out of n evaluable patients, further accrual is stopped, and the results of the trial will be published. The probability of crossing the boundary is at most 5% when the rate of DLTs is equal to 25%, our acceptable rate of DLTs. If the boundary is NOT crossed in the first 9 patients at dose level -1, the IDMC will decide whether level -1 is the RP2D or whether further accrual is recommended at dose level 1.

ii) In case 1/3 DLTs are observed at Level 1, the EWOC algorithm will include a further 3 patients at the same dose level. However, if there are 0/3 DLTs at the first levels tested, EQOC will increase the dose rapidly. To protect the safety of research subjects, the dose at any dose level, n, will not be more than a two times that of the previous level, n-1. In case on no DLTs at all, the escalation will then go through the dose levels, 50, 100, 200, 400, 800 mg with 3 patients per level. As soon as DLTs are observed, the next level will generally be that selected by the EWOC algorithm.

iii) Accrual will be stopped and the data will be analyzed and published if the relative width from the lower bound of the Bayesian 90% credible interval to the estimated RP2D is less than 20%. This early stopping rule could be activated if the dose-response relationship is unexpectedly steep.

iv) Alternatively, if 9 patients have been enrolled at three dose levels without a change in dose varying by more than ±10 mg, the IDMC will be tasked with deciding whether accrual should be stopped. This decision will be made considering also the estimate from ii) above. Also in this case, RP2D will be estimated as the median of the marginal posterior distribution of the RP2D.

v) If the convergence toward the RP2D is unexpectedly slow, i.e. the dose-response relationship is very shallow, accrual will be halted and the dose-response data will be analyzed and published once the maximum sample size of 40 patients is reached.

Late neurotoxicity will be reviewed by the independent DSMB who will be charged with considering cessation of the trial if the long term (6 months) grade 3 symptomatic neurotoxicity is >20%. A formal stopping rule will not be defined, mainly due to the lack of good clinical data to build on.

13.2.3 Group 2 (Correlative Pre-Craniotomy Cohort)

Six patients will be accrued in this group. The low number was chosen considering the logistics of arranging for a study screening, consent, registration prior to the craniotomy, which may need to be performed on an urgent/emergent basis limiting the number of potentially eligible patients. This is an exploratory cohort with the primary goal to assess in vivo CSF and tumor penetration of the drug and to measure the proportion of cases with elevated DNA damage repair biomarkers. With a sample size of N=6, we will have a “proof of principle” of a PD effect if at least 2 PD responses are seen among the 6 patients. This allows rejection of the null hypothesis of no PD response at a significance level of .02-.03, allowing for a 4-5% false positive rate for individual biopsies. It yields 77% power to detect a 40% PD response rate and 89% power to detect a 50% rate. The proportion of responders for various biomarkers will be reported.

No formal hypothesis will be tested in relation to the parallel cohort of 12 craniotomy cases without M6620 (VX-970, berzosertib) (see 2.6.3) and the 6 patients in Group 2, but distributions of biomarkers will summarized in box-and-whiskers plots and be compared using the Mann-Whitney test.

13.2.4 Accrual Rate and Study Duration

The anticipated accrual rate is two to six evaluable patients per month. Therefore, the accrual period for this study is expected to be approximately 18 months. Analysis for DLTs will be done regularly through the course of study duration, since this will be an integral component for the estimation of next dose level through the EWOC

design. The final analysis of secondary end-points can begin approximately 2 years after the trial begins, i.e. as soon as the last patient has been off treatment for 6 months.

13.2.5 Inclusion of Women and Minorities

13.2.5.1 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

13.2.5.2 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

13.2.5.3 The geographical region served by University of Maryland has a population that includes approximately 46% minorities. Based on prior studies involving similar disease sites, we expect about 26% of patients will be classified as minorities by race and about 43% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

PLANNED ENROLLMENT REPORT

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	7	0	0	10
White	15	16	1	2	34
More Than One Race	0	0	0	0	0
Total	19	24	1	2	46

13.3 Stratification Factors

None.

13.4 Analysis of Secondary and Exploratory Endpoints

Because of the non-randomized nature of the phase-I trial, all analyses of secondary end-points will be exploratory. Since this is a first-in-class drug that has never been tested in combination with WBRT (or radiation at any other body site) in humans, there is no estimate of the potential positive and negative effects of the combination. The results from these exploratory analyses will help determine the statistical power calculations for a future randomized comparison. All treatment effect and toxicity endpoints will be reported separately from analyses including all cases vs. evaluable patients only. We will give a full account of all dose modifications or treatment interruptions that occurred during the trial.

13.4.1. Incidence of events will be expressed as proportions with exact 95% confidence limits.

13.4.2. For end-points that are being compared from pre-treatment baseline (e.g. delayed-recall, FACT-BR score, changes in DSC-MRI perfusion or ADC measurements, pharmacodynamic biomarker assessments), descriptive statistics of the actual change scores will also be provided. The median change score and quartiles will be reported. Where relevant the proportion of patients experiencing a clinically significant change in score will be reported with 95% confidence limits.

13.4.3 Kaplan-Meier estimates of 6 month intracranial PFS (icPFS) and 12 month overall survival (OS) will be calculated. For estimation of icPFS, patients alive without intracranial progression at last follow-up will be censored at the date of the last radiologic assessment whereas intracranial progression or death will be scored as events. The icPFS estimates at 2, 4, and 6 months with their standard error of the estimate will be reported. For calculation of OS, patients alive at last follow-up will be censored. An exploratory Cox regression analysis with M6620 (VX-970, berzosertib) dose as a covariate will be performed if judged reasonable in view of our sample size.

REFERENCES

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 2004;22:2865-2872.
2. DeAngelis LM, Posner JB. Intracranial metastases. New York: Oxford University Press; 2009.
3. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Current oncology reports* 2012;14:48-54.
4. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494-500.
5. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998;280:1485-1489.
6. Scott C, Suh J, Stea B, Nabid A, Hackman J. Improved survival, quality of life, and quality-adjusted survival in breast cancer patients treated with efaproxiral (Efaproxyn) plus whole-brain radiation therapy for brain metastases. Am J Clin Oncol 2007;30:580-587.
7. Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, Kunkler I, Caudrelier JM, Eisenberg PD, Meerwaldt J, Siemers R, Carrie C, Gaspar LE, Curran W, Phan SC, Miller RA, Renschler MF. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. J Clin Oncol 2004;22:157-165.
8. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L, Mueller RP. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011;29:134-141.
9. Brown PD, Asher AL, Ballman KV, Farace E, Cerhan JH, Anderson SK, Carrero XW, Barker FG, Deming RL, Burri S, Menard C, Chung C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Jaeckle KA. NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. ASCO Annual Meeting. Chicago. 2015.
10. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. J Clin Oncol 2007;25:1260-1266.
11. Mehta MP, Shapiro WR, Phan SC, Gervais R, Carrie C, Chabot P, Patchell RA, Glantz MJ, Recht L, Langer C, Sur RK, Roa WH, Mahe MA, Fortin A, Nieder C, Meyers CA, Smith JA, Miller RA, Renschler MF. Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients

with brain metastases: results of a phase III trial. Int J Radiat Oncol Biol Phys 2009;73:1069-1076.

12. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, Bhatt A, Jensen AW, Brown PD, Shih H, Kirkpatrick J, Schwer A, Gaspar LE, Fiveash JB, Chiang V, Knisely J, Sperduto CM, Mehta M. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010;77:655-661.
13. Qin H, Pan F, Li J, Zhang X, Liang H, Ruan Z. Whole brain radiotherapy plus concurrent chemotherapy in non-small cell lung cancer patients with brain metastases: a meta-analysis. PloS one 2014;9:e111475.
14. Lee SM, Lewanski CR, Counsell N, Ottensmeier C, Bates A, Patel N, Wadsworth C, Ngai Y, Hackshaw A, Faivre-Finn C. Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases. J Natl Cancer Inst 2014;106.
15. Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, Morcos PN, Lee RM, Garcia L, Yu L, Boisserie F, Di Laurenzio L, Golding S, Sato J, Yokoyama S, Tanaka T, Ou SH. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. The Lancet Oncology 2014;15:1119-1128.
16. Fokas E, Prevo R, Hammond EM, Brunner TB, McKenna WG, Muschel RJ. Targeting ATR in DNA damage response and cancer therapeutics. Cancer Treat Rev 2014;40:109-117.
17. Weber AM, Ryan AJ. ATM and ATR as therapeutic targets in cancer. Pharmacol Ther 2015;149:124-138.
18. Zeman MK, Cimprich KA. Causes and consequences of replication stress. Nature cell biology 2014;16:2-9.
19. Pitts TM, Davis SL, Eckhardt SG, Bradshaw-Pierce EL. Targeting nuclear kinases in cancer: development of cell cycle kinase inhibitors. Pharmacol Ther 2014;142:258-269.
20. Yan S, Sorrell M, Berman Z. Functional interplay between ATM/ATR-mediated DNA damage response and DNA repair pathways in oxidative stress. Cell Mol Life Sci 2014;71:3951-3967.
21. Dickson MA, Schwartz GK. Development of cell-cycle inhibitors for cancer therapy. Current oncology 2009;16:36-43.
22. Reaper PM, Griffiths MR, Long JM, Charrier JD, Maccormick S, Charlton PA, Golec JM, Pollard JR. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nature chemical biology 2011;7:428-430.
23. Fokas E, Prevo R, Pollard JR, Reaper PM, Charlton PA, Cornelissen B, Vallis KA, Hammond EM, Olcina MM, Gillies McKenna W, Muschel RJ, Brunner TB. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. Cell Death and Disease 2012;3:e441.

24. Hall AB, Newsome D, Wang Y, Boucher DM, Eustace B, Gu Y, Hare B, Johnson MA, Milton S, Murphy CE, Takemoto D, Tolman C, Wood M, Charlton P, Charrier JD, Furey B, Golec J, Reaper PM, Pollard JR. Potentiation of tumor responses to DNA damaging therapy by the selective ATR inhibitor M6620 (VX-970, berzosertib). Oncotarget 2014;5:5674-5685.

25. Kuo LJ, Yang LX. Gamma-H2AX - a novel biomarker for DNA double-strand breaks. In Vivo 2008;22:305-309.

26. White D, Rafalska-Metcalf IU, Ivanov AV, Corsinotti A, Peng H, Lee SC, Trono D, Janicki SM, Rauscher FJ, 3rd. The ATM substrate KAP1 controls DNA repair in heterochromatin: regulation by HP1 proteins and serine 473/824 phosphorylation. Molecular cancer research : MCR 2012;10:401-414.

27. Suh JH, Stea B, Nabid A, Kresl JJ, Fortin A, Mercier JP, Senzer N, Chang EL, Boyd AP, Cagnoni PJ, Shaw E. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. J Clin Oncol 2006;24:106-114.

28. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ, Jr. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665-1672.

29. Viani GA, Manta GB, Fonseca EC, De Fendi LI, Afonso SL, Stefano EJ. Whole brain radiotherapy with radiosensitizer for brain metastases. J Exp Clin Cancer Res 2009;28:1.

30. Eich M, Roos WP, Nikolova T, Kaina B. Contribution of ATM and ATR to the resistance of glioblastoma and malignant melanoma cells to the methylating anticancer drug temozolomide. Molecular cancer therapeutics 2013;12:2529-2540.

31. Lin NU, Lee EQ, Aoyama H, Barani IJ, Baumert BG, Brown PD, Camidge DR, Chang SM, Dancey J, Gaspar LE, Harris GJ, Hodi FS, Kalkanis SN, Lamborn KR, Linskey ME, Macdonald DR, Margolin K, Mehta MP, Schiff D, Soffietti R, Suh JH, van den Bent MJ, Vogelbaum MA, Wefel JS, Wen PY, Response Assessment in Neuro-Oncology g. Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group. The Lancet Oncology 2013;14:e396-406.

32. Lin NU, Wefel JS, Lee EQ, Schiff D, van den Bent MJ, Soffietti R, Suh JH, Vogelbaum MA, Mehta MP, Dancey J, Linskey ME, Camidge DR, Aoyama H, Brown PD, Chang SM, Kalkanis SN, Barani IJ, Baumert BG, Gaspar LE, Hodi FS, Macdonald DR, Wen PY, Response Assessment in Neuro-Oncology g. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. The Lancet Oncology 2013;14:e407-416.

33. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, Bendszus M, Brown PD, Camidge DR, Chang SM, Dancey J, de Vries EG, Gaspar LE, Harris GJ, Hodi FS, Kalkanis SN, Linskey ME, Macdonald DR, Margolin K, Mehta MP, Schiff D, Soffietti R, Suh JH, van den Bent MJ, Vogelbaum MA, Wen PY, Response Assessment in Neuro-Oncology g. Response assessment criteria for brain metastases: proposal from the RANO

group. The Lancet Oncology 2015;16:e270-278.

34. Cha S. Update on brain tumor imaging: from anatomy to physiology. AJNR Am J Neuroradiol 2006;27:475-487.
35. Weber MA, Thilmann C, Lichy MP, Gunther M, Delorme S, Zuna I, Bongers A, Schad LR, Debus J, Kauczor HU, Essig M, Schlemmer HP. Assessment of irradiated brain metastases by means of arterial spin-labeling and dynamic susceptibility-weighted contrast-enhanced perfusion MRI: initial results. Invest Radiol 2004;39:277-287.
36. Hoefnagels FW, Lagerwaard FJ, Sanchez E, Haasbeek CJ, Knol DL, Slotman BJ, Vandertop WP. Radiological progression of cerebral metastases after radiosurgery: assessment of perfusion MRI for differentiating between necrosis and recurrence. J Neurol 2009;256:878-887.
37. Mitsuya K, Nakasu Y, Horiguchi S, Harada H, Nishimura T, Bando E, Okawa H, Furukawa Y, Hirai T, Endo M. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. J Neurooncol 2010;99:81-88.
38. Chiang IC, Kuo YT, Lu CY, Yeung KW, Lin WC, Sheu FO, Liu GC. Distinction between high-grade gliomas and solitary metastases using peritumoral 3-T magnetic resonance spectroscopy, diffusion, and perfusion imagings. Neuroradiology 2004;46:619-627.
39. Gasparetto EL, Pawlak MA, Patel SH, Huse J, Woo JH, Krejza J, Rosenfeld MR, O'Rourke DM, Lustig R, Melhem ER, Wolf RL. Posttreatment recurrence of malignant brain neoplasm: accuracy of relative cerebral blood volume fraction in discriminating low from high malignant histologic volume fraction. Radiology 2009;250:887-896.
40. Barajas RF, Chang JS, Sneed PK, Segal MR, McDermott MW, Cha S. Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. AJNR Am J Neuroradiol 2009;30:367-372.
41. Jakubovic R, Sahgal A, Soliman H, Milwid R, Zhang L, Eilaghi A, Aviv RI. Magnetic resonance imaging-based tumour perfusion parameters are biomarkers predicting response after radiation to brain metastases. Clin Oncol (R Coll Radiol) 2014;26:704-712.
42. Jakubovic R, Sahgal A, Ruschin M, Pejovic-Milic A, Milwid R, Aviv RI. Non Tumor Perfusion Changes Following Stereotactic Radiosurgery to Brain Metastases. Technology in cancer research & treatment 2015;14:497-503.
43. Hayashida Y, Hirai T, Morishita S, Kitajima M, Murakami R, Korogi Y, Makino K, Nakamura H, Ikushima I, Yamura M, Kochi M, Kuratsu JI, Yamashita Y. Diffusion-weighted imaging of metastatic brain tumors: comparison with histologic type and tumor cellularity. AJNR Am J Neuroradiol 2006;27:1419-1425.
44. Nadal Desbarats L, Herlidou S, de Marco G, Gondry-Jouet C, Le Gars D, Deramond H, Idy-Peretti I. Differential MRI diagnosis between brain abscesses and necrotic or cystic brain tumors using the apparent diffusion coefficient and normalized diffusion-weighted images. Magn Reson Imaging 2003;21:645-650.

45. Meyer HJ, Fiedler E, Kornhuber M, Spielmann RP, Surov A. Comparison of diffusion-weighted imaging findings in brain metastases of different origin. Clin Imaging 2015;39:965-969.

46. Provenzale JM, Mukundan S, Barboriak DP. Diffusion-weighted and perfusion MR imaging for brain tumor characterization and assessment of treatment response. Radiology 2006;239:632-649.

47. Tomura N, Narita K, Izumi J, Suzuki A, Anbai A, Otani T, Sakuma I, Takahashi S, Mizoi K, Watarai J. Diffusion changes in a tumor and peritumoral tissue after stereotactic irradiation for brain tumors: possible prediction of treatment response. J Comput Assist Tomogr 2006;30:496-500.

48. Huang CF, Chou HH, Tu HT, Yang MS, Lee JK, Lin LY. Diffusion magnetic resonance imaging as an evaluation of the response of brain metastases treated by stereotactic radiosurgery. Surg Neurol 2008;69:62-68; discussion 68.

49. Mahmood F, Johannesen HH, Geertsen P, Opheim GF, Hansen RH. The effect of region of interest strategies on apparent diffusion coefficient assessment in patients treated with palliative radiation therapy to brain metastases. Acta Oncol 2015;54:1529-1534.

50. Zakaria R, Das K, Radon M, Bhojak M, Rudland PR, Sluming V, Jenkinson MD. Diffusion-weighted MRI characteristics of the cerebral metastasis to brain boundary predicts patient outcomes. BMC medical imaging 2014;14:26.

51. Essig M, Waschkies M, Wenz F, Debus J, Hentrich HR, Knopp MV. Assessment of brain metastases with dynamic susceptibility-weighted contrast-enhanced MR imaging: initial results. Radiology 2003;228:193-199.

52. Lee CC, Wintermark M, Xu Z, Yen CP, Schlesinger D, Sheehan JP. Application of diffusion-weighted magnetic resonance imaging to predict the intracranial metastatic tumor response to gamma knife radiosurgery. J Neurooncol 2014;118:351-361.

53. Sperduto PW, Shanley R, Luo X, Andrews D, Werner-Wasik M, Valicenti R, Bahary JP, Souhami L, Won M, Mehta M. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). Int J Radiat Oncol Biol Phys 2014;90:526-531.

54. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. Neurology 1989;39:789-796.

55. Regine WF, Schmitt FA, Scott CB, Dearth C, Patchell RA, Nichols RC, Jr., Gore EM, Franklin RL, 3rd, Suh JH, Mehta MP. Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: results of Radiation Therapy Oncology Group trial BR-0018. Int J Radiat Oncol Biol Phys 2004;58:1346-1352.

56. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial.

The Lancet Oncology 2009;10:1037-1044.

57. Welzel G, Fleckenstein K, Mai SK, Hermann B, Kraus-Tiefenbacher U, Wenz F. Acute neurocognitive impairment during cranial radiation therapy in patients with intracranial tumors. Strahlenther Onkol 2008;184:647-654.

58. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, Rowley H, Kundapur V, DeNittis A, Greenspoon JN, Konski AA, Bauman GS, Shah S, Shi W, Wendland M, Kachnic L, Mehta MP. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol 2014;32:3810-3816.

59. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998;17:1103-1120.

60. Xu Z, Tighiourart M, Rogatko A. EWOC 2.0: interactive software for dose escalation in cancer phase I clinical trials. Drug Inf J 2007;41:221-228.

61. Rogatko A, Tighiouart M, Cook-Wiens G, Quanlin L. Escalation with overdose control. User's guide. Version 3.1.2012. In: Editor, editor^editors. Book Escalation with overdose control. User's guide. Version 3.1.2012; 2012.

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: GRADED PROGNOSTIC ASSESSMENT (GPA) SCORE FOR BRAIN METASTASES FON NON-SMALL CELL LUNG CANCER (NSCLC)

Prognostic Factor	**GPA Scoring Criteria**			
	0	0.5	1.0	
Age (Years)	>60	50-60	<50	
KPS	<70	70-80	90-100	
Extracranial Metastases	Present		Absent	
Number of Brain Metastases	>3	2-3	1	
Sum Total				Total:

Median Overall Survival (months) by GPA:

GPA	Median Survival
0-1.0	3.0 months
1.5-2.0	5.5 months
2.5-3.0	9.4 months
3.5-4.0	14.8 months

From: Sperduto, P. Kased, N., and Roberge, D. *et al.* Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012 **30**(4): p. 419-25.

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

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

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

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

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

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

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

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

Version *Apr2021*

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

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

APPENDIX D: PATIENT DEXAMETHASONE DIARY

Please take the dexamethasone tablets as instructed by your doctor. Record the date and total number of dexamethasone tablets you took for each day. If you have any comments, please record them in the comments column. If you should make a mistake on the diary, draw through the mistake with one line and then sign your initials. Thank you.

Day	***Date***	***Number of Dexamethasone Tablets Taken***	***Dose of Dexamethasone Tablets Taken***	***Comments***
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				

20				
21				

Patient's Signature_____ Date _____

APPENDIX E: MRI PROTOCOL

MRI sequences will be followed per the consensus recommendations as detailed in the article: Consensus recommendations for standardized brain tumor imaging protocol in clinical trials. Benjamin M. Ellingson *et al.* Neuro Oncol. 2015 Sep; 17(9):1188-98. doi: 10.1093/neuonc/nov095. Epub 2015 Aug 5.

There is no defined consensus describing the perfusion sequences. Attached below are the perfusion sequences for 1.5T and 3T MRI used at the University of Maryland, Baltimore. Though defined for the Siemens machine, the parameters noted here are vendor non-specific and should be reproduced at the participating institution. Please contact the PI or the Radiology Co-Investigator on the protocol with any questions.

1.5 T MRI, Perfusion Sequence, University of Maryland, Baltimore

\\USER\BRAIN\BRAIN\PRIMARY BRAIN TUMOR\PERFUSION (1.5 -T)
TA: 2:08 PAT: 2 Voxel size: 1.9×1.9×5.0 mm Rel. SNR: 1.00 SIEMENS: ep2d_fid

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	Off
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	On
Start measurements	single

Routine	
Slice group 1	
Slices	21
Dist. factor	20 %
Position	L5.8 A43.8 H0.3
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	240 mm
FoV phase	100.0 %
Slice thickness	5.0 mm
TR	2000 ms
TE	35 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	HE2,4

Contrast	
MTC	Off
Flip angle	90 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	60
Delay in TR	0 ms
Multiple series	Off

Resolution	
Base resolution	128
Phase resolution	100 %
Phase partial Fourier	7/8
Interpolation	On
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Matrix Coil Mode	Auto (Triple)
Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	Off
Elliptical filter	Off
Hamming	Off

Geometry	
Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System	
Body	Off
HE2	On
HE4	On
SP4	Off
SP2	Off
SP8	Off
SP6	Off
SP3	Off
SP1	Off
SP7	Off
SP5	Off
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Sum of Squares
AutoAlign	---
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	L5.8 A43.8 H0.3
Orientation	Transversal
Rotation	0.00 deg
R >> L	240 mm
A >> P	240 mm
F >> H	125 mm

Physio	
1st Signal/Mode	None

Sequence	
Introduction	On
Bandwidth	952 Hz/Px
Free echo spacing	Off
Echo spacing	1.13 ms
EPI factor	128
RF pulse type	Normal
Gradient mode	Fast

3T MRI: Perfusion Sequence, University of Maryland, Baltimore

\\USER\BRAIN\BRAIN\TUMOR WITH PERFUSION\PERFUSION (3T)

TA: 1:31 PAT: 2 Voxel size: 1.7×1.7×5.0 mm Rel. SNR: 1.00 SIEMENS: ep2d_fid

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	On
Start measurement without further preparation	On
Wait for user to start	On
Start measurements	single

Routine

Slice group 1	
Slices	19
Dist. factor	20 %
Position	R5.4 A7.4 H11.4
Orientation	T > C-17.1 > S-0.1
Phase enc. dir.	A >> P
Rotation	0.63 deg
Phase oversampling	0 %
FoV read	220 mm
FoV phase	100.0 %
Slice thickness	5.0 mm
TR	1400 ms
TE	32 ms
Averages	1
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP

Contrast

MTC	Off
Flip angle	90 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	60
Delay in TR	0 ms
Multiple series	Off

Resolution

Base resolution	128
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	On
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	40
Matrix Coil Mode	CP
Reference scan mode	Separate
Distortion Corr.	Off
Unfiltered images	Off
Prescan Normalize	On
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Hamming	Off

Geometry

Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System

Body	Off
HEP	On
HEA	On
SP4	Off
SP2	Off
SP8	Off
SP6	Off
SP3	Off
SP1	Off
SP7	Off
SP5	Off
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Sum of Squares
AutoAlign	---
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	R5.4 A7.4 H11.4
Orientation	T > C-17.1 > S-0.1
Rotation	0.63 deg
R >> L	220 mm
A >> P	220 mm
F >> H	113 mm

Physio

1st Signal/Mode	None

Perf

GBP	On
PBP	On
TTP	On
Original images	On
Starting ignore meas	2

Sequence

Introduction	On
Bandwidth	1346 Hz/Px
Free echo spacing	Off
Echo spacing	0.83 ms
EPI factor	128
RF pulse type	Normal
Gradient mode	Fast*