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A Phase I/II Trial of Topotecan with VX-970 (M6620), an ATR Kinase Inhibitor in Small Cell Cancers

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Investigational Agent:

Drug Name:	VX-970 (M6620)
IND Number:	126291
Sponsor:	Center for Cancer Research, National Cancer Institute
Manufacturer:	EMD Serono

Commercial Agent: topotecan

PRÉCIS

Background:

- Small cell lung cancer (SCLC) is an aggressive cancer with a poor prognosis.
- Although highly responsive to chemotherapy initially, SCLC relapses quickly and becomes refractory to treatment within a few months.
- There is only one FDA approved treatment for patients with relapsed SCLC after first-line chemotherapy: topotecan, which inhibits religation of topoisomerase I-mediated single-strand DNA breaks leading to lethal double-strand DNA breaks.
- The inability to destroy residual SCLC cells despite initial chemosensitivity suggests the existence of a highly effective DNA damage response network.
- SCLC is characterized by high replication stress (RB1 inactivation, MYC and CCNE1 activation) and defective ATM-p53 signaling pathway, which cause an excessive reliance on ATR for survival following DNA damage.
- We hypothesize that a combination of ATR kinase inhibition with DNA damaging agents will provide an attractive synthetically lethal therapeutic option for SCLC.
- VX-970 (M6620) is a potent and selective kinase inhibitor of ATR, and in vitro data support the hypothesis that ATR inhibition can improve SCLC responses to DNA damaging agents.

Primary objectives:

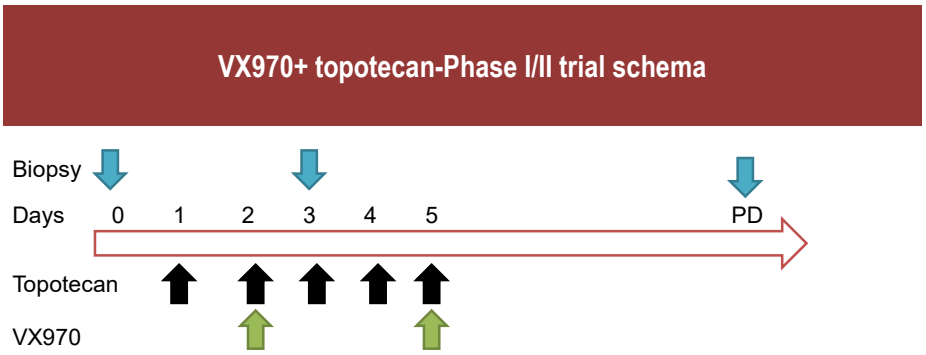
- Phase I: To identify the maximum tolerated dose (MTD) of topotecan in combination with VX-970 (M6620).
- Phase II: To assess the efficacy with respect to clinical response rate of a combination of topotecan and VX-970 (M6620) in previously treated patients with SCLC and extra-pulmonary small cell carcinomas.

Eligibility:

- Both Phase I and II: Subjects must be ≥ 18 years of age and have a performance status (ECOG) ≤ 2. Subjects must not have received chemotherapy, or undergone major surgery within 2 weeks and radiotherapy within 24 hours prior to enrollment.
- Phase I: Subjects with histologically confirmed SCLC, NSCLC, ovarian cancer, cervical cancer, and neuroendocrine cancers, and at least one prior chemotherapy. Patients with other histologies will be allowed if no standard treatment options exist. Patients with evaluable, but not measurable disease will be eligible for Phase I.
- Phase II: Subjects with histological confirmation of SCLC and extra-pulmonary small cell carcinomas. Patients with both platinum-sensitive and platinum-refractory disease will be eligible. Patients must have measurable disease to be eligible for Phase II.

Design:

- Participants meeting inclusion and exclusion criteria will receive topotecan and VX-970 (M6620) administered every 21 days (1 cycle), until disease progression or development of intolerable side effects.
- Blood and hair samples will be collected at multiple time points during cycle 1 (pre-treatment on day 1, post treatment on days 2, and 3) for PD analyses.
- Blood for pharmacokinetic analysis, which is optional, may be collected before and after topotecan and VX-970 (M6620) on days 1 and 2 during cycle 1, if feasible with regard to scheduling.
- Tumor biopsies, which are optional, will be obtained at baseline, during the first treatment cycle (approximately 15 hours after the first dose of VX-970 (M6620) on day 3) and at disease progression except for subjects at the first dose level.
- PBMCs will be collected cycle 1 days 1 and 2 (pre-treatment), post-treatment on cycle 1 day 5 (optional) and cycle 2 day 1 (pre-treatment).
- Participants at the first dose level will undergo biopsies on day 3 prior to third dose of topotecan.
- Participants will be monitored weekly during the first cycle by clinic visit and basic labs.
- Toxicity will be graded according to CTCAE version 4.0, and tumor assessments will be made using CT scans (chest, abdomen and pelvis) at baseline and after every 2 cycles according to RECIST version 1.1.
- Follow-up for survival will be carried out every 3 months.



Dose level	Topotecan- mg/m2 IV (days 1-5)	VX970- mg/m2 IV
1	1	140 on day 5
2	1	140 on days 2,5
3	1.25	140 on days 2,5
4	1.25	210 on days 2,5
21 day cycles		

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

- Phase I: To identify the maximum tolerated dose (MTD) of topotecan in combination with VX-970 (M6620).
- Phase II: To assess the efficacy with respect to clinical response rate of a combination of topotecan and VX-970 (M6620) in previously treated patients with SCLC and extra-pulmonary small cell carcinomas.

1.1.2 Secondary Objectives

- To determine the progression-free survival (PFS) and overall survival (OS) of a combination of topotecan and VX-970 (M6620) in SCLC.
- To assess safety and tolerability of a combination of topotecan and VX-970 (M6620).
- To identify pharmacodynamic markers of response.
- To assess duration of response to the combination in both platinum sensitive and refractory patients.

1.1.3 Exploratory Objectives

- To characterize gene expression and mutations which predict response and changes associated with development of chemoresistance.
- To characterize circulating tumor cells (CTC) and circulating DNA bearing tumor-specific mutations.
- To characterize the immunomodulatory effects of DNA damage-inducing cytotoxic therapy.

1.2 BACKGROUND AND RATIONALE

Small cell lung cancer (SCLC) is an aggressive cancer with a poor prognosis. Annually there are approximately 34,000 new cases of SCLC in the United States. SCLC is characterized by rapid doubling time, high growth fraction and early and widespread metastatic involvement. Approximately two thirds of patients present with extensive-stage disease with tumor involvement of contralateral lung, liver, adrenal glands, brain, bones and/or bone marrow.

The primary treatment modality for patients with extensive-stage SCLC (ES-SCLC) is systemic chemotherapy consisting of platinum and etoposide followed by prophylactic cranial irradiation in patients with a response [1]. Although highly responsive to chemotherapy initially, SCLC relapses quickly and becomes refractory to treatment within a few months. The median survival for patients with ES-SCLC ranges from 8 to 13 months. Less than 5% of patients survive two years and less than 2% are alive five years after diagnosis. There is only one FDA approved treatment for patients with relapsed SCLC after first-line chemotherapy: topotecan, which inhibits religation of topoisomerase I-mediated single-strand DNA breaks leading to lethal

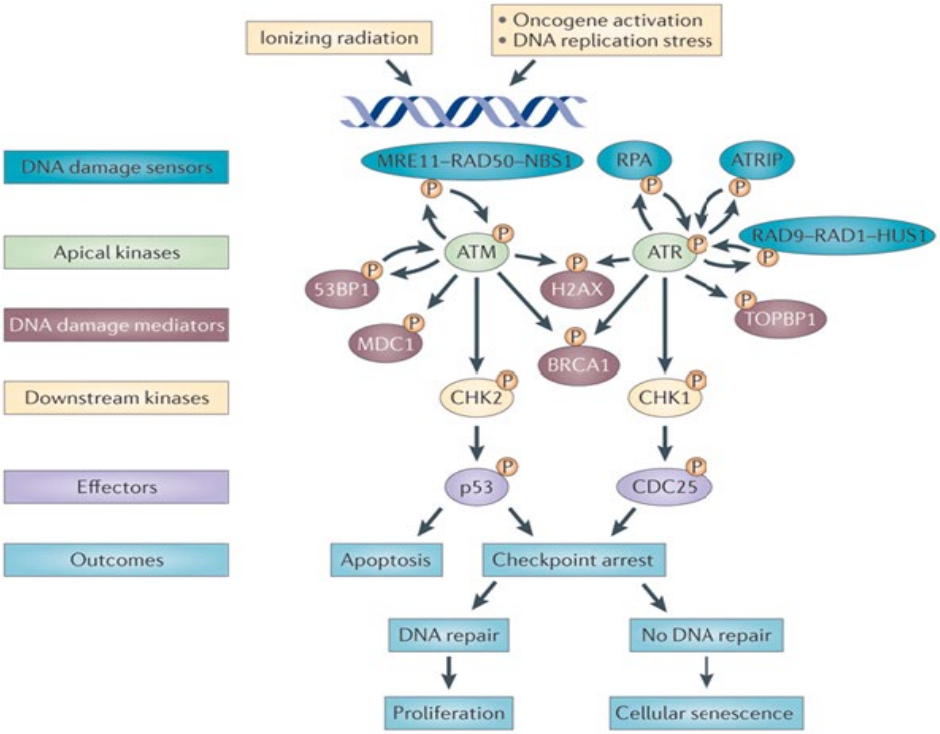
double-strand DNA breaks. In patients with disease that is refractory to or relapsed after first-line chemotherapy, the median survival ranges from 2 to 6 months.

The standard treatment of ES-SCLC today reflects the prevailing state-of-the-art from the early 1980s. Among the many strategies that have been evaluated unsuccessfully over the last three decades are dose-dense chemotherapy regimens, addition of a third drug to standard two drug chemotherapies, alternating non-cross resistant chemotherapy regimens, maintenance therapy and more recently targeted therapies. Not unexpectedly, the outcomes for these patients have also largely remained poor. Clearly there is a critical need for newer therapeutic approaches for patients with SCLC and patients with extrapulmonary small cell carcinomas.

DNA damaging agents are the cornerstone of SCLC treatment, yet they provide only transient benefit. The inability to destroy residual SCLC cells despite initial chemosensitivity suggests the existence of a highly effective DNA damage response network. The DNA damage response pathways may therefore have a role in chemotherapy resistance in SCLC.

The DNA damage response pathway is depicted in **Figure 1**[2]. Apical kinases ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) are recruited via DNA damage sensors. In addition to single-stranded DNA breaks, ATR responds to genotoxic stress that is caused by DNA replication stress, caused by oncogenes. Eventually via phosporylation of a number of mediators, DNA damage response signaling converges on downstream effectors such as p53 and the cell division cycle 25 (CDC25) phosphatases.

Figure 1. DNA damage response pathway



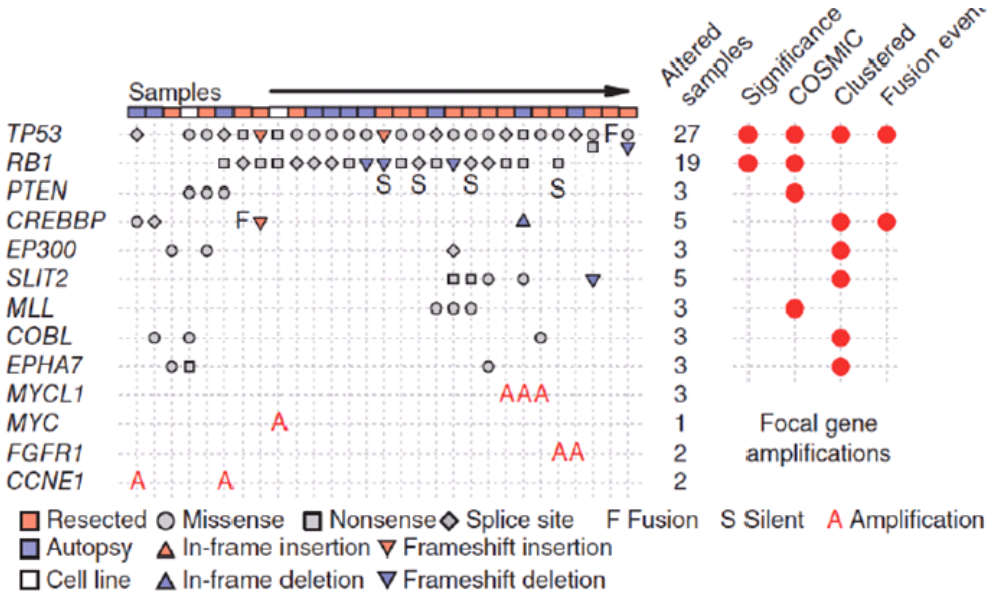
Despite the importance of the DNA damage response for cell survival following DNA damage, defects in this pathway are common in cancer. For example, loss of ATM signaling capacity is frequently observed, either through loss of expression of ATM itself, or through defects in

upstream regulators and downstream effectors such as p53. Although they appear to confer a growth advantage, defects in ATM signaling cause an excessive reliance on remaining DNA damage response components, such as ATR, and thus provide an 'Achilles' heel' that could be targeted by drugs.

Most frequently mutated genes in SCLC are shown in **Figure 2** [3]. SCLC is remarkable for the high frequency of alterations in the ATM pathway. SCLC is characterized by high frequency of alterations in p53, a key downstream effector of the ATM pathway. Furthermore, SCLC is also characterized by the widespread expression of oncogenes that drive replication stress. This combination of high replication stress and defective ATM-p53 signaling pathway may provide a strong reliance on ATR for survival following DNA damage in SCLC.

Consequently, the combination of an inhibitor of ATR kinase with DNA damaging agents could be an attractive synthetic lethal therapeutic option for SCLC.

Figure 2. Most frequently mutated genes in SCLC



Durable clinical response from synthetic lethal interactions between the two DNA damage response pathways was recently reported in a patient with small cell cancer of the urothelial tract [4]. The patient with metastatic disease was treated with a combination of irinotecan and an experimental CHK1 inhibitor resulting in a complete response which was ongoing at three years at the time of the report. Functional studies revealed somatic mutations that impaired Mre11 function, which likely resulted in synthetically lethal activity of the combination of CHK1 inhibitor with a DNA damaging agent.

1.2.1 Hypothesis

The inability to destroy residual SCLC cells despite initial chemo-sensitivity to DNA damaging agents suggests the existence of a highly effective DNA damage response. SCLC is characterized by high replication stress (RB1 inactivation, MYC and CCNE1 activation) and defective ATM-p53 signaling pathway. SCLC therefore relies strongly on ATR for survival following DNA damage. We hypothesize that a combination of ATR kinase inhibition with DNA damaging agents will provide an attractive synthetically lethal therapeutic option for SCLC.

1.2.2 VX-970 (M6620)

VX-970 (M6620) is an adenosine triphosphate (ATP)-competitive, highly potent, tightly binding inhibitor of ATR with an inhibition constant (Ki) <300 pM (range <0.1 to 0.3 nM) that blocks ATR activity in cells, with a concentration associated with 50% inhibition (IC50) of 20 nM [5]. VX-970 (M6620) is very selective in inhibiting ATR; it showed >100-fold selectivity against the closely related DDR proteins, ATM (Ki 38 ± 30 nM [mean ± SD]) and DNA-dependent protein kinase (Ki >4000 nM). ATR and ATM have overlapping functions in the cellular response to dsDNA breaks and replication stress. Accordingly, cells with defects in ATM signaling, for example from loss of p53, have been shown to be especially sensitive to ATR inhibition by VX-970 (M6620). Minimal inhibitory activity was observed against a large panel of unrelated protein kinases, with 278 of 291 kinases tested having a measured IC50 of >400 nM and a measured Ki >200 nM, corresponding to >500-fold selectivity for ATR. For 12 of the remaining 13 kinases, the Ki was >15 nM (>50- fold selectivity for ATR) and ≥8 nM for one of the 13 kinases, Flt4 kinase (>25-fold selectivity for ATR).

1.2.2.1 Pre-Clinical Toxicology and Compound Safety

Good laboratory practices (GLP) toxicology studies have been performed with both oral and intravenous formulations of VX-970 (M6620). VX-970 (M6620) administered orally to dogs for 28 days at doses of 30, 60, and 90 mg/kg/day, given every other day, resulted in cachexia and overall deterioration of animals requiring early termination at all doses; however, all findings showed evidence of reversibility after termination of dosing. Pathologic findings included periportal vacuolation, bile duct hyperplasia, and cholestasis in the liver and testicular degeneration, as well as effects on peripheral blood cell populations. Oral administration of VX-970 (M6620) to rats for 28 days at doses of 50, 150, and 300 mg/kg/day, every other day, resulted in mortality in 9 of 50 animals at the highest dose only with decreases in red blood cell mass and testicular atrophy. The animal-to-human exposure multiple calculated on a weekly area under the concentration versus time curve (AUC) basis at the MTD (150 mg/kg/day) was 107-fold to the weekly projected human exposure at the estimated efficacious dose [6].

VX-970 (M6620) was administered to dogs intravenously for 28 days at dosages of 7.5, 15, and 20 mg/kg/day on a twice a week schedule. No mortality or adverse clinical findings were observed; decreases in hematocrit, and increases in reticulocytes, and transient elevations in alanine aminotransferase (ALT) were noted at the 20 mg/kg/day dose, but there were no correlative findings on pathologic examination. The highest non-severely toxic dose (HNSTD) was determined to be 20 mg/kg/day. The animal-to-human exposure coverage for safety was calculated based upon weekly AUC parameter estimates at the HNSTD (19-fold the weekly projected human exposure at the efficacious dose). VX-970 (M6620) was administered intravenously twice weekly to rats for 28 days at doses of 5, 10, and 30 mg/kg/day. At the highest dose, animals had mild increases in reticulocytes and platelets, and there was mortality in 4 of 48 animals. Animals at the 10- and 30-mg/kg/day dose exhibited chronic phlebitis and animals at all doses exhibited extramedullary hematopoiesis in the spleen. The severely toxic dose in 10% of animals (STD_{10}) was considered to be 30 mg/kg/day. The animal-to-human exposure multiple calculated on a weekly AUC basis at the STD_{10} was 13-fold to the weekly projected human exposure at the estimated efficacious dose [6].

1.2.2.2 Clinical Studies

At this time, the following studies of VX970 are ongoing: 1) VX12 970 001 (Study 001), Phase 1 First in human 2) VX13 970 002 (Study 002) Phase 1 3) 9771 16-C-0087 NCI 160087 ClinicalTrials.gov Identifier: NCT02723864 Phase I Study of Veliparib (ABT-888), an Oral PARP Inhibitor, and VX 970, an ATR Inhibitor, in Combination With Cisplatin in Patients With Refractory Solid Tumors 4) 9938 NCI-2015-01915 UPCI 15-164 ClinicalTrials.gov Identifier: NCT02595931 Phase I Clinical Trial of VX-970 in Combination With the Topoisomerase I Inhibitor Irinotecan in Patients With Advanced Solid Tumors 5) DF/HCC Protocol 16 322 NCI Protocol 9944 ClinicalTrials.gov Identifier: NCT02595892 Phase 2 Study of VX 970 (NSC# 780162) in Combination with Gemcitabine versus Gemcitabine Alone in Subjects with Platinum-Resistant Recurrent Ovarian or Primary Peritoneal Fallopian Tube Cancer 6) PhII 135 NCI Protocol 9947 ClinicalTrials.gov Identifier: NCT02567409 Phase 2 A Randomized Phase 2 Trial of Cisplatin/Gemcitabine with or without VX 970 in Metastatic Urothelial Carcinoma.

1.2.2.3 Clinical Safety

Single-agent Therapy

VX-970 (M6620) was administered as a single agent in the lead-in periods of Study 001 Parts A and B (doses of 18 mg/m^2 to 210 mg/m^2, lead-in periods of 7 to 21 days); during Study 002 Part A1 (once weekly, doses of 60 mg/m^2 to 480 mg/m^2) and Part A1 (twice weekly, doses of 240 mg/m^2); and during the single-agent phase of Study 002 Part C (doses of 240 mg/m^2).

VX-970 (M6620) was generally well tolerated as a single agent. There were no dose-limiting toxicities (DLTs), few adverse events (AEs) leading to study drug discontinuation, and 1 AE leading to death. Most subjects receiving single-agent VX-970 (M6620) had AEs. The System Organ Classes (SOCs) in which AEs occurred most frequently were Gastrointestinal Disorders and General Disorders and Administration Site Conditions. The most commonly occurring AE was nausea.

The SOCs in which serious adverse events (SAEs) occurred most frequently were Neoplasms Benign, Malignant, and Unspecified; Respiratory, Thoracic, and Mediastinal Disorders; and Gastrointestinal Disorders. SAEs that occurred in more than 1 subject receiving single-agent VX-970 (M6620) were metastases to central nervous system, malignant neoplasm progression, dyspnea, nausea, and blood creatinine increased. Most of the SAEs were assessed as not related to study drug.

Combination Therapy

VX-970 (M6620) + Gemcitabine

In Study 001 Part A1, 49 of 50 subjects (98.0%) had at least 1 AE. AEs of nausea, fatigue, alanine transaminase (ALT) increased, and anemia occurred in more than 50% of subjects. Twenty-four subjects (48.0%) had at least 1 SAE. The SAEs that occurred in more than 1 subject were pyrexia (6 subjects, 12.0%) and cellulitis, dehydration, musculoskeletal pain, thrombocytopenia, and vomiting (each in 2 subjects, 4.0%). Thirty-eight subjects (76.0%) had at least 1 Grade ≥3 AE. Grade ≥3 AEs that occurred in at least 10% of subjects were neutropenia, anemia, thrombocytopenia, ALT increased, and fatigue. DLTs occurred in 4 of 45 subjects (8.9%) in the DLT Evaluable Set and included ALT increased and aspartate transaminase (AST) increased, each in 2 subjects (4.4%) and blood alkaline phosphatase increased,

thrombocytopenia, and fatigue, each in 1 subject (2.2%). Nine subjects (18.0%) had AEs leading to study drug discontinuation. One subject (2.0%) had a fatal SAE of disease progression of NCSLC that was unrelated to either study drug.

In Study 001 Part C1, 31 of 33 subjects (93.9%) had at least 1 AE. The most common AEs were anemia (15 subjects, 45.5%) and fatigue (14 subjects, 42.4%). Seventeen subjects (51.5%) had at least 1 SAE. The SAEs that occurred in more than 1 subject were vomiting, fatigue, pneumonia, sepsis, and dyspnea (each in 2 subjects, 6.1%). Nineteen subjects (57.6%) had at least 1 Grade ≥3 AE. Grade ≥3 AEs that occurred in at least 10% of subjects were fatigue and neutropenia. Two subjects (6.1%) had AEs leading to study drug discontinuation, which included vomiting and fatigue, each in 1 subject. One subject (3.0%) had an AE leading to death (coded as abdominal pain).

VX-970 (M6620) + Cisplatin

In Study 001 Part B, 29 of 30 subjects (96.7%) had at least 1 AE, and the most common AE was nausea (15 subjects, 50.0%). Eleven subjects (36.7%) had at least 1 SAE. The SAEs that occurred in more than 1 subject were infusion-related reaction, ALT increased, and AST increased (each in 2 subjects, 6.7%). Twenty-one subjects (70.0%) had at least 1 Grade ≥3 AE. Grade ≥3 AEs that occurred in at least 10% of subjects were neutropenia and anemia. DLTs occurred in 2 of 29 subjects (6.9%) in the DLT Evaluable Set and included ALT increased and flushing, each in 1 subject. Six subjects (20.0%) had AEs leading to study drug discontinuation. There were no AEs leading to death.

In Study 001 Part C2, 34 of 35 subjects (97.1%) had at least 1 AE. AEs of nausea and fatigue occurred in more than 50% of subjects. Seven subjects (20.0%) had at least 1 SAE. The SAEs that occurred in more than 1 subject were vomiting (3 subjects, 8.6%) and nausea and pyrexia (each in 2 subjects, 5.7%). Eighteen subjects (51.4%) had at least 1 Grade ≥3 AE. Grade ≥3 AEs that occurred in at least 10% of subjects were neutropenia, anemia, and vomiting. Eight subjects (22.9%) had AEs leading to study drug discontinuation. There were no AEs leading to death.

In Study 001 Part C3, 2 subjects received VX-970 (M6620) in combination with cisplatin. Both subjects had at least 1 AE. The AEs that occurred in both subjects were constipation and fatigue. Neither subject had an SAE. One subject (50.0%) had 3 Grade ≥3 AEs, including 2 events of Grade 4 thrombocytopenia and 1 event of Grade 3 neutropenia. Neither subject had an AE leading to study drug discontinuation or to death.

VX-970 (M6620) + Carboplatin

In Study 002 Part B1, all 23 subjects (100%) had at least 1 AE. AEs of nausea and anemia occurred in more than 50% of subjects. Eight subjects (34.8%) had at least 1 SAE. The only SAE that occurred in more than 1 subject was pyrexia (3 subjects, 13.0%). Eleven subjects (47.8%) had at least 1 Grade ≥3 AE. Neutropenia was the only Grade ≥3 AE that occurred in at least 10% of subjects. DLTs occurred in 3 of 23 subjects (13.0%) in the DLT Evaluable Set and included febrile neutropenia, neutropenia, thrombocytopenia, hypersensitivity, and lower respiratory tract infection. Four subjects (17.4%) had AEs leading to study drug discontinuation. There were no AEs leading to death.

In Study 001 Part C3, 8 subjects (80.0%) had at least 1 AE, and the most common AEs were thrombocytopenia and fatigue (each in 4 subjects, 40.0%). Two subjects (20.0%) had at least

1 SAE; SAEs were superior vena cava syndrome and failure to thrive. Six subjects (60.0%) had at least 1 Grade ≥3 AE. The Grade ≥3 AEs that occurred in more than 1 subject were thrombocytopenia, neutropenia, anemia, and platelet count decreased. One subject (10.0%) had an AE leading to study drug discontinuation. There were no AEs leading to death.

In Study 002 Part C, all 11 subjects (100.0%) in the Combination Safety Set had at least 1 AE, and the most common AE was anemia (5 subjects, 45.5%). Five subjects (45.5)% had at least 1 SAE. The only SAE that occurred in more than 1 subject was thrombocytopenia (2 subjects, 18.2%). Seven subjects (63.6%) had at least 1 Grade ≥3 AE. Grade ≥3 AEs that occurred in more than 1 subject were thrombocytopenia (3 subjects, 27.3%) and neutropenia and anemia (each in 2 subjects, 18.2%). Four subjects (36.4%) had AEs leading to study drug discontinuation, and 1 subject (9.1%) had a fatal AE of bronchitis.

VX-970 (M6620) + Gemcitabine + Cisplatin

In Study 001 Part A2, all 8 subjects in the Combination Safety Set had at least 1 AE. AEs that occurred in more than 50% of subjects were fatigue, nausea, and neutropenia. Five subjects (62.5%) had at least 1 SAE, and no SAE occurred in more than 1 subject. All 8 subjects (100.0%) had at least 1 Grade ≥3 AE. The only Grade ≥3 AEs that occurred in more than 1 subject were neutropenia (5 subjects, 62.5%) and thrombocytopenia (3 subjects, 37.5%). Three subjects (37.5%) had DLTs, including neutropenia, febrile neutropenia, and thrombocytopenia. One subject had AEs leading to study drug discontinuation. No subject had a fatal AE.

VX-970 (M6620) + Carboplatin + Paclitaxel

In Study 002 Part B2, 8 of 9 subjects (88.9%) had at least 1 AE. AEs that occurred in more than 50% of subjects were neutropenia and fatigue. Two subjects (22.2%) had at least 1 SAE; SAEs were febrile neutropenia and thrombocytopenia. Seven subjects (77.8%) had at least 1 Grade ≥3 AE. Grade ≥3 AEs that occurred in more than 1 subject were neutropenia (6 subjects, 66.7%), anemia (3 subjects, 33.3%), and thrombocytopenia (2 subjects, 22.2%). One subject (11.1%) had a DLT of thrombocytopenia. Two subjects (22.2%) had AEs leading to study drug discontinuation, including neutropenia, thrombocytopenia, and drug hypersensitivity. No subject had a fatal AE.

1.2.2.4 Adverse Drug Reactions

After careful assessment, infusion-related reactions, nausea, and vomiting are considered adverse drug reactions (ADRs) for VX-970 (M6620), and myelosuppression events are considered ADRs for VX-970 (M6620) in combination with carboplatin.

Infusion-related reactions are common with IV administration of drugs used to treat cancer. These reactions occur during or shortly after administration of the drug, may be local and/or systemic, and are diverse.

Systemic infusion-related reactions to VX-970 (M6620) may include signs or symptoms such as pruritus, flushing, chills/rigors, urticaria/rash, headache, bronchospasm/dyspnea, and hypotension or hypertension, among others. Some systemic infusion-related reactions to VX-970 (M6620) have been serious, including those described as acute hypersensitivity reactions. Local infusion-related reactions to VX-970 (M6620), sometimes described as infusion site reactions, may include signs or symptoms such as infusion site erythema, swelling, or pain.

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

Myelosuppression AEs for subjects who received VX-970 (M6620) in combination with carboplatin have included neutropenia, thrombocytopenia, platelet count decreased, and febrile neutropenia.

1.2.3 Topotecan

Topotecan has been approved by the FDA for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy, small cell lung cancer sensitive disease after failure of first-line chemotherapy, and as a combination therapy with cisplatin for Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy. Topotecan is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single-strand breaks. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks. Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan.

1.2.4 Rationale

VX-970 (M6620) is a potent and selective kinase inhibitor of ATR. In vitro data support the hypothesis that ATR inhibition can improve SCLC responses to DNA damaging agents. Specifically, VX-970 (M6620) markedly sensitized SCLC cell lines, but not normal cells, to multiple DNA damaging drugs. In matched NSCLC cell lines differing only in p53 status, p53 loss of function, through deletion, influenced cell sensitivity to ATR inhibition [7, 8]. The Pommier lab has shown that VX-970 (M6620) potentiates the cytotoxicity of both camptothecins and the non-camptothecin LMP-400 [8]. In NSCLC and colon cancer models, VX-970 (M6620) enhanced the in vivo tumor response to a broad range of DNA damaging agents without additional toxicity.

Although our goal is to assess the activity of the combination primarily in SCLC, we propose to include NSCLC, neuroendocrine cancers, cervical and ovarian cancers in the phase I trial to expedite the determination of the MTD of the combination and to assess for any potential early signals of activity in these other tumors. Topotecan is an approved agent for previously treated cervical and ovarian cancers. Although not an approved treatment, topotecan has activity in NSCLC where a phase III trial has found that topotecan was not inferior to docetaxel [9]. Patients with other histologies will be allowed if no standard treatment options exist.

1.2.5 Topotecan plus VX-970 (M6620) Phase I summary

Between September 2016 and February 2017, 21 patients (DL1: 6; DL2: 6; DL3: 3; DL4: 6) were treated. M/F: 9/12, ECOG PS 1/2: 19/2, median age: 61 years (range 27-69), primary tumor: small cell 6 (small cell lung 5, small cell cervix 1), mesothelioma 4, non-small cell lung cancer, pancreatic, rectal neuroendocrine carcinoma 2 each, others 4), median prior lines of systemic therapies 3 (range 1-6). VX-970 (M6620) was generally well tolerated in combination

with topotecan with mainly Gr1-2 toxicities. One patient each at DL1, DL2 and DL4 had DLTs (Gr4 neutropenia > 7 days, Gr4 thrombocytopenia requiring transfusion, Gr3 elevation of AST/ALT; Gr4 thrombocytopenia requiring transfusion, Gr3 febrile neutropenia; Gr4 thrombocytopenia requiring transfusion). DL4 was determined to be the MTD. Gr 3/4 toxicities in ≥10% of patients included neutropenia (n=3/8), lymphopenia (n=7/2), anemia (9/0), thrombocytopenia (2/3), and leucopenia (8/2). Of 19 evaluable patients, 2 had partial responses, 8 had stable disease and 9 had progressive disease. Among 6 evaluable patients with small cell cancer, all of whom had platinum resistant or refractory disease, 1 patient had a partial response, 2 patients had prolonged stable disease (11 months and ongoing at 3 months). In summary, VX-970 (M6620) was generally well tolerated in combination with topotecan. The MTD of the combination was VX-970 (M6620) 210 mg/m2 on days 2 and 5 with topotecan 1.25 mg/m2 on days 1-5.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Both Phase I and Phase II:

2.1.1.1.1 Male and female subjects ≥ 18 years of age. Because no dosing adverse event data are currently available on the use of topotecan in combination with VX-970 (M6620) in subjects <18 years of age, children are excluded from this study, but will be eligible for future pediatrics trials.

2.1.1.1.2 ECOG performance status ≤2 (See **Appendix A**)

2.1.1.1.3 Patients must have measurable disease, per RECIST 1.1. See Section **6.2** for the evaluation of measurable disease. Subjects with evaluable, but not measurable disease will be eligible for Phase I.

2.1.1.1.4 Subjects must not have received chemotherapy, or undergone major surgery within 2 weeks and radiotherapy within 24 hours prior to enrollment.

2.1.1.1.5 Adequate organ functions

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count ≥ $1.5x10^9$/L
- Platelets ≥ $100x10^9$/L
- Total Bilirubin ≤ 2.0 mg/dL
- Transaminases ≤ 2 x ULN or if liver metastases were present, ≤ 3 x ULN
- Creatinine ≤ 1.5 mg/dL or creatinine clearance by Cockcroft-Gault formula ≥ 60 mL/min

2.1.1.1.6 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.1.7 The effects of VX-970 (M6620) on the developing human fetus are unknown. For this reason and because topotecan is known to be teratogenic, 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, during study participation and for 6 months after the last dose study therapy. 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.

2.1.1.2 Phase I:

2.1.1.2.1 Subjects with histologically confirmed SCLC, NSCLC, ovarian cancer, cervical cancer, and neuroendocrine cancers will be eligible. Pathological confirmation of diagnosis will be done at NCI Laboratory of Pathology. Patients with other histologies will be allowed if no standard treatment options exist.

2.1.1.2.2 At least one prior chemotherapy

2.1.1.2.3 NSCLC subjects with EGFR mutations or ALK translocations should have previously received appropriate FDA approved therapies in addition to prior chemotherapy

2.1.1.3 Phase II:

2.1.1.3.1 Histological confirmation of SCLC or extrapulmonary small cell cancer. Although NCI confirmation of pathology is not required prior to starting treatment, every effort will be made to obtain outside pathology to be reviewed by an NCI pathologist.

2.1.1.3.2 Subjects with both platinum-sensitive and platinum-refractory disease will be eligible

2.1.2 Exclusion Criteria

2.1.2.1 Subjects with tumor amenable to potentially curative therapy.

2.1.2.2 Subjects who are receiving any other investigational agents.

2.1.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to (study agent) or other agents used in study.

2.1.2.4 Subjects with symptomatic brain metastases will be excluded from trial secondary to poor prognosis. However, subjects who have had treatment for their brain metastasis and whose brain disease is stable without steroid therapy for 1 week or on physiologic doses of steroids may be enrolled.

2.1.2.5 Subjects requiring any medications or substances that are strong inhibitors or inducers of CYP3A during the course of the study are ineligible. Lists including strong inhibitors and inducers of CYP 3A4 are provided in **Appendix B** (Strong Inhibitors and Inducers of CYP3A).

2.1.2.6 Subjects with evidence of severe or uncontrolled systemic disease, or any concurrent condition, which could compromise participation in the study, including, but not limited to, active or uncontrolled infection, immune deficiencies, Hepatitis B, Hepatitis C, uncontrolled diabetes, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia, stroke/cerebrovascular accident within the past 6 months, or psychiatric illness/social situations which would jeopardize compliance with the protocol.

2.1.2.7 HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with VX-970 (M6620). In addition, these subjects are at increased risk of lethal infections when treated with marrow-suppressive therapy.

2.1.2.8 Pregnant women are excluded from this study because topotecan is a Class D agent with the potential for teratogenic or abortifacient effects and because the effects of VX-970 (M6620) on the developing human fetus are currently unknown. In addition, because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with topotecan or VX-970 (M6620), breastfeeding should be discontinued if the mother is treated with these agents.

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms.

2.2 SCREENING EVALUATION

Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols). Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Screening must be completed within 2 weeks (except viral markers screen that could be performed within 4 months) prior to enrolling subjects onto the protocol.

1. History and physical exam (including height, weight, and vital signs)
2. Blood tests (for organ function):
   - Complete blood count (CBC/Diff)
   - Acute care panel
   - Hepatic panel
   - Mineral panel
   - Prothrombin time (PT)
   - Partial thromboplastin time (PTT)
3. Viral Markers Protocol Screen (HBsAg, anti-HCV, anti-HIV)
4. Confirmation of diagnosis by the NCI Laboratory of Pathology (can be done prior to the two-week screening window) Note: NCI confirmation of pathology is not required prior to starting treatment, but every effort should be made to obtain outside pathology to be reviewed by an NCI pathologist.
5. CT scan of disease sites
6. Electrocardiogram (12 lead)

7. Urine or serum HCG for women of child-bearing potential (to be performed within 5 days prior to C1D1)

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here

2.4 TREATMENT ASSIGNMENT PROCEDURES

Cohorts

Number	Name	Description
1	*Phase I*	*Patients with measurable or evaluable SCLC, NSCLC, ovarian cancer, cervical cancer, and neuroendocrine cancer. Other histologies allowed if no standard treatment exists*
2	*Phase II (SCLC)*	*Patients with measurable SCLC.*
3	*Phase II (extrapulmonary small cell cancer)*	*Patients with measurable SCLC or extrapulmonary small cell cancer.*

Arms

Number	Name	Description
1	*Phase I*	*VX-970 (M6620) + topotecan at escalating doses*
2	*Phase II*	*VX-970 (M6620) + topotecan at MTD/RP2D*

Arm Assignment

Up to 24 subjects in cohort 1 will be directly assigned to arm 1.

Up to 25 subjects with Small Cell Lung Cancer and up to 15 subjects with extrapulmonary small cell cancers in cohorts 2 and 3 respectively will be directly assigned to arm 2.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a Phase I/II, open label clinical trial. The objectives of this study are to identify the maximum tolerated dose (MTD) of topotecan in combination with VX-970 (M6620) in a phase I trial, and to assess the efficacy with respect to clinical response rate of a combination of topotecan and VX-970 (M6620) in the second-line treatment of subjects with SCLC in a phase II trial. Participants meeting inclusion and exclusion criteria (Section **2.1**) will receive topotecan (on days 1-5) and VX-970 (M6620) (on day 5 or 2 and 5) administered every 21 days (1 cycle), either in the in-patient or out-patient setting, until disease progression or development of intolerable side effects. Subjects will be monitored weekly during the first cycle by basic labs (CBC with differential on days 8 and 15; chemistries- acute panel, hepatic panel, mineral panel and troponin on days 8 and 15). During the first cycle, basic labs may be performed at patient's

local physician and faxed to the research team. For the following cycles, subjects will be seen every 3 weeks. After study treatment, follow-up for survival will be carried out every 3 months.

Blood and hair samples will be collected at multiple time points during cycle 1 (pre-treatment, day on day 1, post treatment on days 2 and 3) for PD analyses. Tumor biopsies which are optional will be obtained at baseline, during the first treatment cycle (approximately 15 hours after the first dose of VX-970 (M6620) on day 3) and at disease progression except for subjects at the first dose level. Subjects at the first dose level will undergo biopsies on day 3 prior to third dose of topotecan.

3.1.1 Phase I: Dose Limiting Toxicity

Subjects will be monitored for DLTs during the first cycle. DLTs will be defined using the National Cancer Institute (NCI) CTCAE (Version 4).

A DLT is defined as related or possibly drug-related:

- Neutropenia Grade 4 for >7 days duration*
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)
- Infection (documented clinically or microbiologically) with Grades 3 or 4 neutropenia (absolute neutrophil count <1.0 x 10^9/L)
- Thrombocytopenia Grade 3:
    - associated with clinically significant bleeding
    - requiring platelet transfusion
- Thrombocytopenia Grade 4 for >7 days duration*
- Grades 3 or 4 toxicity to organs other than the bone marrow including Grades 3 and 4 biochemical AEs and DLTs, excluding the following:
    - Grade 3 nausea
    - Grade 3 vomiting in subjects who have not received optimal treatment with antiemetics
    - Grade 3 diarrhea in subjects who have not received optimal treatment with antidiarrheal
    - Grade 3 fatigue
    - Grades 3 or 4 mucositis in subjects who have not received optimal therapy for mucositis
- Death due to drug related adverse events
- Cardiac:
    - QTcF prolongation (any QTcF interval ≥500 msec or any change in QTcF interval ≥60 msec from baseline) on ECG, unless related to an electrolyte abnormality and prolongation resolves with correction of electrolyte abnormality

- Any of the following (CTCAE criteria): Grade 2 or greater ventricular arrhythmia (second or third degree atrioventricular (AV) block), severe sustained/symptomatic sinus bradycardia less than 45 beats per minute (bpm) or sinus tachycardia >120 bpm not due to other causes (e.g., fever), persistent supraventricular arrhythmia (e.g., uncontrolled/new atrial fibrillation, flutter, atrioventricular nodal tachycardia, etc.) lasting more than 24 hours, ventricular tachycardia defined as >9 beats in a row or any length of torsades de pointes (polymorphic ventricular tachycardia with long QTcF), or unexplained recurrent syncope
- Symptoms suggestive of congestive heart failure with confirmed Ejection Fraction (EF) <40% (by 2D-echocardiogram or Multiple Gated Acquisition [MUGA] scan) or a relative decrease >20% from historical assessment of EF performed within 12 months
- Troponin-T: level which is consistent with myocardial infarction

- Any drug related toxicity that causes interruption of treatment for >3 weeks (21 successive days). If a subject is deemed fit to restart treatment on Day 21then this is not a DLT.

*Note: In the event of a Grade 4 neutropenia or thrombocytopenia, a full blood count must be performed no more than 7 days after the onset of the event to determine if a DLT has occurred. The subject will be closely monitored until resolution to Grade 3 or less.

3.1.2 Phase I: Dose Escalation

The starting dose of VX-970 (M6620) is based on the safety information from the trial of single-agent VX-970 (M6620) and preliminary data from trials combining VX-970 (M6620) with gemcitabine, cisplatin or carboplatin. The study will follow a 3+3 design: dose will be escalated in cohorts of 3 patients with the individual dose of VX-970 (M6620) and topotecan increased in successive dose levels as outlined in the dose escalation table below. In case there is safety problem with the first dose, there will be a dose de-escalation to 105 mg/m2 of VX-970 (M6620) (25%), as indicated in the table below.

The MTD is the dose level at which no more than 1 of up to 6 subjects experience DLT during one cycle of treatment, and the dose below that at which at least 2 (of ≤6) subjects have DLT as a result of the drug. If a subject did not experience DLT and did not finish treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level.

Table 1. Dose Escalation Schedule

Dose Level	Topotecan – mg/m2 IV (days 1-5)	VX-970 (M6620) – mg/m2 IV
Level -1	1	105 on day 5
Level 1	1	140 on day 5
Level 2	1	140 on days 2,5
Level 3	1.25	140 on days 2,5

Level 4	1.25	210 on days 2,5
21 day cycles		

Dose escalation will follow the rules outlined in the Table below.

Table 2. Dose Escalation rules

Number of Subjects with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter up to 3 subjects at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
1 out of 3	Enter up to 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. At least 6 subjects must be entered at the recommended phase 2 dose.

3.1.3 Phase II

The study will initially enroll 16 evaluable subjects. If 2 or more of the first 16 subjects have a response, then accrual would continue to a total of 25 subjects. Subjects will be treated at the identified MTD.

3.2 DRUG ADMINISTRATION

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects. The drugs will be administered sequentially, with topotecan followed 15 minutes later by VX-970 (M6620).

3.2.1 VX-970 (M6620) Administration

VX-970 (M6620) will be supplied as 20 mg/mL VX-970 (M6620) to be diluted with 5% dextrose in water solution before intravenous infusion as detailed in section **13.1.12**.

An appropriate volume of concentrated drug product solution is diluted before use, according to the dose indicated in **Table 1**. Total dose is not to exceed 800 mg of VX-970 (M6620)/dose.

The dose of VX-970 (M6620) in dextrose in water solution will be infused intravenously over 60 minutes (+/- 10 minutes).

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

If any subject develops phlebitis or signs or symptoms of inflammation that may progress to phlebitis or which the subject cannot tolerate, standard measures should be employed to ameliorate these symptoms, including removal of the infusion catheter and resumption of infusion through a different vein. If any subject develops pruritus or evidence of allergic reaction, standard measures may be employed to ameliorate these symptoms or to prevent recurrence of these symptoms (e.g., premedication with acetaminophen 325 mg PO approximately 30 minutes before the infusion, 200 mg hydrocortisone intravenously approximately 60 minutes before infusion, and 25 mg diphenhydramine intravenously approximately 30 minutes before infusion; alternative antihistamine and steroid combinations may be considered, as long as not prohibited by protocol). If standard procedures to limit symptoms of injection site reaction or pruritus are insufficient, then the infusion time may be extended beyond 60 minutes, but no more than 90 minutes.

3.2.2 Topotecan Administration

Topotecan is a cytotoxic anticancer drug. Prepare topotecan under a vertical laminar flow hood while wearing gloves and protective clothing. If topotecan solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If topotecan contacts mucous membranes, flush thoroughly with water. Use procedures for proper handling and disposal of anticancer drugs.

Each 4-mg vial of topotecan is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration. Topotecan will be administered as an intravenous infusion over 30 minutes.

3.3 DOSE MODIFICATIONS

3.3.1 VX-970 (M6620) dose modification

No dose modifications of VX-970 (M6620) may be made during Cycle 1.

The dose of VX-970 (M6620) may be reduced other than in Cycle 1 for toxicity using the following guidelines depending on the toxicities (and drug deemed to be responsible for toxicity) observed:

1. For Grade 4 hematologic toxicity: The dose of VX-970 (M6620) will be reduced by 25%.

2. For Grade 3 non-hematologic toxicity (except disease related hyponatremia for which dose reduction will only be made for grade 4): The dose of VX-970 (M6620) will be reduced by 25%.

3. For Grade 4 non-hematologic toxicity: The dose of VX-970 (M6620) will be reduced by 50%.

Based on the criteria above, a maximum of 2 dose reductions will be permitted. If a grade 4 non-hematologic toxicity were to recur, treatment will be discontinued. Please see table below indicating VX-970 (M6620) dose reductions within each dose level.

Dose Level	Dosage Schedule		
	100%	75%	50%
1	140 mg/m^2 on Day 5	105 mg/m^2 on Day 5	70 mg/m^2 on Day 5
2 & 3	140 mg/m^2 per dose, Days 2 and 5	105 mg/m^2 per dose, Days 2 and 5	70 mg/m^2 per dose, Days 2 and 5
4	210 mg/m^2 per dose, Days 2 and 5	158 mg/m^2 per dose, Days 2 and 5	105 mg/m^2 per dose, Days 2 and 5
- 1	105 mg/m^2 on Day 5	79 mg/m^2 on Day 5	Exceeds 2 dose reductions

In addition, in case of Grade 3 or higher toxicity during any cycle beyond Cycle 1, treatment may be interrupted and may be resumed when all toxicities have returned to Grade 2 or less, at the discretion of the investigator. Treatment interruptions may occur for a maximum of 21 days.

Subjects who have a DLT for VX-970 (M6620) will continue on topotecan.

3.3.2 Topotecan dose modification

No dose modifications of topotecan may be made during cycle 1.

The dose of topotecan may be reduced other than in Cycle 1 for toxicity using the following guidelines depending on the toxicities (and drug deemed to be responsible for toxicity) observed, see **Table 3**. Topotecan dose reductions will be accomplished by decreasing the dose of topotecan for each of the 5 days.

To initiate subsequent cycles of topotecan the day 1 ANC should be >1500/mm3 and platelets >100,000/mm3. Treatment interruptions may occur for a maximum of 21 days.

Based on the below criteria, a maximum of 2 dose reductions will be permitted.

Table 3. Dose Adjustments

A. Dose adjustments for renal functions		
Creatinine clearance (Cockcroft-Gault formula)	Dose adjustment (% decrease in topotecan dose)	
	DL1 and 2	DL3 and 4
>60	no adjustment	no adjustment
40-59	-20%	-20%
20-39	-25%	-25%

<20	Discontinue	Discontinue

B. Dose adjustments for non-hematologic toxicities		
Non-hematologic toxicity	Dose adjustment (% decrease in topotecan dose)	
	DL1 and 2	DL3 and 4
Grades 1 and 2	no adjustment	no adjustment
Grades 3 and 4 (except grade 3 nausea)	-20%	-20%

C. Dose adjustments for hematologic toxicities		
Hematologic toxicity	Dose adjustment (topotecan mg/m2)	
	DL1 and 2	DL3 and 4
Grades 1 and 2	no adjustment	no adjustment
Grade 3 neutropenia persisting after day 21	-20%	-20%
Grade 4 thrombocytopenia or Grade 4 neutropenia with fever or infection or of duration ≥ 7 days	-20%	-20%

In addition, in case of Grade 3 or higher toxicity during any cycle beyond Cycle 1, treatment may be interrupted and may be resumed when all toxicities have returned to Grade 2 or less, at the discretion of the investigator.

Subjects who develop intolerance to topotecan, but who may be benefiting from therapy, may continue on single agent VX-970 (M6620), administered once weekly (on days 1, 8, 15 of 21 day cycle) at the same dose they have received in combination therapy, until disease progression.

3.4 STUDY CALENDAR

On-study assessments can be performed within ±7 days of the specified time, unless otherwise indicated.

Next cycle treatment may be delayed up to 7 days to accommodate scheduling conflicts.

Procedure	***Screening***	***Cycles = 21 days[1]***								***End of Treatment[17]/ Disease Progression***	***Post Therapy Follow-up[4]***
		Day 1	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 8***	***Day 15***	***Day 21***		
History	*x*									*x*	
Physical exam[3]	*x*	*x*				*x*				*x*	
PT, PTT	*x*										
Viral Markers Protocol Screen	*x*										
CBC diff[5]	*x*	*x*					*x[18]*	*x[18]*		*x*	
Acute Care Panel[6]	*x*	*x*					*x[15]*	*x[15]*		*x*	
Hepatic pannel[7]	*x*	*x*					*x[15]*	*x[15]*		*x*	
Mineral panel[16]	*x*	*x*					*x[15]*	*x[15]*		*x*	
Troponin		*x*					*x[15]*	*x[15]*			
Pregnancy test[14]	*x*	*x*									
CT scan	*x*								*x[12]*		
Clinical disease assessment									*x[12]*	*x*	
ECG	*x*		*x[13]*			*x[13]*					
Correlative Studies[2]:											
Blood		*x*	*x*	*x*							
Hair		*x*	*x*	*x*							
Circulating Nucleic Acids		*x[9]*								*x*	
Circulating Tumor Cells		*x[9]*								*x*	
PBMC[19]		*x*	*x*			*x[20]*					
PK[21]		*x*									
Biopsies[10] (optional)		*x*		*x*						*x*	
Topotecan		*x*	*x*	*x*	*x*	*x*					
VX-970 (M6620)[11]			*x*			*x*					
Follow-up phone call											*x*

1 Number of cycles depends on disease progression and development of intolerable side effects.
2 Correlative studies are only performed during cycles 1, 2 and at disease progression.
3 Symptom-directed physical examinations will be performed as clinically indicated in the investigator's judgment
4 Follow-up for survival will be carried out every 3 months
5 Includes Neutrophils, Lymphs, Monos, Eos, Basos, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet

[6] Includes Sodium (NA), Potassium (K), Chloride (CL) Total CO2 (Bicarbonate), Creatinine, Glucose, Urea nitrogen, eGFR
[7] Includes Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin
[8] Only for women of child-bearing potential
[9] Will be collected at cycle 2 day 1 in addition to cycle 1 day 1.
[10] Will be obtained at baseline (pre-treatment), on day 3 before topotecan and at disease progression, except for subjects at the first dose level.
[11] Taken on day 5, or day 2 and 5, as indicated in Section **3.1.2**
[12] Performed after every 2 cycles
[13] ECG will be performed predose (within the 120 minutes before the start of VX-970 (M6620) infusion) on the first treatment day during cycle 1 and immediately after end of VX-970 (M6620) infusion (within the next 120 minutes) on the first day of treatment during Cycle 1. For subsequent cycles, ECG will be performed pre VX-970 (M6620) only on both days 2 and 5 (within the 120 minutes before the start of VX-970 (M6620) infusion).
[14] Only for women of child-bearing potential
[15] Only done in cycle 1
[16] Includes Albumin, Calcium, Magnesium (Mg), Phosphorus
[17] Approximately 4 weeks after treatment discontinuation
[18] Only done in cycles 1 and 2
[19] Will be collected pre-treatment on cycle 1 days 1 and 2; post-treatment on cycle 1 day 5 (within 3 hours of completion of topotecan) and pre-treatment on cycle 2 day 1 as indicated in Section **5.1.6**.
[20] Collection at this time point may be omitted due to scheduling conflicts.
[21] Topotecan: may be collected at pre, end of infusion (EOI), and 0.5, 1, 2, 4, 8, 24 hr post EOI; VX-970 (M6620) collected at pre, end of infusion (EOI), and 0.5, 1, 4, 8, 24, and 48 hr post EOI when feasible with regard to patient scheduling; ex., when the treatment is administered Mon-Fri, and may be omitted when the treatment runs through the weekend when the PK collection is not feasible.

3.5 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.5.1 Criteria for removal from protocol therapy

- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in Sections **3.1.1** and **3.3**
- Toxicity related dose delay lasting longer than 21 days
- Investigator discretion
- Requirement for any of the prohibited study drugs as described in Section **4** and **Appendix B** (Strong Inhibitors and Inducers of CYP3A)
- The subject becomes pregnant

3.5.2 Off-Study Criteria

- Participant lost to follow up
- Participant requests to be withdrawn from study

- Death

4 CONCOMITANT MEDICATIONS/MEASURES

In vitro drug metabolism studies suggest that VX-970 (M6620) is a substrate of CYP3A and its systemic exposure may be affected by concomitant medications that are strong CYP3A inhibitors and inducers. Please see a list of CYP3A inhibitors and inducers in **Appendix B** (Strong Inhibitors and Inducers of CYP3A) or at http://medicine.iupui.edu/clinpharm/ddis/. Prior and concomitant medication/food restrictions are provided in **Table 4**. Based upon in vitro data, VX-970 (M6620) is not a potent inhibitor or inducer of human CYP enzymes in isolated enzyme systems, therefore the probability of VX-970 (M6620) interaction with other medications that are substrates of CYP metabolism is expected to be low.

Table 4. Study Restrictions

Restricted Medication/Food/Activity	Study Period	
	Screening Period	**Treatment Period**
Grapefruit/grapefruit juice Seville or blood oranges/marmalade	None allowed within 14 days before the first administration of study drug	None allowed
Strong CYP3A inhibitors or inducers	None allowed within 14 days before the first dose of study drug	None allowed

CYP: cytochrome P450

Medications taken from 28 days before the first dose of study drug will be documented as a prior medication. Medications taken after the first dose of study drug through the end of the study will be documented as concomitant medications. All medications must be recorded with indication, route of administration, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each clinic visit.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

Table 5. Summary of Collection of Correlative Samples

Test/assay	Volume blood (approx)	Type of tube	Collection point (+/- 5 days)	Location of specimen analysis
Tumor (optional)	N/A	N/A	(1) Baseline (pretreatment) (2) C1 D3 before topotecan (3) Disease Progression	Trepel lab to p/u
Hair Follicles (15-30)	N/A	N/A	(1) Pretreatment C1D1 (2) C1D2 Post treatment (3) C1D3 Post treatment	Redon (To be done at same time as green top tubes)

Blood	6 mL	Green Top	(1) Pretreatment C1D1 (2) C1D2 Post treatment (3) C1D3 Post treatment	Redon (On ice)
Circulating Nucleic Acids	10 mL	Lavender Top	(1) Pretreatment C1D1 (2) Pretreatment C2D1 (3) Disease Progression	Trepel (Room temperature)
Circulating Tumor Cells	10 mL (x2)	Lavender Top	(1) Pretreatment C1D1 (2) Pretreatment C2D1 (3) Disease Progression	
	2.5 mL (x1)	PAXgene RNA		
Immune Subsets (PBMC)	8 mL (x2)	CPT blue/black	(1) Pretreatment C1D1 (2) Pretreatment C1D2 (3) Posttreatment C1D5 w/in 3 hrs of topotecan (4) Pretreatment C2D1	
PK topotecan	6 ml (x1)	Sodium heparin tube	C1D1: pre, end of infusion (EOI), and 0.5, 1, 2, 4, 8, 24 hr post EOI (8 time points total).	Blood Processing Core (Dr. Figg) (On ice)
PK VX-970 (M6620)	6 ml (x1)	Sodium heparin tube	C1D1 pre, end of infusion (EOI), and 0.5, 1, 4, 8, 24, and 48 hr post EOI (8 time points total).	

5.1.1 γ-H2AX Detection in Tumor Biopsies, hair follicles and PBMC

Phosphorylated H2AX (γ-H2AX) plays an important role in the recruitment and/or retention of DNA repair and checkpoint proteins such as BRCA1, MRE11/RAD50/NBS1 complex, MDC1 and 53BP1 (see **Figure 1**). DNA damage has been shown to increase H2AX phosphorylation in cancer cells following exposure to camptothecins. If VX-970 (M6620) is able to increase the degree of DNA damage due to topotecan, it may be detectable by measurement of H2AX phosphorylation. We have successfully employed an immunofluorescence assay in previous clinical studies. We plan to study γ-H2AX incidences in patient PBMCs, hair follicles, and in tumor biopsies if there is readily accessible disease. Tumor and hair follicles will be obtained if patients are suitable candidates and willing to allow such sampling.

This analysis will be exploratory only and data will be used in planning biomarker endpoints in subsequent trials with the combination of VX-970 (M6620) and topotecan. This analysis will be exploratory only and data will be used in planning biomarker endpoints in subsequent trials with the combination of VX-970 (M6620) and topotecan. These studies are of interest in an early phase clinical trial and will be done primarily for Phase I part of the study. Additionally, these studies may be done in selected patients in Phase II.

5.1.2 Sample Collection

5.1.2.1 Tumor tissue (optional)

Paired tumor biopsies will be obtained by minimally invasive methods such as CT guided percutaneous biopsies at baseline (pre-treatment), and after treatment (on day 3 before topotecan), and at disease progression. Patients on dose level 1 who will have the second biopsy on day 3 (before topotecan) will serve as "controls" to show the induction of γ-H2AX with topotecan alone.

The site of biopsy will be determined in discussion with interventional radiologist. If it can be safely obtained, 4 cores of tumor tissue will be collected. Two cores will be sent to pathology-one for confirmation of diagnosis and another will be used for making an FFPE block. The other 2 cores will be flash frozen at the time of biopsy. When the patient is scheduled, the Trepel lab will be contacted [by email to trepelj@mail.nih.gov and Sunmin Lee lees@pop.nci.nih.gov]. Interventional Radiology will call the lab at 240-760-6330 when the patient arrives in IR and a lab member will be present at Interventional Radiology for the procedure. The cores will be flash frozen, 2D barcoded, and stored in liquid nitrogen.

5.1.2.2 Blood samples

Blood will be collected in a 6-ml green top tube at the following time points during cycle 1: Pre-treatment on cycle 1 day 1, and post treatment on day 2 and 3 within 3 hours of completion of topotecan. When the patient is scheduled, the Trepel lab will be contacted [by email to trepelj@mail.nih.gov and Sunmin Lee lees@pop.nci.nih.gov]. Blood from heparinized syringe will be mixed with a 1:1 ratio of room temperature PBS and layered over a 1:1 blood-PBS/Ficoll ratio in a conical centrifuge tube. The conical centrifuge tube should be centrifuged 25 minutes at room temperature at approximately 1000 rpm. The cell layer resting above the Ficoll and containing the peripheral blood mononuclear cells (PBMCs) will be aspirated and transferred to a 15 ml conical tube for washing in 15 ml PBS. PBMCs will be fixed with paraformaldehyde, spun onto a microscope slide and stain for γH2AX detection. Images from γ-H2AX-stained PBMCs will be recorded by using a confocal microscope (**Figure 3**, image at the top).

5.1.2.3 Hair follicles

Hair follicles will be collected at multiple time points: Pre-treatment on cycle 1 day 1, post treatment on cycle 1 days 2 and 3. At least 24 hours prior to the start of the study, the research nurse will contact Dr. Redon in Dr. Aladjem's lab (LMP/CCR/NCI, Bldg 37/ Rm 5056) to inform him when samples will be taken (Tel: 240-760-7338 (L); 301-760-6275 (Cell); redonc@mail.nih.gov). Dr. Redon will provide tubes for collecting the plucked hairs. The tubes contain ice cold PBS labeled with the date/time of sampling, the protocol, and the unique 900 identifier. Dr. Redon will also provide forceps for plucking. Dr. Redon should be notified of when the samples should be picked up.

Single hairs are plucked from the scalp with forceps. Plucked hairs from eyebrows will be collected **only** if scalp hairs cannot be provided. The aim is to acquire 15-30 hairs that contain a full intact follicle and sheath (**Figure 3**, image in the middle). If it is determined by Dr. Redon that the hairs collected at the first 2 time points do not contain a full intact follicle and sheath, hair collection at the third time-point may be omitted. All the hairs from a patient are placed in microfuge tubes containing cold PBS and stored on ice. Upon delivery in Dr. Aladjem's lab,

hairs will be fixed with paraformaldehyde and analyzed under a dissection microscope to select those containing a full intact follicle and sheath. Plucked hairs will be fluorescently stained for γ-H2AX and images will be recorded by using a confocal microscope (**Figure 3**, image at the bottom).

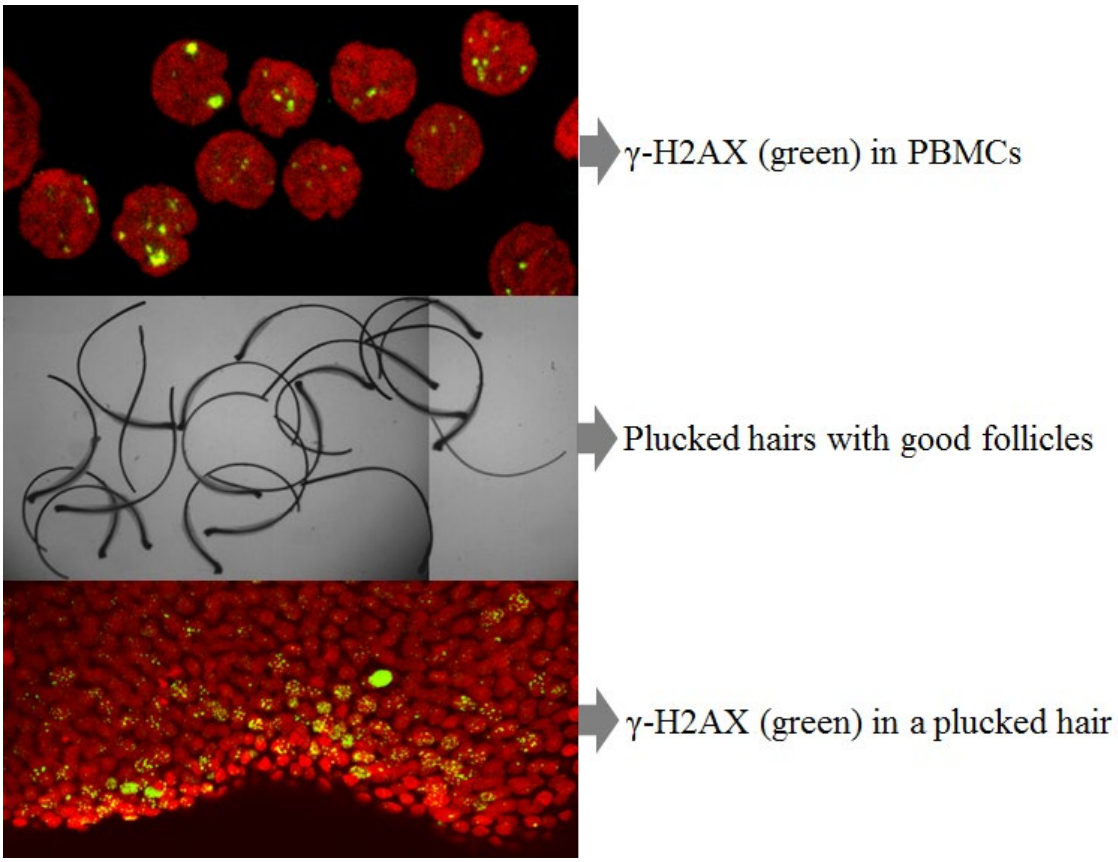


Figure 3

5.1.3 Genomic analysis

Formalin fixed paraffin embedded tumor tissue (FFPE) from the new biopsies and or from archived FFPE tissue from prior biopsies/surgical procedures will be sent to the Trepel lab as described above. Genomic DNA and RNA will be extracted from the tumor. We will assess gene expression by Illumina sequencing, NanoString or droplet digital PCR technology and also perform whole exome sequencing on pre- and post-treatment samples.

The tumor tissue obtained before start of treatment will be used for the following assessments: γ-H2AX (as described before), depending on the availability of tissue in the following sequence of priority 1. genes expression including the following genes: SLFN11, RAD51, RAD54L, BLM, TOP1, ATM, ATR, TOPBP1, POLQ, MCM2, FANCI, MGMT, ATAD5, ASCL1, ESRP1, CAV1, CCNE1, MYCL, MYC, MYCN and RB1 expression, 2. If more tissue is available, it will be archived for whole exome sequencing.

Tumor tissue obtained during and after treatment will be assessed for the following: γ-H2AX and gene expression studies.

5.1.4 Circulating Nucleic Acids

Circulating DNA will be isolated from plasma separated from peripheral blood drawn into 10-ml lavender top tubes pre-treatment on cycle 1 day 1, pre-treatment on cycle 2 day 1, and at disease progression. Mutations identified by analysis of patient tumor samples may be included as personalized tumor markers in the circulating nucleic acid analysis. Mutations will be assessed by the appropriate technology, i.e. nested PCR, droplet digital PCR, Sanger sequencing, or next generation sequencing on MiSeq (Illumina). These assessments will be performed by the Trepel lab.

5.1.5 Circulating Tumor Cells

Circulating tumor cells (CTCs), which can be prevalent in SCLC, present a readily accessible 'liquid biopsy'. Peripheral blood will be collected (pre-treatment on cycle 1 day 1, pre-treatment on cycle 2 day 1 and at disease progression) to correlate circulating tumor cell (CTC) levels at baseline or levels pre- and post-therapy with clinical response and survival. CTCs will be assessed using ferrofluidic enrichment and multiparameter flow cytometric detection. CTCs will be identified as viable, nucleated cells, that positively express one or more epithelial or tumor markers and are negative for expression of hematopoietic markers. CTCs will be enumerated and if sufficient, gene expression will be analyzed by droplet digital PCR. NanoString, whole transcriptome by Illumina or another platform as appropriate to the sample. Peripheral blood will be drawn into two 10-ml lavender top tubes and one 2.5 ml PAXgene RNA tube for each time point. These assessments will be performed by the Trepel lab

5.1.6 Immune Subsets

Little is known of the immunomodulatory effects of DNA damage-inducing cytotoxic therapy. Peripheral blood mononuclear cells (PBMC) obtained before and during treatment (pre-treatment on cycle 1 day 1, pre-treatment on cycle 1 day 2, post-treatment on cycle 1 day 5 within 3 hours of completion of topotecan (collection at this time point may be omitted due to scheduling conflicts), and pre-treatment on cycle 2 day 1) will be assessed by the Trepel Lab in the Developmental Therapeutics Branch using multiparameter flow cytometry for immune subsets including but not necessarily limited to Tregs, myeloid-derived suppressor cells, effector and exhausted CD4+ and CD8+ T-cells, and CD14+ monocytes. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4, CD40, HLA-DR, and/or PD-L1. Members of the lab will procure the peripheral blood samples, enter the samples in a secure patient database, process the samples for viable cell storage, label each sample with a unique 2D barcode, and viably store the samples. They will prepare the samples for staining, stain and run the samples by multiparametric flow cytometry (MACSQuant, Miltenyi Biotec, Bergisch Gladbach, DE), the data will be analyzed by FlowJo v.X.0.6. Peripheral blood will be drawn into two 8-ml CPT citrate blue/black tubes for each time point. These assessments will be performed by the Trepel lab.

5.1.7 Pharmacokinetic Studies

<u>Topotecan</u>

Blood samples for the determination of plasma levels of topotecan may be obtained from each patient, when feasible with regard to scheduling, via 6mL sodium heparin tube (BD, Franklin Lakes, NJ) collected on the first daily dose on cycle 1 day 1 at the following time points: pre, end of infusion (EOI), and 0.5, 1, 2, 4, 8, 24 hours post EOI (8 time-points total). Bioanalytical

measurements will be conducted on an ultra HPLC-MSMS system using an assay developed and validated by the Blood Processing Core.

VX-970 (M6620)

Blood samples for the determination of plasma levels of VX-970 (M6620) may be obtained from each patient, when feasible with regard to scheduling, via 6mL sodium heparin tube (BD, Franklin Lakes, NJ) collected on the first daily dose on cycle 1 day 2 at the following time points: pre, end of infusion (EOI), and 0.5, 1, 4, 8, 24, and 48 hours post EOI (8 time-points total). Bioanalytical measurements will be conducted on an ultra HPLC-MSMS system using an assay developed and validated by the Blood Processing Core (BPC).

This data will be used to monitor topotecan and VX-970 (M6620) plasma concentrations in order to correlate to pharmacodynamic endpoints, clinical response, and toxicity.

The samples will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet.

Please e-mail mailto: BPC at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact BPC by e-mail.

Upon arrival in the Blood Processing Core, samples will be centrifuged and the plasma transferred into cryovials for storage at -80 °C until the time of analysis. In addition, samples will be barcoded as described in Section **5.2.2**.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

All samples (except the two cores of tissue which will be stored in the Laboratory of Pathology and the PK samples which will be processed by the Figg lab) will be sent to and stored in Jane Trepel's Lab at NCI, Bldg 10, Room 12C208, Bethesda, MD. Place all samples at room temperature, phone the Trepel Lab at 240-760-6330 and a laboratory member will come to pick up the sample.

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the subject withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.2.1 Laboratory of Jane Trepel

Tracking and disposition of samples will conform to the NCI CCR Biospecimen Guidelines.

All samples will be barcoded and data entered and stored in the LabMatrix system utilized by the NIH Clinical Center. This is a secure system with access limited to defined personnel. All such personnel with access to subject information annually complete the NIH online Protection of Human Subjects course.

LabMatrix creates a unique barcode ID for every sample which cannot be traced back to subjects without LabMatrix access. The data recorded for each sample includes the subject ID, name, trial name/protocol number, date/time drawn, as well as box and freezer location. Subject demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.). Access to personally identifiable information (PII) is limited to the PI and associate investigators.

An additional layer of encryption will be added for samples undergoing genetic analysis in Dr. Trepel's lab where a separate clinically annotated unique sample ID will be generated linked with the sample ID in LabMatrix. As additional clinical information is generated and linked to the unique patient ID, it is also electronically linked via LabMatrix to the sample ID. Dr. Trepel's lab will proceed with sample analysis and record data under the unique sample ID.

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C or in liquid nitrogen according to stability requirements. These freezers are located onsite, and access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the LabMatrix System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the NCI. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Samples will be stored in a freezer at either -4° C or -70° C behind a door locked after working hours. Samples will be tracked by a designated member of the laboratory who is responsible for notifying the PI about requests for use of the material, for allocating the material to other members of the laboratory, for recording the disposition of the allocated material.

5.2.2 Blood Processing Core (Laboratory of Dr. William Figg)

5.2.2.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the

patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.2.2.2 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested). Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported per **7.2.1**.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.2.3 Future Use/IRB Reporting/Protocol Completion/Sample Destruction

Blood and tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study, including optional germline analysis. However, this research may only be done if the risks of the new questions were covered in the consent document and the proposed research has undergone prospective IRB review and approval. If new risks are associated with the research (e.g., analysis of germ line genetic mutations.) the Principal Investigator must amend the protocol and obtain informed consent from all research subjects.

Following completion of this study, samples will remain in storage as detailed above only for those subjects that agreed to future use in the Optional Studies section of the consent form. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material. Currently, there is no plan to use these samples outside of the use described in the protocol.

If the subject withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the scope of genetic/genomic analysis

One of the exploratory endpoints of this protocol is to characterize mutations which predict response and changes associated with the development of chemoresistance. To this end, whole and targeted exome sequencing will be performed on tumor samples collected pre-treatment and/or post-progression. Since analysis of germline variants is essential to fully characterize the somatic mutations identified in exome sequencing, these assays will involve both somatic and germline DNA.

5.3.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Please refer to Section **5.2**.

5.3.3 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality which helps to protect personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

5.3.4 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D and Labmatrix) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1 through 30 days after the agent was last administered. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the subject's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.2 RESPONSE CRITERIA

For the purposes of this study, subjects should be re-evaluated for response every 2 cycles. In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks (not less than 4) following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [10]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.2.1 Definitions

Evaluable for toxicity: All subjects will be evaluable for toxicity from the time of their first treatment with topotecan.

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

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

6.2.2 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:

- By chest x-ray: ≥20 mm
- By CT scan:
    - Scan slice thickness 5 mm or under as ≥10 mm with CT scan
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam ≥10 mm.

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

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

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

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

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

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

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

6.2.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease.

Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [11-13]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [14].

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

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

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

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

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

6.2.4 Response Criteria

6.2.4.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (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 of diameters while on study.

6.2.4.2 Evaluation of Non-Target Lesions

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

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump

target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

6.2.4.3 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 subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 6. For Subjects with Measurable Disease (i.e., Target Disease)

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as

	disease progression.
Note:	Subjects 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.

Table 7. For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

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

6.2.5 Duration of Response

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

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

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

6.2.6 Progression-Free Survival

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

6.2.7 Response Review

Tumor measurements will be performed by the Center for Cancer Research Radiology and Imaging Sciences image processing service.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each subject while on the study. 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 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when subjects are being actively treated on the trial to discuss each subject. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior subjects.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each subject to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32).

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

8.4.1 EMD-Serono

8.4.1.1 The following reportable events must be submitted to EMD Serono by the Sponsor

The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the mandatory MedWatch form 3500a or equivalent. The Sponsor will assume responsibility for submitting the reportable event(s) below to EMD Serono as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events (refer to section **8.1.2**)
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)

8.4.1.2 The following reportable events must be submitted to EMD Serono by the PI or designee

- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.
- In addition, all AEs will be collected in tabulated form and reported to EMD Serono as outlined in the Collaborative Agreement.
- Reporting of Overdose of M6620: An overdose is defined as any dose 5% greater than the highest dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF. For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported. There are no known symptoms of M6620 overdose to date. The Investigator should monitor closely for AEs should an overdose occur and use his or her clinical judgment in providing symptomatic/supportive care as medically indicated. There is no known antidote for M6620.

8.4.1.3 Contact information for submission of reportable events to EMD Serono:

Fax: +49 6151 72 6914

OR

E-mail: ICSR_CT_GPS@merckgroup.com

Specifying:
PROTOCOL Number and/or Title
EMD Serono assigned Study Number: MS201923-0023
SUBJECT Number
SITE Number/PI Name

8.5 SAE/ONSET DATE REPORTING PREGNANCY

8.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (**8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for (6 months) after the last dose of VX-970 (M6620).

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until (6 months) after the last dose should, if possible, be followed up and documented.

8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6 and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

Primary Objectives:

- Phase I: To identify the maximum tolerated dose (MTD) of topotecan in combination with VX-970 (M6620).
- Phase II: To assess the efficacy with respect to clinical response rate of a combination of topotecan and VX-970 (M6620) in previously treated subjects with SCLC and extra-pulmonary small cell carcinomas.

Secondary Objectives:

- To determine the progression-free survival (PFS) and overall survival (OS) of a combination of topotecan and VX-970 (M6620) in SCLC.
- To assess safety and tolerability of a combination of topotecan and VX-970 (M6620).
- To identify pharmacodynamic markers of response.
- To assess duration of response to the combination in both platinum sensitive and refractory patients.

Exploratory Objectives:

- Assess target modulation by VX-970 (M6620)
- Characterize gene expression and mutations which predict response and changes associated with development of chemoresistance
- Characterize CTC and ct-DNA

The initial portion of the trial will be a phase I dose escalation study using a standard 3 + 3 design to determine a MTD over increasing dose levels of VX-970 (M6620). The phase II trial will be conducted using a Simon two-stage Minimax design in order to rule out an unacceptably low 10% response rate (p0=0.10) in favor of a targeted response rate of 30% (p1=0.30). Based on historical controls, actually observing a response rate of 20% would be considered clinically meaningful in this setting. With alpha=0.10 and beta = 0.10, the study will initially enroll 16 evaluable subjects. If 2 or more of the first 16 subjects have a response, then accrual would continue to a total of 25 subjects. If there were 2-4 responses in 25 subjects, this would not be considered promising in this population. If there were 5 or more subjects of the 25 (20.0%) who have a response, this would be sufficiently interesting to warrant further study of this combination in a future randomized trial of topotecan vs. topotecan+ VX-970 (M6620). The probability of early termination is 51.5% if the true response rate were 10%. In addition, with amendment B, up to 15 patients with extrapulmonary small cell cancers may be enrolled on the protocol. Response rates of these patients will not be included in the primary statistical analysis and will be described in an exploratory manner.

Overall survival will be determined from the on-study date until date of death or last follow-up. Progression free survival will be determined from the on-study date until date of progression. The probabilities of survival and of progression free survival will be determined by the Kaplan-Meier method.

10.1 Determination of Sample Size

The theoretical maximum number of subjects required to determine the MTD in the phase I portion of the study is 24 subjects (6 per dose level), although it is expected that as few as 12 subjects in 3 dose levels would be required to reach an MTD. As of amendment C, 21 subjects have been enrolled on the phase I portion of the study, and accrual for the phase I portion is complete. For the phase II portion of the study, 25 subjects with Small Cell Lung Cancer and 15 subjects with extrapulmonary small cell cancers are to be recruited. To allow room for a small number of inevaluable subjects, an accrual ceiling of 70 will be set for this study.. The cohort of patients with extrapulmonary small cell cancers will have their response rate reported along with appropriate confidence intervals.

We anticipate that it will take approximately 4 years to accrue 40 evaluable subjects to the phase II portion of the trial.

11 COLLABORATIVE AGREEMENTS

11.1 Cooperative Research and Development Agreement (CRADA)

The study drug VX-970 (M6620) was initially provided under a CRADA (#2999) between the manufacturer, Vertex, and the Thoracic Gastrointestinal Oncology Branch, National Cancer Institute.

Amendment 1 to the CRADA executed in July 2017 transfers EMD Serono as the manufacturer of the study drug.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale For Subject Selection

As previously described, the subjects for this study will include all subjects who meet the eligibility criteria outlined in section **2.1.** No gender, racial, or ethnic groups will be excluded from participation in this trial.

12.2 Participation of Children

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

12.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **12.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another

person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

12.4.1 Risks

12.4.1.1 Study drugs risks

12.4.1.1.1 VX-970 (M6620)

VX-970 (M6620) was generally well tolerated when administered as either single-agent therapy or in combination with 1 or 2 chemotherapeutic agents to subjects with solid tumors. There were no dose-limiting toxicities (DLTs), few adverse events (AEs) leading to study drug discontinuation, and 1 unrelated AE leading to death. Most subjects receiving VX-970 (M6620) as single-agent or combination therapy had AEs.

Risks due to M6620 alone

- Nausea 32%
- Vomiting 12%
- Infusion site reactions 9%
- Systemic infusion reactions 17%

Risks when M6620 is given with chemotherapy

- Nausea 54%
- Vomiting 33%
- Infusion site reactions 10%
- Systemic infusion reactions 15%

Additional risks of M6620 given in combination with carboplatin

- Anemia 52%
- Low neutrophils 45%
- Low platelets 38%

In addition, the following very common adverse events were observed in at least 15% of subjects receiving M6620 monotherapy. There is not enough experience in M6620 whether these truly are side effects.

- Diarrhea 15%
- Fatigue 20%

There is a possibility that M6620 may make patient more sensitive to sunlight. VX-970 (M6620) absorbs in the UV-visible radiation spectrum and is widely distributed including skin, so patients receiving VX-970 (M6620) should take protective measures to minimize sun exposure.

12.4.1.1.2 Topotecan

Likely, some may be serious (experienced by more than 20% of subjects taking the drug)

- Anemia which may require a blood transfusion
- Low white blood cell counts
- Constipation, diarrhea, nausea, vomiting
- Fever
- Pain
- Bruising, bleeding
- Infection, especially when white blood cell count is low
- Tiredness
- Shortness of breath

Less likely, some may be serious (experienced by between 3 and up to 20% of subjects taking the drug)

- Sores in mouth which may cause difficulty swallowing
- Headache
- Cough
- Scarring of the lungs

Rare but Serious (experienced by 3% of fewer of subjects taking the drug)

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Low white blood cell counts which may result in life-threatening infections

12.4.1.2 Biopsy risks

The risks associated with biopsies are pain and bleeding at the biopsy site. In order to minimize pain, local anesthesia will be used. Rarely, there is a risk of infection at the sampling site. CT guidance may be used in obtaining biopsies.

12.4.1.3 Radiation risks

There will be a risk of exposure to radiation from 3 CT guided biopsies and 9 CT scans. The amount of radiation exposure is 12.3 rem. The risk of getting cancer from the radiation exposure in this study is 1.2 out of 100 (1.2%) and of getting a fatal cancer is 0.6 out of 100 (0.6%).

12.4.1.4 CT contrast risks

Itching, hives or headaches are possible risks associated with contrast agents that may be used during CT imaging. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body. Very rarely, the contrast agents used in CT can cause kidney problems for certain patients, such as those with impaired kidney function.

12.4.1.5 Release of medical records

In the course of applying for certain types of insurance (e.g., medical insurance, life insurance, or disability insurance), people are often asked to sign forms that authorize insurance companies to

obtain their medical records. If subjects sign such a release form at some point in the future, it is possible that the insurance company would present this signed release form to the Clinical Center of the National Institutes of Health. In that event, the National Institutes of Health would comply with the subject's request to provide the insurance company with their medical record. It is possible that information contained in the subject's medical record, including any diagnosis of cancer, might affect the willingness of the insurance company to sell them insurance.

In addition, the genomic data generated from samples will be uploaded to a shared database such as dbGaP. Such databases may be useful beyond the aims of this particular study, especially as various diseases turn out to have mechanisms in common. The value of these data can increase when they are shared with the broader research community. While no traditionally identifying information will be shared, it is possible that a subject or a family member may be identified.

12.4.1.6 Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

12.4.1.7 Risk related to the possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

12.4.1.8 Risk to family or relatives

Family members or relatives may or may not want to be aware of familial tendencies or genetic risks of disease which may cause anxiety about possible future health problems. As previously noted, patients will be notified of any medically significant and actionable incidental findings. Study results will not be shared with patients.

12.4.1.9 Risks related to blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.4.1.10 Risk related to hair collection

The only risk associate with hair collection is pain.

12.4.2 Benefits

The benefits include a possible decrease in the size of the tumor and the scientific knowledge that could be acquired through this trial.

12.5 Risks/Benefits Analysis for Subjects Able and Unable To Provide Consent

Small cell cancer is an aggressive cancer with a poor prognosis. Patients are in continuous need of improved therapy options. This is especially true for patients who have progressed on standard therapy such as the patient population that will be eligible for this trial. Phase I clinical data (see section **1.2**) suggest that Topotecan plus VX-970 (M6620) may improve outcomes in patients with small cell cancers, particularly in those with platinum resistant or refractory disease. A

number of clinically appropriate strategies to minimize risk to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. Overall, the study presents more than minimal risk due to protocol-related procedures and interventions with the prospect of direct benefit due to the potential for protocol treatment to reduce tumor burden.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant or consent designee(s) (e.g., the parent/guardian if participant is a minor, legally authorized representative [LAR] if participant is an adult unable to consent) for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person in a private area (e.g., clinic consult room) or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s).

13 PHARMACEUTICAL INFORMATION

13.1 VX-970 (M6620)

13.1.1 Source

VX-970 (M6620) was initially manufactured and provided by Vertex Pharmaceuticals Inc. As of July 2018, the drug is manufactured and provided by EMD Serono. Toxicity

13.1.1.1 Pre-clinical toxicity

VX-970 (M6620) was administered by both oral and IV routes to rats and dogs for up to 28 days. The oral studies used a frequent dosing regimen (every other day) to define the toxicity profile, while the IV dosing regimen in the GLP 28-day studies (biw) were more representative of the planned clinical dosing schedule (intravenously, once per week). The rat STD10 was determined to be 30 mg/kg/day and the dog HNSTD was determined to be 20 mg/kg/day, both administered via 3-hour IV infusion. Major toxicities in the dog included cholestasis, bile duct hyperplasia and periportal vacuolation of the liver, which were reflected by increases in AST, ALT, bilirubin and alkaline phosphatase; changes in red cell mass in the periphery without corresponding bone marrow pathology; and testicular atrophy. Major toxicities in the rat also included alterations in red cell mass, without microscopic correlates in the bone marrow and testicular atrophy, as well as phlebitis. No corresponding change in testes weights were observed in dogs, although microscopic findings of degeneration/atrophy were identified. Importantly, degeneration/atrophy in the testes was reduced during the recovery period in both rats and dogs, providing evidence that these changes are reversible.

13.1.1.2 Clinical Toxicity

VX-970 (M6620) was being evaluated by Vertex in Study VX12-970-001 (Study 001). This is a first-in-human (FIH) study, evaluating the safety, tolerability, and PK of VX-970 (M6620) as a

single agent and in combination with gemcitabine, cisplatin and gemcitabine, cisplatin, and cisplatin and etoposide. Preliminary safety data from Study 001 (data cut-off date: 19 June 2013) are available for 6 subjects in the first 2 dose cohorts in Part A. All 6 subjects in Study 001 Cohorts 1 and 2 of Part A had at least 1 adverse event (AE) which was considered related or possibly related to the study drug (VX-970 (M6620) or gemcitabine) by the investigator. The most common related or possibly drug-related AEs by system organ class were associated with gastrointestinal disorders, followed by general disorders and administration site conditions, nervous system disorders, and skin and subcutaneous tissue disorders. The most common drug-related or possibly drug-related AEs by preferred term were nausea (5 subjects), vomiting (4 subjects), fatigue (3 subjects), and rash (3 subjects).

In addition to the detailed data on AEs through 19 June 2013, data on SAEs are available through 18 September 2014. A total of 30 SAEs occurred in 16 subjects in Study 001 and a second study, Study 002, which is testing the safety, tolerability, and pharmacokinetic/pharmacodynamic profile of VX-970 (M6620) as a single agent and in combination with carboplatin in subjects with advanced solid tumors. Three of these SAEs, all of which were unrelated to study drug, were fatal. The most common SAEs (>1 subject) were pyrexia (4 subjects) and disease progression (2 subjects). A total of 12 SAEs in 7 subjects were considered related to the study drug by the investigator. Acute hypersensitivity, observed in a single subject receiving 140 mg/m2 VX-970 (M6620), has been identified as an adverse drug reaction (ADR) for VX-970 (M6620).

Target organs for VX-970 (M6620) toxicity were considered the liver, testes, and peripheral blood cell populations. Importantly, liver and peripheral blood toxicities were reversed within 4 weeks of discontinuation of VX-970 (M6620), and both toxicities are readily monitored by peripheral blood count and liver function tests in the first-in-human study. Testicular degeneration is not an infrequent complication of cytotoxic chemotherapy, and sperm counts are not routinely followed in subjects receiving chemotherapy. Importantly, testicular findings showed evidence of reversibility in both rats and dogs. Finally, subjects will be required to use contraception while on study drug and for 6 months afterwards [6].

13.1.2 VX-970 (M6620) (NSC 780162) Other Names

VRT-0768079, VE-822

13.1.3 Classification

ATR inhibitor

13.1.4 Molecular Formula: C24H26ClN5O3S M.W.: 500.01 Da

13.1.5 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. VX-970 (M6620) disrupts ATR-mediated DNA damage response signaling and leads to sustained accumulation of DNA damage in cancer cells co-treated with DNA-damaging agents.

13.1.6 Description

The drug substance for VX-970 (M6620) is the HCl salt.

13.1.7 How Supplied

VX-970 (M6620) is supplied by EMD Serono as single-use 200 mg vials containing a sterile solution (20 mg/mL). VX-970 (M6620) solution for injection is a yellow liquid formulated in 20% betadex sulfobutyl ether sodium (w/v) and 86 mM acetate buffer, 10 mL total volume, supplied in clear glass vials in cardboard boxes with foam inserts.

13.1.8 Preparation

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

Details of dose preparation for VX-970 (M6620) are provided in (Dose Preparation of VX-970 (M6620) IV Solution).

13.1.9 Storage

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

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

13.1.10 Stability

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

13.1.11 Route of Administration

Intravenous (IV) infusion

13.1.12 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. VX-970 (M6620) 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, VX-970 (M6620) should be administered through a large bore catheter into a large caliber peripheral vein or central venous access.

13.1.13 Patient Care Implications

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

13.1.14 Potential Drug Interactions

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

13.1.15 Incompatibilities

In vitro drug metabolism studies suggest that VX-970 (M6620) is a substrate of CYP3A and its systemic exposure may be affected by concomitant medications that are strong CYP3A inhibitors and inducers. Prior and concomitant medication and food restrictions are provided in **Table 4**. Based upon in vitro data, VX-970 (M6620) is not a potent inhibitor or inducer of human CYP enzymes in isolated enzyme systems, therefore the probability of VX-970 (M6620) interaction with other medications that are substrates of CYP metabolism is expected to be low.

13.2 TOPOTECAN

For pharmaceutical information, see the Topotecan Package Insert.

13.2.1 Administration Procedures

Please refer to section **3.1.2**.

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15 APPENDICES

15.1 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.

15.2 APPENDIX B- STRONG INHIBITORS AND INDUCERS OF CYP3A

Strong Inhibitors	**Strong Inducers**
boceprevir clarithromycin conivaptan grapefruit juice (1) indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil (2) nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	avasimibe (4) carbamazepine phenytoin rifampin St. John's wort (3)

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit

1. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
2. Withdrawn from the United States market because of safety reasons.
3. The effect of St. John's wort varies widely and is preparation-dependent.
4. Not a marketed drug.