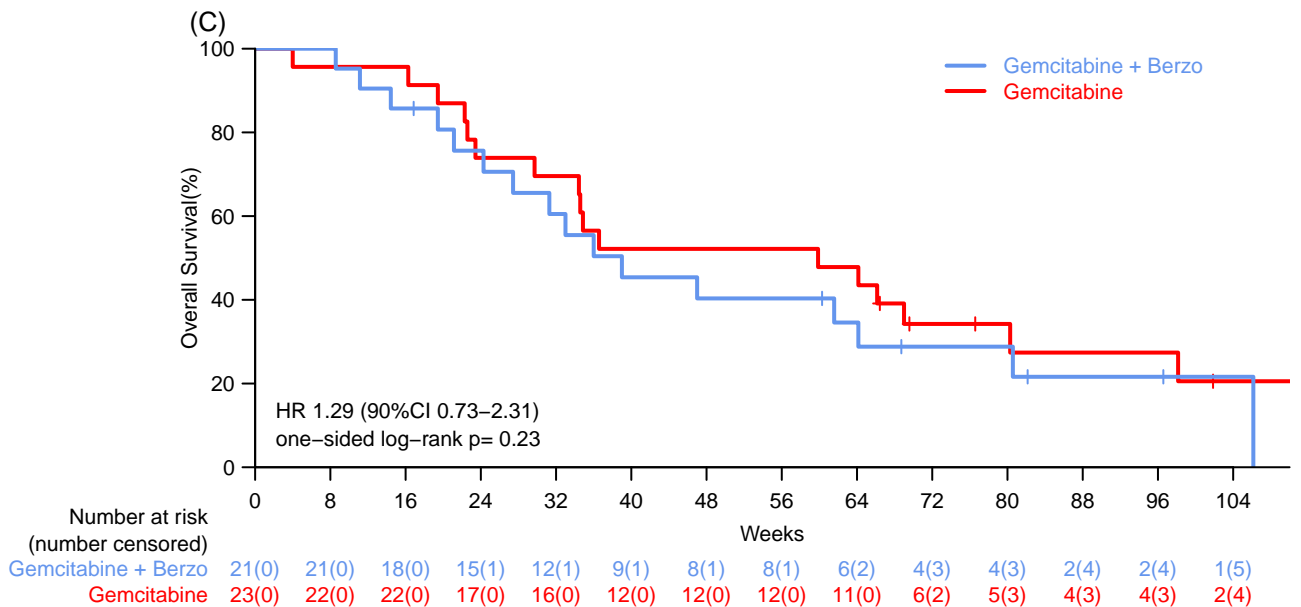
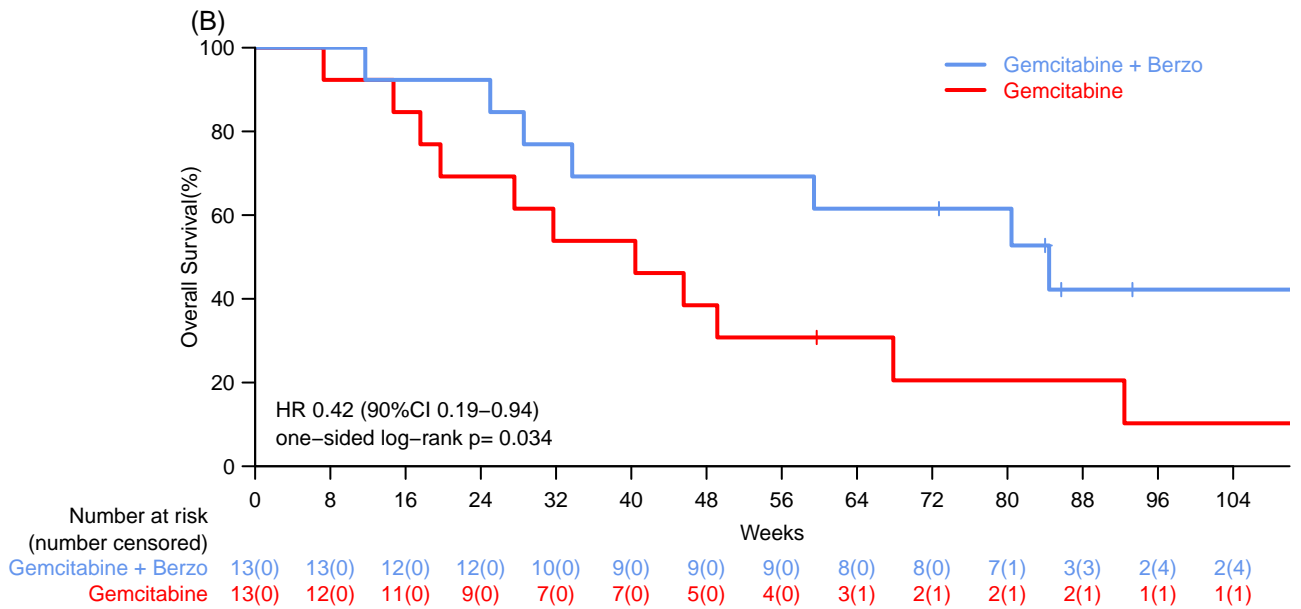
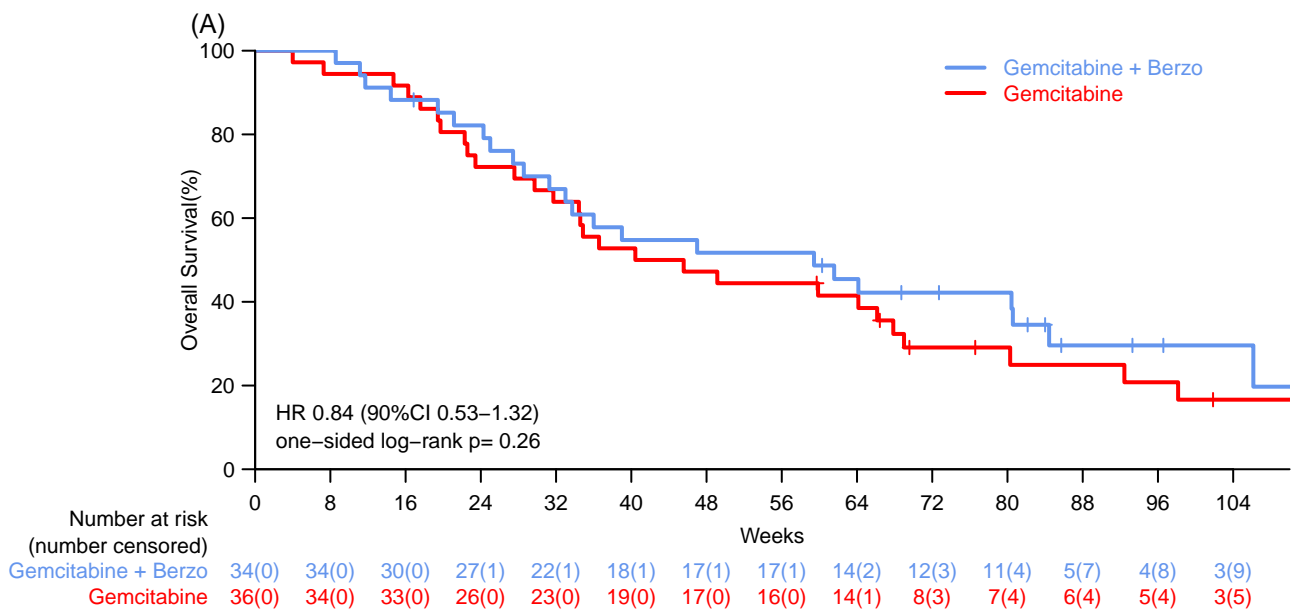
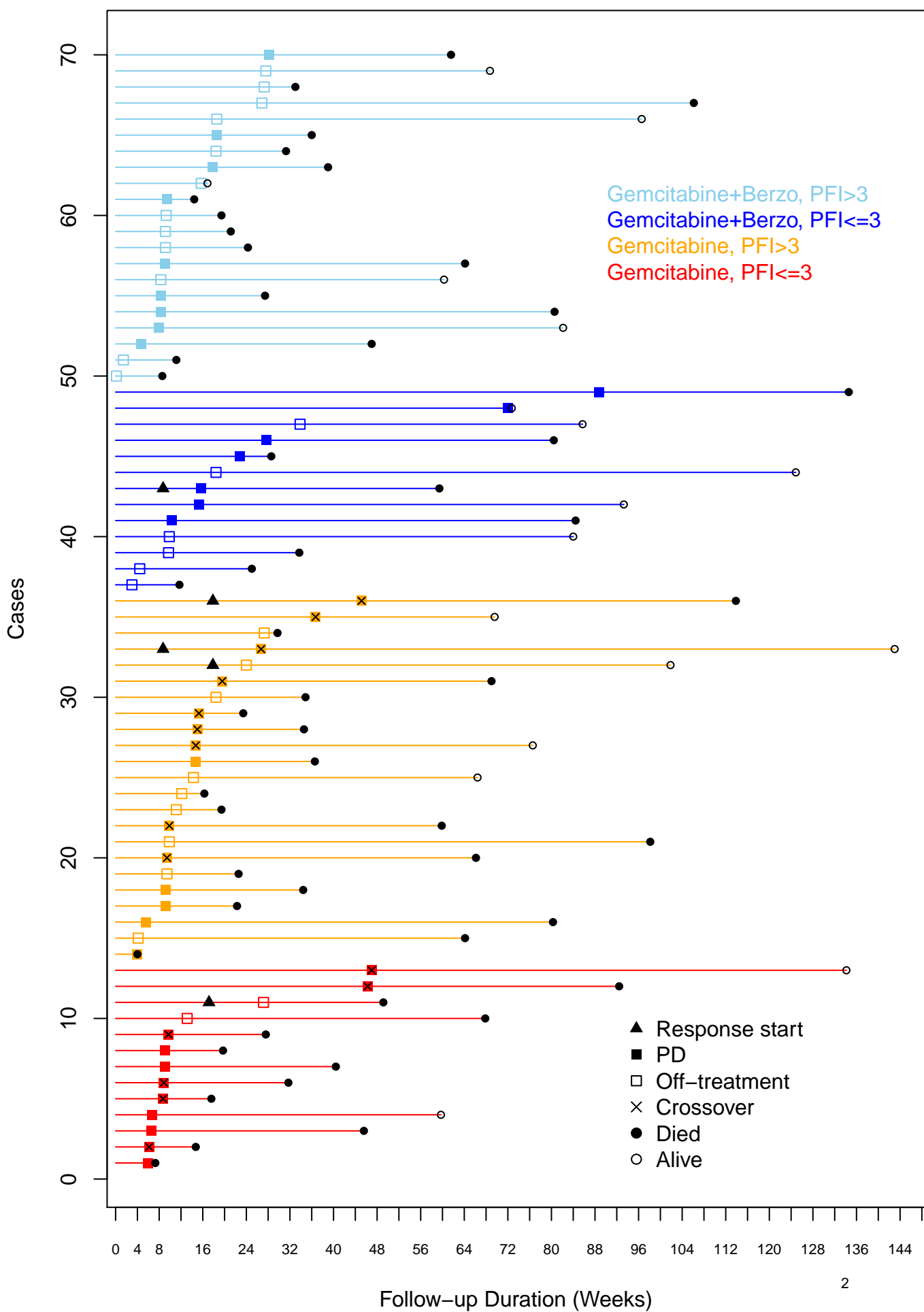


Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Konstantinopoulos PA, Cheng S-C, Wahner Hendrickson AE, et al. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2020; published online June 15. [http://dx.doi.org/10.1016/S1470-2045\(20\)30180-7](http://dx.doi.org/10.1016/S1470-2045(20)30180-7).





Treatment related toxicities

Max Grade	Gemcitabine (n=36)				Gemcitabine + Berzosertib (n=34)			
	1	2	3	4	1	2	3	4
Blood and Lymphatic System Disorders								
Anemia	8(22%)	13(36%)	4(11%)	0	3(9%)	15(44%)	5(15%)	0
Blood Bilirubin Decreased	1(3%)	0	0	0	0	0	0	0
Decreased BUN	0	0	0	0	1(3%)	0	0	0
Decreased Hematocrit	2(6%)	0	0	0	2(6%)	0	0	0
Decreased MCHC	2(6%)	0	0	0	0	0	0	0
Decreased RBC	1(3%)	0	0	0	1(3%)	0	0	0
Febrile Neutropenia	1(3%)	0	1(3%)	0	0	0	1(3%)	0
Hemolytic Uremic Syndrome	0	0	1(3%)	0	0	0	0	0
Increased Absolute Immature Granulocyte	0	0	0	0	1(3%)	0	0	0
Increased MCV	1(3%)	0	0	0	0	0	0	0
Increased RDW	1(3%)	0	0	0	1(3%)	0	0	0
Increased Red Blood Cell Distribution	0	0	0	0	1(3%)	0	0	0
Lymphocyte Count Decreased	2(6%)	3(8%)	1(3%)	0	0	0	1(3%)	0
Neutrophil Count Decreased	4(11%)	3(8%)	10(28%)	4(11%)	5(15%)	3(9%)	12(35%)	4(12%)
Platelet Count Decreased	3(8%)	1(3%)	0	2(6%)	7(21%)	2(6%)	2(6%)	6(18%)
Thrombocytosis	0	0	0	0	1(3%)	0	1(3%)	0
Thrombotic Thrombocytopenic Purpura	0	0	0	0	1(3%)	0	0	0
White Blood Cell Decreased	3(8%)	1(3%)	4(11%)	0	0	5(15%)	3(9%)	0
Cardiac Disorders								
Myocardial Infarction	0	0	1(3%)	0	0	0	0	0
Ear and Labyrinth Disorders								
Tinnitus	0	0	0	0	1(3%)	0	0	0

Endocrine Disorders								
Addisonian Crisis	0	0	0	0	0	0	1(3%)	0
Increased BUN	1(3%)	0	0	0	0	0	0	0
Eye Disorders								
Eye Pain	0	0	0	0	1(3%)	0	0	0
Gastrointestinal Disorders								
Abdominal Distension	1(3%)	0	0	0	0	0	0	0
Abdominal Pain	0	1(3%)	0	0	0	0	1(3%)	0
Bloating	0	0	0	0	1(3%)	0	0	0
Constipation	3(8%)	1(3%)	0	0	5(15%)	1(3%)	0	0
Decreased Appetite	1(3%)	0	0	0	0	0	0	0
Diarrhea	6(17%)	0	0	0	6(18%)	2(6%)	1(3%)	0
Dry Mouth	0	0	0	0	1(3%)	0	0	0
Gastric Hemorrhage	0	0	1(3%)	0	0	0	0	0
Gastroesophageal Reflux Disease	0	1(3%)	0	0	0	0	0	0
Mucositis Oral	1(3%)	0	0	0	4(12%)	2(6%)	0	0
Nausea	15(42%)	2(6%)	1(3%)	0	16(47%)	3(9%)	1(3%)	0
Oral Pain	0	0	0	0	1(3%)	0	0	0
Small Intestinal Mucositis	1(3%)	0	0	0	0	0	0	0
Vomiting	5(14%)	2(6%)	0	0	10(29%)	2(6%)	1(3%)	0
General Disorders and Administration Site Conditions								
Chills	2(6%)	0	0	0	5(15%)	1(3%)	0	0
Edema Limbs	5(14%)	1(3%)	1(3%)	0	1(3%)	0	0	0
Fatigue	10(28%)	8(22%)	3(8%)	0	11(32%)	8(24%)	3(9%)	0
Fever	2(6%)	1(3%)	0	0	6(18%)	2(6%)	0	0
Flu Like Symptoms	3(8%)	1(3%)	0	0	4(12%)	0	0	0
Infusion Related Reaction	1(3%)	0	0	0	1(3%)	1(3%)	0	0
Infusion Site Extravasation	0	0	0	0	0	2(6%)	0	0

Injection Site Reaction	0	0	0	0	1(3%)	0	0	0
Localized Edema	1(3%)	1(3%)	0	0	0	0	0	0
Malaise	1(3%)	0	0	0	0	0	0	0
Non-cardiac Chest Pain	0	0	0	0	1(3%)	0	0	0
Immune System Disorders								
Allergic Reaction	0	0	0	0	0	1(3%)	0	0
Infections and Infestations								
Mucosal Infection	0	1(3%)	0	0	0	0	0	0
Rash Pustular	0	0	0	0	0	1(3%)	0	0
Skin Infection	0	1(3%)	0	0	0	0	0	0
Injury, Poisoning and Procedural Complications								
Bruising	0	0	0	0	3(9%)	0	0	0
Fall	0	0	1(3%)	0	0	0	0	0
Investigations								
Alanine Aminotransferase Increased	6(17%)	1(3%)	0	0	7(21%)	3(9%)	0	0
Alkaline Phosphatase Increased	1(3%)	0	0	0	1(3%)	0	0	0
Aspartate Aminotransferase Increased	8(22%)	0	0	0	6(18%)	6(18%)	0	0
Cardiac Troponin T Increased	0	0	1(3%)	0	0	0	0	0
Creatinine Increased	1(3%)	0	0	0	0	1(3%)	0	0
Lipase Increased	0	0	0	0	1(3%)	0	0	0
Metabolism and Nutrition Disorders								
Anorexia	5(14%)	0	0	0	6(18%)	1(3%)	0	0
Dehydration	0	1(3%)	0	0	0	2(6%)	0	0
Hypercalcemia	1(3%)	0	0	0	0	0	0	0
Hyperkalemia	1(3%)	0	0	0	0	0	0	0
Hypernatremia	1(3%)	0	0	0	0	0	0	0
Hypoalbuminemia	2(6%)	1(3%)	0	0	2(6%)	0	0	0

Hypocalcemia	1(3%)	1(3%)	0	0	0	0	0	0
Hypokalemia	4(11%)	0	0	0	1(3%)	0	0	0
Hypomagnesemia	2(6%)	0	0	0	0	0	0	0
Hyponatremia	1(3%)	0	0	0	0	0	0	0
Musculoskeletal and Connective Tissue Disorders								
Arthralgia	1(3%)	1(3%)	0	0	2(6%)	0	0	0
Back Pain	0	1(3%)	0	0	0	1(3%)	0	0
Bone Pain	0	0	0	0	1(3%)	0	0	0
Flank Pain	0	0	0	0	1(3%)	0	0	0
Generalized Muscle Weakness	1(3%)	0	0	0	1(3%)	1(3%)	1(3%)	0
Joint Range Of Motion Decreased	0	0	0	0	1(3%)	0	0	0
Joint Stiffness	0	0	0	0	1(3%)	0	0	0
Leg Cramping	1(3%)	0	0	0	0	0	0	0
Muscle Aches	1(3%)	0	0	0	0	0	0	0
Muscle Weakness Lower Limb	0	0	0	0	1(3%)	0	0	0
Myalgia	1(3%)	2(6%)	0	0	5(15%)	0	0	0
Restless Legs	0	1(3%)	0	0	0	0	0	0
Nervous System Disorders								
Dizziness	0	0	0	0	2(6%)	0	0	0
Dysgeusia	0	1(3%)	0	0	0	0	0	0
Headache	3(8%)	0	0	0	6(18%)	1(3%)	1(3%)	0
Peripheral Sensory Neuropathy	1(3%)	0	0	0	0	1(3%)	0	0
Unbalanced	1(3%)	0	0	0	0	0	0	0
Psychiatric Disorders								
Confusion	0	0	0	0	1(3%)	0	0	0
Insomnia	0	0	0	0	1(3%)	0	0	0
Restlessness	0	0	0	0	1(3%)	0	0	0
Renal and Urinary Disorders								

Acute Kidney Injury	0	2(6%)	0	0	0	0	0	0
Proteinuria	0	0	0	0	1(3%)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders								
Cough	1(3%)	0	0	0	3(9%)	0	0	0
Dyspnea	2(6%)	0	1(3%)	0	2(6%)	3(9%)	0	0
Pneumonitis	0	1(3%)	0	0	0	2(6%)	0	0
Shortness Of Breath	0	1(3%)	0	0	0	0	0	0
Wheezing	1(3%)	0	0	0	0	0	0	0
Skin and Subcutaneous Tissue Disorders								
Alopecia	1(3%)	0	0	0	5(15%)	0	0	0
Derm Other-left Wrist	0	0	0	0	1(3%)	0	0	0
Itch	1(3%)	0	0	0	0	0	0	0
Nonfluid Filled Blisters On Thumbs	0	0	0	0	1(3%)	0	0	0
Pruritus	0	0	0	0	2(6%)	0	0	0
Rash	1(3%)	1(3%)	0	0	0	0	0	0
Rash Acneiform	1(3%)	1(3%)	0	0	1(3%)	1(3%)	0	0
Rash Maculo-papular	4(11%)	1(3%)	0	0	3(9%)	1(3%)	0	0
Red Painful Finger/thumbs	0	0	0	0	1(3%)	0	0	0
Red Painful Thumbs And Toes	0	0	0	0	1(3%)	0	0	0
Vascular Disorders								
Capillary Leak Syndrome	0	0	1(3%)	0	0	0	0	0
Flushing	0	0	0	0	1(3%)	0	0	0
Thromboembolic Event	0	0	0	0	1(3%)	0	0	0

Dose Reductions per arm

Patient ID	Arm	Drug Reduced	Level	New Dose	REASON
1	Gem alone	Gemcitabine	-1	750 mg/m ²	Anemia
2	Gem alone	Gemcitabine	-1	750 mg/m ²	Fatigue
3	Gem alone	Gemcitabine	-1	750 mg/m ²	Fatigue
4	Gem alone	Gemcitabine	-1	750 mg/m ²	Fatigue
5	Gem alone	Gemcitabine	-1	750 mg/m ²	Fatigue
6	Gem alone	Gemcitabine	-1	750 mg/m ²	Flu-like symptoms post infusion
7	Gem alone	Gemcitabine	-1	750 mg/m ²	Neutropenia
8	Gem alone	Gemcitabine	-1	750 mg/m ²	Neutropenia
9	Gem alone	Gemcitabine	-1	750 mg/m ²	Neutropenia
10	Gem alone	Gemcitabine	-1	750 mg/m ²	Neutropenia
11	Gem alone	Gemcitabine	-1 then -2	750 mg/m ² --> 500 mg/m ²	Neutropenia then Anemia
12	Gem alone	Gemcitabine	-1 then -2	750 mg/m ² --> 500 mg/m ²	SOB both times
13	Gem alone	Gemcitabine	-1	750 mg/m ²	Thrombocytopenia & Neutropenia

Patient ID	Arm	Drug Reduced	Level	New Dose	REASON
1	Gem/M6620	Gem	-1 then -2	750 mg/m ² --> 500 mg/m ²	Abdominal pain then Neutropenia/Fatigue
2	Gem/M6620	Gem	-1	750 mg/m ²	Hypoalbuminemia
3	Gem/M6620	Gem and M6620	-1	750 mg/m ² ; 165 mg/m ²	Nausea, vomiting, diarrhea
4	Gem/M6620	Gem	-1	750 mg/m ²	Nausea, vomiting, fatigue
5	Gem/M6620	Gem	-1	750 mg/m ²	Neutropenia
6	Gem/M6620	Gem	-1	750 mg/m ²	Neutropenia

7	Gem/M6620	Gem	-1	750 mg/m2	Neutropenia
8	Gem/M6620	Gem	-1	750 mg/m2	Neutropenia
9	Gem/M6620	Gem and M6620	-1	750 mg/m2; 165 mg/m2	Neutropenia and Thrombocytopenia for gem, Thrombocytopenia for M6620
10	Gem/M6620	Gem	-1	750 mg/m2	Pneumonitis
11	Gem/M6620	Gem	-1	750 mg/m2	Thrombocytopenia
12	Gem/M6620	Gem	-1	750 mg/m2	Thrombocytopenia
13	Gem/M6620	Gem	-1	750 mg/m2	Thrombocytopenia

Site	Site PI	Total Accrual
Dana Farber Cancer Institute	Konstantinopoulos, Panagiotis A.	27
Mayo Clinic	Wahner Hendrickson, Andrea E.	8
Massachusetts General Hospital Cancer Center	Penson, Richard T.	7
University of Virginia Cancer Center	Duska, Linda Rosenbaum	5
Vanderbilt University/Ingram Cancer Center	Crispens, Marta Ann	4
University of Pittsburgh Cancer Institute (UPCI)	Olawaiye, Alexander Babatunde	4
Wayne State University/Karmanos Cancer Institute	Winer, Ira Seth	4
University of Wisconsin Hospital and Clinics	Barroilhet, Lisa Marie	4
M D Anderson Cancer Center	Fu, Siqing	3
UC San Diego Moores Cancer Center	McHale, Michael T.	3
Thomas Jefferson University Hospital	Schilder, Russell J.	1

70

NCI Protocol #: 9944
Local Protocol #: 16-724

ClinicalTrials.gov Identifier: NCT02595892

TITLE: 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

Corresponding Organization: LAO-MA036 / Dana-Farber/Harvard Cancer Center LAO

Principal Investigator: Panagiotis A. Konstantinopoulos MD, PhD
Dana Farber Cancer Institute
YC-1424, 450 Brookline Ave
Boston, MA 02215
617-632-5269
617-632-3479
Panagiotis_konstantinopoulos@dfci.harvard.edu

Participating Organizations:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO

Statistician:
William T Barry, PhD
Center for Life Sciences Bldg, Room 11005
450 Brookline Ave.
Boston, MA 02215
Phone: 617-632-5134
Fax: 617-632-2444
bbarry@jimmy.harvard.edu

Research Project Manager:
Sarah Farooq, MPH
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Phone: 617 632-5735
Fax: 617 394-2662
sarah_farooq@dfci.harvard.edu

NCI Protocol #: 9944
Version Date: May 10, 2017

Responsible Research Nurse:

Christin Whalen RN
Dana Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Phone: 617-582-7738
Fax: 617-582-7921
Pager: 617-632-3352 Pager #41948
Christin_Whalen@dfci.harvard.edu

Study Coordinator:

Haley Makuch
Dana-Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Phone: 617 632-2668
Fax: 617 582-7921
Haley_Makuch@DFCI.HARVARD.EDU

NCI-Supplied Agent(s): VX-970 NSC# 780162

Other Agent(s): gemcitabine, NSC# 613327, Commercial

IND #: 129798

IND Sponsor: DCTD, NCI

Version Date: May 10, 2017

SCHEMA

PROTOCOL SYNOPSIS

A Phase 2 Study of VX-970 (NSC# 780162) in Combination with Gemcitabine (NSC# 613327) versus Gemcitabine alone in Subjects with Platinum-Resistant Ovarian or Primary Peritoneal Fallopian Tube Cancer

STUDY DRUG: **VX-970**

PHASE: **2**

INDICATION: **Platinum-Resistant Ovarian or Primary Peritoneal or Fallopian Tube Cancer**

RESEARCH HYPOTHESIS:

Based on *in vitro* and *in vivo* data, we hypothesize that VX-970 may enhance activity of gemcitabine and show acceptable toxicity and superior efficacy to gemcitabine alone in platinum resistant ovarian or primary peritoneal or fallopian tube cancer.

OBJECTIVES:

Primary Objective(s)

- To assess and compare progression free survival (PFS) between gemcitabine/VX-970 and gemcitabine alone arms

Secondary Objective(s)

- To determine and compare overall response rate (ORR) by RECIST between gemcitabine/VX-970 and gemcitabine alone arms
- To determine and compare the safety profile of gemcitabine/VX-970 and gemcitabine alone regimens
- To assess and compare PFS at 6 months between gemcitabine/VX-970 and gemcitabine alone arms
- To determine and compare the clinical benefit rate (CBR) between gemcitabine/VX-970 and gemcitabine alone arms
- To determine and compare the duration of response (DOR) between gemcitabine/VX-970 and gemcitabine alone arms
- To determine and compare CA125 reduction by $\geq 50\%$ between gemcitabine/VX-970 and gemcitabine alone arms
- To determine and compare OS between gemcitabine/VX-970 and gemcitabine alone arms
- To determine the ORR for subjects in the gemcitabine alone arm who cross over to the gemcitabine/VX-970 arm

Exploratory Objective(s)

- To explore whether the presence of genetic alterations in HR pathway and NER pathway genes are predictive of clinical outcome after gemcitabine/VX-970 in archival FFPE specimens
- To explore whether TP53, ATM and ATR mutations are predictive of clinical outcome after gemcitabine/VX-970 in archival FFPE specimens
- To explore whether amplification of Cyclin E1 (CCNE1) or ATR or MYC are predictive of clinical outcome after gemcitabine/VX-970 in archival FFPE specimens
- To explore whether homozygous deletion of PTEN is predictive of clinical outcome after gemcitabine/VX-970 in archival FFPE specimens
- To explore whether presence of Alternative Lengthening of Telomeres (ALT) is predictive of clinical outcome after gemcitabine/VX-970 in archival FFPE specimens

STUDY DESIGN:

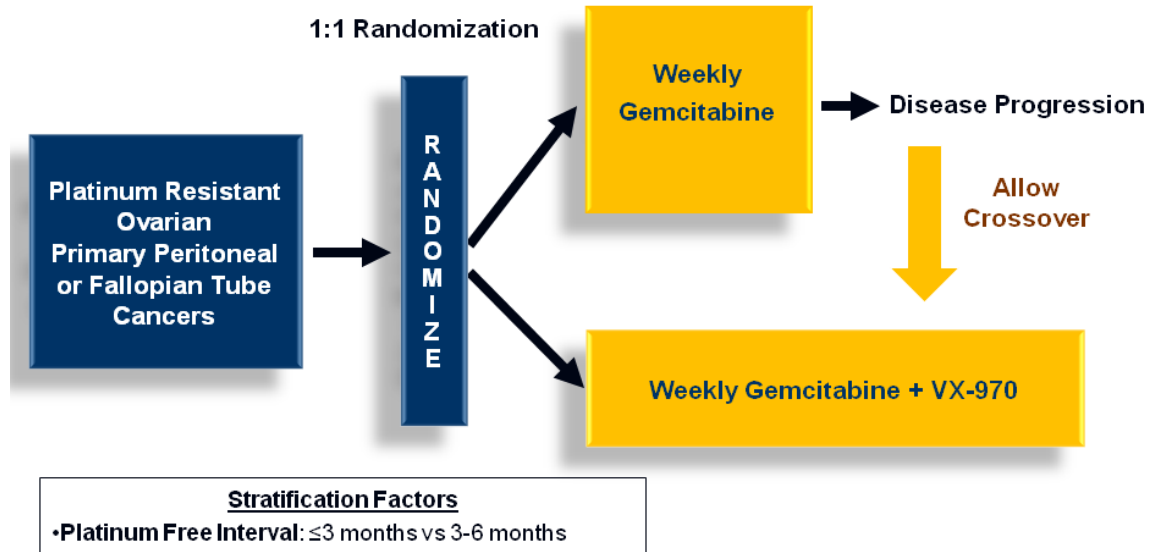
This is a Phase 2, multicenter, open-label, randomized study of VX-970 combined with gemcitabine compared with gemcitabine alone in subjects with platinum resistant recurrent high-grade serous epithelial ovarian cancer (HGS EOC). The randomized design is selected to evaluate the efficacy and safety of the combination of gemcitabine/VX-970 against single agent gemcitabine in platinum-resistant ovarian cancer. Furthermore, the proposed study design allows crossover from standard arm to gemcitabine/VX-970 after disease progression to enable the investigation of the efficacy of the gemcitabine/VX-970 following failure of single agent gemcitabine. Specifically, patients with recurrent platinum resistant high grade serous ovarian or primary peritoneal or fallopian tube cancers will be randomized 1:1 to either gemcitabine alone or gemcitabine/VX-970. There is no limit in the number of previous platinum therapies for platinum sensitive recurrence, but patients cannot have received more than 1 prior regimen in the platinum resistant setting. Treatment will continue until disease progression as measured by RECIST 1.1; patients who progress by RECIST 1.1 on weekly gemcitabine alone will be allowed to crossover to the experimental gemcitabine/VX-970 arm. Patients with CA125 elevation alone may continue on study as long as they have not developed progressive disease by RECIST. Furthermore, patients on weekly gemcitabine alone arm are not allowed to cross over to the combined gemcitabine/VX-970 arm based on CA125 elevation alone; Progressive disease by RECIST must be documented before they are allowed to cross over to the combined gemcitabine/VX-970 arm. Only patients with available archival FFPE tissue (either one paraffin embedded tissue block OR 10 5-micron unstained slides from the block on regular (non-plus) slides and 1 H&E slide) will be eligible to participate in this study.

The primary endpoint of the study is to compare the PFS between gemcitabine/VX-970 and gemcitabine alone arms.

Subjects may begin protocol treatment at least 4 weeks after their last dose of prior chemotherapy or hormonal therapy, assuming they are otherwise eligible. Patients on the gemcitabine alone arm will receive IV gemcitabine 1000mg/m² IV on Days 1 and 8 of a 21 day cycle which is the most widely studied and most commonly used regimen of single agent gemcitabine in platinum resistant ovarian cancer. Patients on the gemcitabine/VX-970 arm will receive IV gemcitabine 1000mg/m² on Days 1 and 8 and IV VX-970 210mg/m² on Days 2 and

9 of a 21-day cycle.

Treatment will continue until disease progression or intolerable toxicity and patients who progress on weekly gemcitabine alone will be allowed to crossover to the experimental gemcitabine/VX-970 arm. Subjects can voluntarily withdraw at any time during the study. Participants will be followed for 3 years after removal from study treatment or until death, whichever occurs first.



TUMOR ASSESSMENTS:

RECIST v1.1 criteria will be used to assess patient response to treatment by PFS, ORR and DCR. The RECIST v1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective TUMOR response criteria (CR, PR, SD or progression of disease) are presented in Section 11.

STATISTICAL METHODS:

In this exploratory trial, in order to have 80% power to detect improvement of median PFS (primary endpoint) from 15 weeks with gemcitabine alone to 27.3 weeks with gemcitabine/VX-970 (HR=0.55) using a stratified log-rank test (with the platinum free interval as the stratification factor) with a one-sided alpha level of 0.1, 64 patients would be randomized (32 patients on each arm). Final analysis would occur when 50 PFS events are to be observed. This assumes a constant accrual over 1 year with 6 months of additional follow-up, and a constant hazard of PFS and dropout such that 5% of patients are lost-to-follow-up at 1 year. Although the target number of evaluable patients is 64, it is anticipated that 10% of subjects will not be evaluable and thus the maximum total number of patients to be enrolled will be 70. An interim analysis will be planned at 25 PFS events to stop for futility only.

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1. OBJECTIVES

1.1 Primary Objectives

The primary objective of the study is to:

- Assess and compare progression free survival (PFS) between gemcitabine/VX-970 and gemcitabine alone arms

1.2 Secondary Objectives

The secondary objective of the study is to:

- Determine and compare overall response rate (ORR) by RECIST between gemcitabine/VX-970 and gemcitabine alone arms
- Determine and compare the safety profile of gemcitabine/VX-970 and gemcitabine alone regimens
- Assess and compare PFS at 6 months between gemcitabine/VX-970 and gemcitabine alone arms
- Determine and compare the clinical benefit rate (CBR) between gemcitabine/VX-970 and gemcitabine alone arms
- Determine and compare the duration of response (DOR) between gemcitabine/VX-970 and gemcitabine alone arms
- Determine and compare CA125 reduction by $\geq 50\%$ between gemcitabine/VX-970 and gemcitabine alone arms
- Determine and compare OS between gemcitabine/VX-970 and gemcitabine alone arms
- Determine the ORR for subjects in the gemcitabine alone arm who cross over to the gemcitabine/VX-970 arm

2. BACKGROUND

2.1 Ovarian Cancer

Ovarian Cancer and high grade serous histology

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy and the fifth most common cause of female cancer death in the United States^{1,2}. Fallopian tube and primary peritoneal cancers are less frequently diagnosed, but exhibit histological and prognostic features that are identical to those of ovarian cancer and are treated similarly to EOC^{3,4}.

High-grade serous carcinomas (HGSCs) represent the most common histologic subtype and account for approximately 70% of all EOCs. HGSCs are characterized by high degree of genomic instability with high frequency of DNA copy number changes and almost universal presence of TP53 mutations⁵. A number of molecular studies and most recently The Cancer

Genome Atlas (TCGA) project have shown that HGSCs are characterized by frequent genetic and epigenetic alterations in gene members of the homologous recombination (HR) DNA repair pathway⁶⁻⁸. Specifically, in the TCGA dataset, approximately 20% of HGSCs harbored germline *BRCA1* or *BRCA2* mutations while approximately 30% harbored alternative molecular HR alterations including somatic *BRCA1/2* mutations, hypermethylation of *BRCA1* or *RAD51C*, amplification or mutation of *EMSY*, focal deletion or mutation of *PTEN*, mutation of *ATM* or *ATR*, and mutation of Fanconi anemia genes (Figure 1). Of note, another 20% of HGSCs harbor cyclin E1 amplification while approximately 8% harbor deficient nucleotide excision repair (NER) (Figure 1)^{8,9}. Finally, another 4% of HGSCs harbor *ATR* amplification which may be a marker of replication stress and dependence on *ATR* signaling.

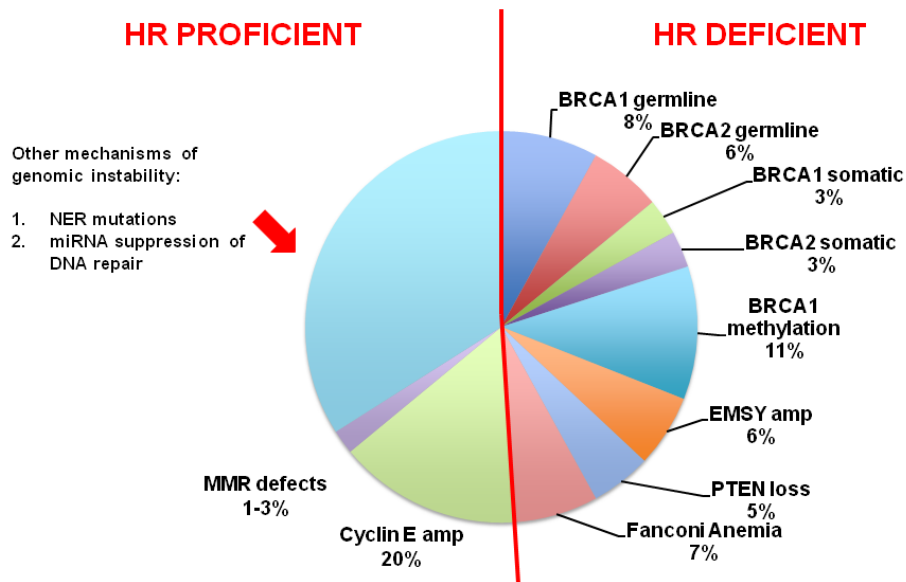


Figure 1. Molecular alterations in DNA repair pathways in high grade serous ovarian cancers (Adapted from Ovarian TCGA dataset, Nature, 2011).

Platinum resistant ovarian cancer

Although first line platinum based chemotherapy results in clinically complete remissions in >70% of EOC patients, relapse occurs in >90% of those responders, at which point the disease is much less responsive to subsequent treatment and is essentially non-curable^{1,10}. Platinum-free interval is a powerful predictor of treatment success in recurrent ovarian cancer and disease that relapses within 6 months after platinum-containing therapy is categorized as platinum resistant^{1,10}.

Platinum resistant EOC is routinely managed using single agents such as anthracyclines (formulated as pegylated liposomal doxorubicin [PLD]), taxanes, topotecan, and gemcitabine¹⁰. Physician decision as to which agent to administer is usually based upon toxicity, patient preference on specific side effects, tumor response and quality of life. Recently, the AURELIA study demonstrated that addition of bevacizumab to chemotherapy (weekly paclitaxel, or topotecan or PLD) statistically significantly improved PFS, response rate and patient reported outcomes^{11,12}, and led to the FDA approval of bevacizumab in combination with weekly paclitaxel, or topotecan or PLD in patients with platinum resistant EOC. However, even with the

addition of bevacizumab, the outlook for patients with platinum resistant disease is poor; median overall survival (OS) is approximately 17 months so novel strategies are needed¹¹.

Role of ATR in Cancer DNA damage and response

The DNA damage response (DDR) requires the integration of cell cycle control via checkpoint signaling to allow time for repair to prevent permanent DNA damage produced by replication and mitosis¹⁷. The PI3K-related protein kinases (PIKKs) Ataxia-telangiectasia mutated (ATM) and Ataxia-telangiectasia and Rad3-related (ATR) have crucial roles by signaling DNA damage to cell cycle checkpoints and DNA repair pathways (Figure 2). The ATM–CHK2 pathway primarily responds to double strand breaks (DSBs) to induce G1 arrest, while the ATR–CHK1 pathway triggers S and G2 phase arrest¹⁷. ATM promotes HR by recruiting BRCA1 to DSBs but can also antagonize BRCA1 and promote NHEJ by recruiting TP53 binding protein 1 (53BP1), and these antagonistic functions are cell cycle regulated. ATR is activated by DNA single-strand–double-strand junctions that arise as intermediates in nucleotide excision repair (NER), by replication stress and at resected DSBs, and it phosphorylates CHK1 to activate S and G2 arrest¹⁸. Replication stress is defined as the slowing or stalling of replication fork progression during DNA synthesis^{18, 19}. Sources of replication stress include single strand DNA accumulation, loss of G1/S checkpoint (as in TP53 loss), DNA damage during S phase, oncogene-driven state (i.e. by HRAS, MYC, cyclin E1 overexpression, EGFR-vIII) and DNA repair deficiency (tumor cells deficient in FA, BLM, or ATM pathways)^{19, 20}. The cellular response to replication stress includes activation of ATR/CHK1 which mediates activation of DNA repair pathways and stabilization of replication fork¹⁸. Activation of ATR triggers the intra-S phase and the G2 checkpoints via phosphorylation of CHK1, which in turn phosphorylates WEE1 (which activates this kinase) and cell division cycle 25 (CDC25) phosphatases (which inhibits it) to inhibit cell cycle progression through the coordinate suppression of cyclin-dependent kinase (CDK) activity. ATR and CHK1 also phosphorylate a number of proteins involved in HRR and ICL repair, including BRCA2, RAD51, FANCD2 and FANCE21.

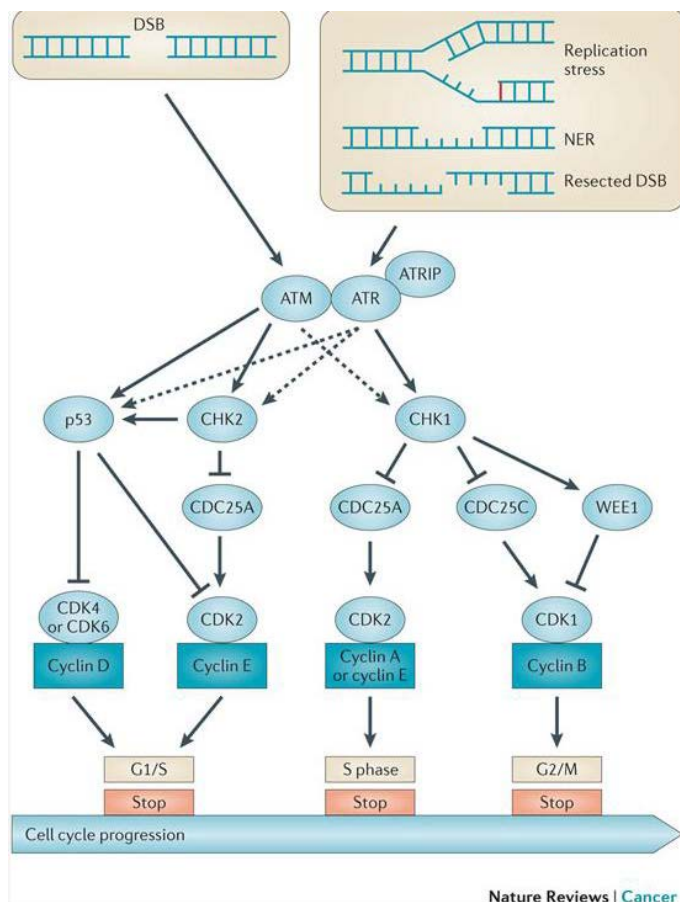


Figure 2. Signaling DNA damage to cell cycle checkpoints via the ATM/CHK2 and ATR/CHK1 pathways (Figure from Curtin N.J. Nat Rev Cancer, 2012).

2.2 CTEP IND Agent(s)

VX-970

VX-970 is a potent highly selective ATR inhibitor (ATR inhibition constant [Ki] <300 pM, ATR IC50 19nM), with more than 500-fold selectivity over 278/291 kinases tested and more than 25 fold selectivity over the remaining 13 kinases (VX-970 Investigator Brochure). Furthermore, VX-970 demonstrates a low potential for drug-drug interactions based on minimal inhibition or induction of cytochrome (CYP) 450 isozymes. In vitro, VX-970 has demonstrated potent sensitization of multiple cancer cell lines and primary human tumor cells but not of normal cell lines, to ionizing radiation (IR) and to a wide range of DNA-damaging agents including cisplatin, gemcitabine, irinotecan, and etoposide. The selective activity of VX-970 in cancer cells is attributed to disruption of alternative DNA damage repair pathways in these cells; in contrast, normal cell tolerance to ATR inhibition is attributed to the presence of alternative, compensatory DDR pathways. Normal cell tolerance to inhibition of ATR by VX-970 is attributed to compensatory DDR signaling that is mediated by ATM. Accordingly, cells with defects in ATM signaling, for example cells with loss of TP53, have been shown to be especially sensitive to

VX-970 treatment²¹.

In mouse xenograft models derived from human cancer cell lines and primary human tumors, VX-970 dose-dependently enhanced the anti-tumor effects of multiple DNA-damaging drugs and of IR with marked regression observed in many cases. Importantly, the combination of VX-970 and a DNA-damaging agent has been shown to be more effective than the DNA-damaging agent alone at its maximum tolerated dose (MTD). However, as a single agent VX-970 did not demonstrate significant impact on the tumor growth in the experimental models examined.

Dose schedule optimization studies in mouse models have demonstrated that VX-970 at a dose of 20 mg/kg/week IV was highly effective in combination with cisplatin or gemcitabine. Furthermore, timing of VX-970 administration is critical, with maximal activity observed when VX-970 is administered 12 to 24 hours after cisplatin or gemcitabine treatment. The dosing schedule for VX-970 is based on modeled human pharmacokinetics (PK) for VX-970 and the optimal timing of ATR inhibition in relation to DNA-damaging drug exposure. In vitro cell culture experiments and animal models suggest that timing of VX-970 administration is critical, with maximal activity observed when VX-970 was given 12 to 24 hours after cisplatin or gemcitabine treatment.

A battery of in vitro and in vivo safety pharmacology studies designed to evaluate effects of VX-970 against multiple protein targets and the cardiovascular system did not demonstrate any toxicologically significant effects at exposures or concentrations that significantly exceed the targeted maximum circulating concentration of VX-970 in humans.

VX-970 demonstrated extensive blood to plasma partitioning, which can vary with dose and species. Whole blood half-lives in rats and dogs were 11.6 and 9.8 hours, respectively. VX-970 had high plasma protein binding and the free fraction in human blood was 2.1%. A low potential for drug-drug interactions was predicted, based on minimal inhibition or induction of cytochrome (CYP) 450 isozymes by VX-970, however strong inducers or inhibitors of CYP3A4 may alter VX-970 kinetics and blood levels. VX-970 was primarily eliminated by oxidative metabolism, with CYP3A4 as the principle isozyme responsible. Metabolites were excreted in the urine and bile. The systemic clearance values of VX-970 following IV administration were determined to be 26 and 13 mL/min/kg in the rat and dog, respectively.

In Study 001 Part A which was a Phase 1 dose escalation study of VX-970 in combination with gemcitabine, gemcitabine was administered on Days 1 and 8 and VX-970 on Days 2 and 9 of a 21 day cycle. VX-970 has been escalated up to 210mg/m² on Days 2 and 9 of a 21 day cycle (the predicted human dose of VX-970 to achieve exposure with maximum activity in mouse = 120 mg/m²). Therefore, 210 mg/m² given on Days 2 and 9 of a 21 day cycle will be the dose that we will use in this Phase 2 study. In study 001 Part A, Gemcitabine was escalated to 1000mg/m² on Days 1 and 8 of a 21 day cycle and this will be the dose (in combination with 210mg/m² on Days 2 and 9 of a 21 day cycle) which will be used in the combination arm of this Phase 2 study.

Clinical Pharmacokinetics

Preliminary clinical pharmacokinetic (PK) data are available from Study 001 and Study 002. Noncompartmental analyses were conducted on whole blood and plasma concentrations of VX

970 for both Studies 001 and 002 in both Parts A and B. The mean VX-970 plasma concentrations versus time profiles were similar in shape to those of the corresponding whole blood profiles. PK exposure estimates tended to increase with increasing dose based upon the maximum observed concentration (C_{max}) and AUC extrapolated to infinity (AUC_{0-∞}). The terminal elimination half-life was approximately 16 hours across all dose groups. Preliminary clinical PK data are available from Study 001 from all cohorts up to cohort 9 (VX-970 210mg/m² / gemcitabine 875mg/m²). Cohorts 7 (n=3), 8 (n=2) and 9 (n=3) included VX-970 210mg/m² and gemcitabine 500mg/m², 750mg/m² and 875mg/m² respectively. The mean AUC extrapolated to infinity (AUC_{0-∞}) estimates (5687 ng·h/mL for Cohort 7, 7857 ng·h/mL for Cohort 8 and 5664 ng·h/mL for Cohort 9) were well above the efficacious exposure (4080 ng·h/mL) predicted from the xenograft efficacy model. The volume of distribution at steady-state (V_{ss}) were 1510L, 1313L and 1306L for Cohorts 7,8 and 9 respectively.

VX-970 PK exposure parameters were similar when dosed alone versus after gemcitabine administration and indicated no apparent interactions between VX-970 and gemcitabine. In summary, after single-agent VX-970 dosing in Study 001 and Study 002, plasma exposure estimates were within a linear range based upon C_{max} and AUC_{0-∞}.

Clinical Efficacy

Preliminary efficacy data are available for 38 subjects from Study 001 and 11 subjects from Study 002.

In Study 001 Part A (VX-970 + gemcitabine combination therapy), 5 of 6 subjects (83.3%) with non-small cell lung cancer (NSCLC), 7 of 13 subjects (53.8%) with other types of cancers, and 4 of 9 subjects (44.4%) with colorectal cancer exhibited stable disease (SD) as best overall response after receiving VX-970 and gemcitabine combination therapy. One subject with EBV+ nasopharyngeal cancer exhibited a partial response (50.5% reduction of tumor lesion diameter) after receiving VX-970 and gemcitabine combination therapy. Several subjects receiving VX-970 and gemcitabine combination therapy had an overall response of stable disease (SD) for at least 4 cycles. Subjects with particularly extended periods of SD included:

- i) 4 subjects with non-small cell lung cancer (NSCLC), including 1 subject with SD for 13 cycles (progressive disease at Cycle 16,
- ii) 1 subject with a gastrointestinal stromal tumor for 8 cycles (withdrawal of consent at Cycle 9), and
- iii) 1 subject with renal cancer for 8 cycles,

In Study 002 Part A (VX-970 single-agent therapy), 3 of 10 subjects (37.5%) with other types of cancers exhibited stable disease as best overall response after receiving VX-970 single-agent therapy. One subject with colorectal cancer exhibited a partial response (80% reduction of tumor lesion diameter).

Clinical Safety

Preliminary safety data are available for 38 subjects from Study 001 and 11 subjects from Study 002. During the 7- to 14-day Lead-in Phase in Part A of Study 001, 2 subjects had serious AEs (SAEs) of palpitations, pyrexia, and dyspnea. No subjects had Grade ≥ 3 AEs, AEs leading to

study drug discontinuation, dose-limiting toxicities (DLTs), or AEs leading to death. During the 21-day Lead-in Phase in Part B of Study 001, 1 subject had an SAE of metastases to central nervous system that led to study drug discontinuation. No subjects had DLTs or AEs leading to death.

In Study 001 Part A (VX-970 + gemcitabine combination therapy), 31 subjects included in the Combination Safety Set received intravenous doses of VX-970 ranging from 18 to 140 mg/m² in combination with intravenous doses of gemcitabine ranging from 500 to 875 mg/m². Four of 27 subjects (14.8%) included in the dose-limiting toxicity (DLT) evaluable set receiving VX-970 in combination with gemcitabine had a total of 7 DLTs: alanine aminotransferase increased (2 subjects [7.4%]); aspartate aminotransferase increased (2 subjects [7.4%]); blood alkaline phosphatase increased (1 subject [3.7%]); thrombocytopenia (1 subject [3.7%]); and fatigue (1 subject [3.7%]). A total of 16 subjects (2 subjects receiving single-agent VX-970 during the Lead-Phase and 14 subjects receiving VX-970 + gemcitabine combination therapy) had serious adverse events (SAEs). In Study 001 Part A (VX-970 + gemcitabine combination therapy) 9 subjects (29.0%) had SAEs classified as related to study drug, 3 subjects (9.7%) had SAEs of Grade 1 pyrexia classified as possibly related or related to study drug, and 2 subjects (6.5%) had SAEs of Grade 4 thrombocytopenia classified as related to study drugs. No other SAEs were reported in more than 1 subject. The most common adverse events (AEs), regardless of causality, were nausea (20 subjects [64.5%]), vomiting (17 subjects [54.8%]), and fatigue (15 subjects [48.4%]). Overall the AST/ALT elevations occurred at the same frequency as with gemcitabine monotherapy and although there was a possible potentiation of gemcitabine-associated myelosuppression, this did not prevent dose escalation.

In Study 001 Part B (VX-970 + cisplatin combination therapy), 6 subjects in the Combination Safety Set received intravenous doses of VX-970 ranging from 90 to 140 mg/m² in combination with intravenous doses of cisplatin 40 mg/m². There were no DLTs. Two subjects had SAEs of metastases to central nervous system (1 subject receiving single-agent VX-970 during the Lead-Phase) and dyspnea (1 subject receiving VX-970 + cisplatin combination therapy), which were not related to study drugs. The most common AEs, regardless of causality, were nausea (4 subjects [66.7%]) and fatigue (4 subjects [66.7%]).

In Study 002 Part A (single-agent VX-970 therapy), 11 subjects included in the Safety Set received intravenous doses of VX-970 ranging from 60 to 480 mg/m². There were no DLTs. Two subjects had SAEs of Grade 3 ascites, which were classified as not related to study drug, and Grade 3 fatigue, which was classified as possibly related to study drug. Five subjects (45.5%) had an AE of fatigue. AEs of nausea, urinary tract infections, headache, and flushing were each reported in 3 subjects (27.3%).

Serious acute hypersensitivity reactions have occurred in a few subjects receiving VX-970. These reactions occurred within minutes of re-exposure to VX-970, and in cases reported to date, they have occurred during the second infusion. They may include hypotension and mental status changes. All subjects have fully recovered with standard treatment for this reaction, including immediate discontinuation of the inciting infusion and administration of IV corticosteroid and antihistamine, as well as IV fluids and oxygen when clinically indicated.

Specifically, after careful assessment, serious acute hypersensitivity is considered an adverse drug reaction (ADR) for VX-970 and, therefore, is assessed as an expected event for regulatory reporting purposes. As of 17 April 2015, a serious acute hypersensitivity reaction to VX-970 occurred in 5 of 71 subjects given doses of VX-970. A third reaction occurred after the SAE data

cut-off date of 17 April 2015, raising the estimated incidence of this ADR to between 4% and 5%.

The first hypersensitivity reaction occurred in a 57-year-old male subject receiving 140 mg/m² VX-970 and 500 mg/m² gemcitabine during their second infusion of VX-970 and consisted of flushing of the face, chest, and neck; increased sweating; shortness of breath; chest tightness; tachycardia; agitation and confusion; nausea; and diarrhea. The subject was not hypotensive. The subject was treated with hydrocortisone and chlorphenamine, and the symptoms resolved in approximately 40 minutes. The second reaction occurred in a 70-year-old female subject receiving 120 mg/m² VX-970 and AUC 5 carboplatin. Ten minutes into her second infusion of VX-970, the subject felt flushed, with mild redness of the chest and cheeks that disappeared within 1 minute. The infusion was stopped. She felt faint, her head dropped, and she was unresponsive for 10 seconds. Blood pressure was 78/40 mmHg, and heart rate was 47 bpm (on bisoprolol). She was afebrile, with oxygen saturation of 98%. She was treated with hydrocortisone, chlorphenamine, and IV fluids and recovered within 30 minutes. The third reaction occurred in a 28-year-old female subject receiving 210 mg/m² of VX-970 and 60 mg/m² of cisplatin. Five minutes into her second infusion of VX-970, she developed dyspnea, abdominal pain, decreased level of consciousness, and nausea followed by 1 episode of vomiting. The infusion was stopped. Her blood pressure went as low as 66/40 mmHg. She was treated with hydrocortisone, diphenhydramine, normal saline bolus, and oxygen and recovered.

After the SAE data cut-off for this IB (17 April 2015), a 28-year-old female in Study 001 also experienced a serious hypersensitivity reaction. She tolerated her first dose of VX-970 (210 mg/m²) and cisplatin (60 mg/m²), and 5 minutes into her second infusion of VX-970, she developed dyspnea, abdominal pain, decreased level of consciousness, and nausea followed by 1 episode of vomiting. Her infusion was stopped. The subject's blood pressure at the time was 170/100 mmHg; pulse was 121 bpm; and oxygen saturation was 95%. The subject was treated with hydrocortisone 100 mg IV and diphenhydramine 50 mg IV, 1 L normal saline bolus, and 6 L oxygen. The subject became minimally verbally responsive, opening her eyes to command. Repeat blood pressure was 88/57 mmHg followed by 66/40 mmHg. Within 15 minutes, her blood pressure stabilized at 111/76 mmHg, and the reaction resolved the same day. This reaction was reported as an infusion-related reaction and assessed as related to VX-970 by the investigator.

2.3 Other Agent

Gemcitabine

Gemcitabine is currently FDA approved in combination with carboplatin, for the treatment of EOC that has relapsed at least 6 months after completion of platinum-based therapy (i.e. in platinum sensitive disease)¹³. Commercially available gemcitabine will be administered (1000mg/m² alone or 1000mg/m² in combination with VX-970) over approximately 30 minutes according to institutional standards. Refer to the gemcitabine package insert for additional information.

Gemcitabine in platinum resistant ovarian cancer

Gemcitabine is a nucleoside analog that kills cells undergoing DNA synthesis; both metabolites of gemcitabine, diphosphate and triphosphate nucleosides, work together to incorporate gemcitabine nucleotide into DNA, which results in apoptotic cell death. Furthermore, gemcitabine irreversibly inhibits the ribonucleotide reductase enzyme leading to cell's inability to produce the deoxyribonucleotides required for DNA replication and repair, and thus inducing apoptosis.

Gemcitabine is currently FDA approved in combination with carboplatin, for the treatment of EOC that has relapsed at least 6 months after completion of platinum-based therapy (i.e. in platinum sensitive disease)¹³. However, gemcitabine has also been studied and is one of the standard treatment options as a single agent in platinum resistant disease. From 12 clinical studies and a total of 411 individual patients (most heavily pretreated with platinum resistant disease), gemcitabine as a single agent exhibited an overall response rate from 14% to 22% with an average of 16.5% across these studies (an additional 30% of patients had stable disease for an overall clinical benefit rate of approximately 50%)¹⁴. Doses higher than 1000 mg/m² in heavily pretreated patients are not advised because of the risk of severe myelosuppression¹⁴.

Gemcitabine has been compared with PLD (which is a standard, FDA approved regimen for platinum resistant EOC) in two randomized phase III clinical trials. In the first trial¹⁵ which included 195 patients with platinum resistant EOC, gemcitabine (1,000 mg/m² days 1 and 8; every 21 days) exhibited similar PFS, ORR and OS compared to PLD (50mg/m² day 1; every 28 days). In the second study¹⁶ which included 153 patients with ovarian cancer who had recurrence within 12 months of primary treatment, gemcitabine (1,000 mg/m² on days 1, 8, and 15 every 28 days) was compared with PLD (40 mg/m² every 28 days). There was no statistically significant difference in time to progression or OS between the two arms among patients with platinum resistant disease (i.e. subgroup with PFI less than 6 months). The median PFS with weekly gemcitabine in platinum resistant EOC in these studies was approximately 15 weeks¹⁴⁻¹⁶.

2.4 Rationale

Rationale for combination of gemcitabine and VX-970

In vitro synergism between gemcitabine and VX-970 has been observed in several cancer cell lines (VX-970 Investigator Brochure). In addition, 76% of lung cancer cell lines and over 70% of pancreatic cell lines showed 3-fold or greater shift in the IC₅₀ of gemcitabine when VX-970 was added. Concurrent treatment of these cell lines with VX-970 and gemcitabine led to sustained and VX-970 dose-dependent decreases in P-CHK1 and concurrent dose-dependent increases in P-H2AX compared gemcitabine alone, suggesting that VX-970 disrupts ATR-mediated DDR signaling and leads to sustained accumulation of DNA damage in cancer cells co-treated with gemcitabine. The synergistic effect of VX-970 was shown to be maximal when VX-970 was administered 24 hours after starting gemcitabine treatment; later administration of VX-970 was less effective. This schedule dependence is attributed to an accumulation of cells in S-phase, and concomitant increase in ATR activity (measured by P-CHK1) that occurs in response to gemcitabine treatment alone. Thus, maximal impact of VX-970 is expected at a time when most cells are in S-phase as a result of gemcitabine treatment. Extended intervals (>48 hours) between

gemcitabine therapy and VX-970 exposure allows DNA damage to be repaired, permitting cells to exit S-phase and dramatically reducing the impact of ATR inhibition.

In vivo synergism of VX-970 and gemcitabine has been shown in a human pancreatic cancer xenograft model (PSN1 human tumor cell line) in nude mice. Oral (Figure 3A) and IV (Figure 3B) administration of VX-970 (in various schedules) dose-dependently sensitized tumors to gemcitabine. All combinations of VX-970 and gemcitabine were well tolerated and animals gained weight during the study. The optimal in vivo dose schedule for VX-970 was assessed in combination with gemcitabine in the same human pancreatic cancer xenograft model (PSN1). VX-970 was most effective when dosed 12 to 24 hours after administration of gemcitabine while dosing with VX-970, within 12 hours of gemcitabine administration, or beyond 24 hours of gemcitabine administration, reduced efficacy. Dosing with VX-970 before gemcitabine, or 48 hours after gemcitabine, provided no benefit over gemcitabine treatment alone (Figure 3C). Based on the in vitro and in vivo data, we hypothesize that VX-970 may enhance activity of gemcitabine and show acceptable toxicity and superior efficacy to gemcitabine alone in platinum resistant HGSCs. Based on the mechanistic effects of the ATR inhibitor VX-970, we expect that HGSCs which are known to be TP53 mutated, and commonly harbor molecular HR and NER alterations and cyclin E1 (*CCNE1*) amplification may be particularly sensitive to the gemcitabine/VX-970 combination (Figure 1). The randomized design is selected to evaluate the efficacy and safety of the combination of gemcitabine/VX-970 against single agent gemcitabine in platinum-resistant ovarian cancer. Furthermore, the proposed study design allows crossover from standard arm to gemcitabine/VX-970 after disease progression to enable the investigation of the efficacy of the gemcitabine/VX-970 following failure of single agent gemcitabine.

It is important to underscore that the platinum resistant HGSCs background may be particularly relevant for the gemcitabine/VX-970 combination. Specifically Huntoon et al.²² have shown that ATR inhibition (via siRNA or the ATR inhibitor VE-821) sensitizes HR proficient platinum resistant ovarian cancer cell lines (OVCAR8 and SKOV3) to gemcitabine. Furthermore, BRCA1 depletion (via siRNA) does not sensitize further to the combination of gemcitabine/ATR-inhibition i.e. combined BRCA1 depletion and ATR inhibition does not sensitize more to gemcitabine compared to ATR inhibition alone²². These data suggest that there is synergism between gemcitabine/ATR-inhibition in the HR-proficient (platinum resistant) setting which is not inferior to the synergism observed in the HR-deficient setting. Finally, gemcitabine/VX-970 may be particularly attractive for the platinum resistant tumors because ATR inhibition is particularly relevant in situations of high replicative stress such as in tumors with *CCNE1* amplification. *CCNE1* amplification is observed in 20% of ovarian cancers and is mutually exclusive with BRCA1 mutations. Ovarian cancers with *CCNE1* amplification are HR proficient and are enriched for platinum resistance and poorer outcome, suggesting that the gemcitabine/ATR inhibition combination may be particularly relevant for the platinum resistant setting.

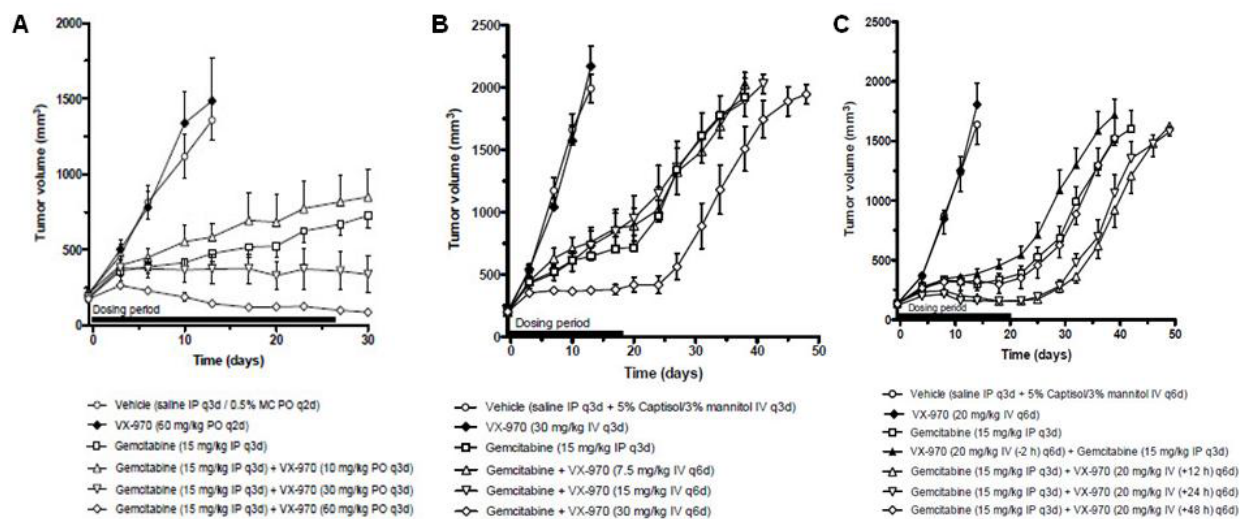


Figure 3. Effect of oral (Panel A), or IV (Panel B) VX-970 on tumor sensitivity to gemcitabine in nude mice bearing PSN1 human pancreatic cancer xenografts. Panel C illustrates the optimization of IV VX-970 dose schedule in combination with gemcitabine in vivo in the same pancreatic cancer xenograft model (Data taken from VX-970 Investigator Brochure).

In summary, we hypothesize that VX-970 may enhance activity of gemcitabine and show acceptable toxicity and superior efficacy to gemcitabine alone in platinum resistant ovarian or primary peritoneal or fallopian tube cancer. We expect that high grade serous ovarian or primary peritoneal or fallopian tube cancers which are known to be TP53 mutated, and commonly harbor molecular HR and NER alterations and cyclin E1 (CCNE1) amplification may be particularly sensitive to the gemcitabine/VX-970 combination. Therefore we propose a randomized open label, Phase 2 trial of VX-970 and gemcitabine versus gemcitabine alone in patients with recurrent platinum resistant high grade serous ovarian or primary peritoneal or fallopian tube cancers. The primary objective of the study would be to compare the PFS between gemcitabine/VX-970 and gemcitabine alone arms while the secondary objective of the study would be to compare safety and other measurements of clinical outcome (i.e. overall response rate (ORR) by RECIST, duration of response, clinical benefit response, CA125 response, PFS at 6 months and overall survival) between gemcitabine/VX-970 and gemcitabine alone arms. Finally, another secondary objective of our study is to enable the investigation of the efficacy (ORR) of the gemcitabine/VX-970 after crossover following failure of single agent gemcitabine. In this regard, we hypothesize that addition of VX-970 to gemcitabine will be clinically effective for patients who develop disease progression on gemcitabine alone.

Rationale for dosing of gemcitabine/VX-970 and gemcitabine alone in this study

In gemcitabine alone arm, gemcitabine IV 1000mg/m² Days 1 and 8 of a 21 day cycle will be used. This is based on a phase III trial comparing gemcitabine with PLD (which is a standard, FDA approved regimen for platinum resistant EOC) in platinum resistant ovarian cancer. In that trial¹⁵ which included 195 patients with platinum resistant EOC, gemcitabine (1,000 mg/m² days 1 and 8; every 21 days) exhibited similar PFS, ORR and OS compared to PLD (50mg/m² day 1; every 28 days).

The doses of gemcitabine and VX-970 that will be used in the combination arm of this Phase II

study were established in Study 001 Part A which was a Phase 1 dose escalation study of VX-970 in combination with gemcitabine. In that study, gemcitabine was administered on Days 1 and 8 and VX-970 on Days 2 and 9 of a 21 day cycle. VX-970 was escalated up to 210mg/m² on Days 2 and 9 of a 21 day cycle (the predicted human dose of VX-970 to achieve exposure with maximum activity in mouse = 120 mg/m²). Therefore, 210 mg/m² given on Days 2 and 9 of a 21 day cycle will be the dose that we will use in this Phase 2 study. In study 001 Part A, Gemcitabine was escalated to 1000mg/m² on Days 1 and 8 of a 21 day cycle (Table below) and this will be the dose (in combination with 210mg/m² on Days 2 and 9 of a 21 day cycle) which will be used in the combination arm of this Phase 2 study.

Table: Study 001 Part A Dose Escalation DLT Overview

Cohort	VX-970 Dose (mg/m²)	Gemcitabine Dose (mg/m²)	# of Subjects Enrolled/# of Evaluable Subjects for DLT	DLTs/Comments
1	18	875	3/3	0
2	36	875	3/3	0
3	72	875	7/6	2 (1 thrombocytopenia, 1 elevated ALT)
4	60	875	4/3	0
5	90	500	6/6	1 (elevated AST)
6	140	500	8/6	1 (elevated ALT)
7	210	500	3/3	0
8	210	750	3/3	0
9	210	875	7/6	0
10	210	1000	6/6	0

2.5 Correlative Studies Background

In the exploratory endpoints of our study, we hypothesize that tumors with high replicative stress may be associated with enhanced sensitivity to VX-970/gemcitabine. Therefore, we propose to explore whether baseline alterations associated with high replicative stress are predictive of clinical outcome after gemcitabine/VX-970 including:

- i) mutations in HR and NER pathway genes,
- ii) mutations in TP53, ATM and ATR,
- iii) Amplification of CCNE1, ATR or MYC,
- iv) homozygous deletion of PTEN
- v) Immunohistochemistry for ATM

Although TP53 mutations are found almost universally in high grade serous ovarian cancers, not all TP53 mutations abrogate TP53 function; a small fraction of TP53 mutations (approximately 10%) are not deleterious. Furthermore, in high grade serous ovarian cancer, approximately one third of TP53 mutations are truncating mutations leading to no expression of TP53 by immunohistochemistry. The remaining two thirds of TP53 mutations are missense mutations or in-frame deletions leading to increased expression of TP53 by immunohistochemistry. Given that the functional consequence of the heterogeneous TP53 mutations in terms of ATR inhibition is not known, we will explore their association with response to gemcitabine/VX-970. For these reasons, we propose to sequence TP53 and to perform TP53 immunohistochemistry (IHC). Of note, TP53 IHC is a standard test that is routinely performed and should be available for most patients prior to enrollment in our trial.

Finally, given that Alternative Lengthening of Telomeres (ALT) has been shown to be associated with response to ATR inhibition²³, we propose to evaluate whether ALT at baseline is predictive of clinical outcome after gemcitabine/VX-970.

The following assays will be performed (all on archival FFPE samples) to evaluate the aforementioned proposed exploratory biomarkers:

1. Multigene next generation sequencing assay (Oncopanel Assay)

At Dana Farber Cancer Institute, in the Department of Pathology Center for Advanced Molecular Diagnostic at Brigham and Women's Hospital, we have developed a cancer genomic assay to detect somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen or formalin-fixed paraffin-embedded samples "(Wagle et al. High-throughput detection of actionable genomic alterations in clinical tumor samples by targeted, massively parallel sequencing. *Cancer Discovery* 2012.)" The OncoPanel assay surveys exonic DNA sequences of 275 cancer genes and 91 introns across 30 genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. The Oncopanel assay assesses genes including mutations and copy number variations in TP53, CCNE1, MYC, ATR, ATM, PTEN and HR pathway and NER pathway genes. This assay will be performed in archival FFPE specimens if has not already been performed (it is now standard for patients at Dana Farber Cancer Institute).

2. TP53 and ATM Immunohistochemistry (IHC)

This will be performed in archival FFPE specimens using standard IHC protocols for TP53 and ATM IHC. TP53 IHC is a standard diagnostic test that is performed in most ovarian cancers to establish the diagnosis; the test will be performed only if it was not previously performed. TP53 IHC will be performed in the Department of Pathology at Brigham and Women's Hospital.

3. Detection of Alternative Lengthening of Telomeres (ALT)

Fluorescent in-situ hybridization (FISH) in archival FFPE samples with telomere specific probes will be performed in our institution in the Center of DNA Damage and Repair (CDDR).

4. Whole Exome Sequencing (WES)

In addition to the Oncopanel assay, archival FFPE samples will be submitted to Dr Levi Garraway's Lab in collaboration with the Broad Institute Genomics Platform for WES. WES allows evaluation of additional potential exploratory biomarkers of replicative stress that are not captured by Oncopanel. The Broad Genomics Platform has made a series of technological innovations that maximize the quality and speed of WES data generation, even when limiting or degraded FFPE starting material is used. As a result the platform is capable of generating WES data using as little as 20ng of genomic DNA. This assay will be performed on an individual basis, i.e. depending on findings from the Oncopanel assay and availability of FFPE tissue.

5. Pharmacokinetic Drug Level Monitoring

Blood samples will be collected from all patients enrolled in the clinical trial to monitor the concentration of VX-970 in plasma achieved at the end of the 60 min i.v. infusion of the drug for the doses given on days 2 and 9 of cycles 1 and 2. The pre-dose PK blood draw should be done 5 to 1 minute before infusion start. There is no time window for the post-infusion PK collection. Blood should be drawn at the same time that the infusion ends.

The concentrations of VX-970 will be determined by validated analytical method based upon reversed-phase high-performance liquid chromatography with electrospray ionization tandem mass spectrometry. The data will be used to estimate the variability in the peak concentration of VX-970 in plasma within and between patients and to assess correlations with measures of toxicity, response, and pharmacodynamic effects.

3. PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients must have histologically confirmed high grade serous ovarian or primary peritoneal or fallopian tube cancer. Platinum Resistant disease is defined as progression within 6 months after last platinum regimen.
- 3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm (≥ 2 cm) with conventional techniques or as ≥ 10 mm (≥ 1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease. Measurable disease by RECIST v1.1 with at least one measurable target lesion.

- 3.1.3 **Prior therapy:** No line limit but no more than 1 prior regimens in the platinum resistant setting. No prior treatment targeting the ATR/CHK1 pathway and no prior gemcitabine as single agent. Hormonal therapies, immunotherapy and antiangiogenic therapies (as single agents) do not count as lines; PARP-inhibitors count as line of therapy. Prior carboplatin/gemcitabine is allowed provided that there was no disease progression within 12 months after completion of the carboplatin/gemcitabine regimen. Subjects may begin protocol treatment at least 4 weeks or 5 half lives, whichever is shorter, after their last dose of chemotherapy or hormonal therapy, assuming they are otherwise eligible.
- 3.1.4 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of VX-970 in combination with gemcitabine in patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
- 3.1.5 ECOG performance status 0 or 1 (Karnofsky $\geq 70\%$, see Appendix A).
- 3.1.6 Life expectancy of greater than 6 months.
- 3.1.7 Adequate hematologic and end-organ function determined within 2 weeks prior to initiation of study treatment. Patients must have normal organ and marrow function as defined below:
- leukocytes $\geq 3,000/\text{mcL}$
 - absolute neutrophil count $\geq 1,500/\text{mcL}$
 - platelets $\geq 100,000/\text{mcL}$
 - total bilirubin within normal institutional limits
 - AST(SGOT)/ALT(SGPT) $\leq 2.5 \times$ institutional upper limit of normal
 - creatinine \leq upper limit of institutional normal
- OR
- creatinine clearance $\geq 60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ for patients with creatinine levels above institutional normal.
- 3.1.8 Confirmation of availability of a formalin-fixed, paraffin-embedded (FFPE) tumor specimen with adequate tumor tissue (either one paraffin embedded tissue block OR 10 5-micron unstained slides from the block on regular (non-plus) slides and 1 H&E slide).
- 3.1.9 All acute, clinically significant treatment-related toxicity from prior therapy, except for alopecia, must have resolved to Grade ≤ 1 prior to study entry.
- 3.1.10 At least 4 weeks since major surgery or radiation therapy.

- 3.1.11 The effects of VX-970 on the developing human fetus are unknown. For this reason and because DNA damage inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and 6 months after completion of study. 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.
- 3.1.12 No known hypersensitivity or contraindication to the components of study treatment (VX-970, gemcitabine).
- 3.1.13 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

- 3.2.1 Patients with primary platinum refractory disease, defined as progression while first line platinum based chemotherapy
- 3.2.2 Patients who have had chemotherapy within 4 weeks or five half lives, whichever is shorter, (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier
- 3.2.3 Patients who have had radiotherapy within 4 weeks
- 3.2.4 Patients who are receiving any other investigational agents.
- 3.2.5 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. A scan to confirm the absence of brain metastasis is not required.
- 3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to VX-970 or gemcitabine.

- 3.2.7 VX-970 is primarily metabolized by CYP3A4; therefore concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients. Patients receiving any medications or substances that are inhibitors or inducers of cytochrome P450 3A (CYP3A4 enzyme) are ineligible. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.
- 3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.9 Pregnant women are excluded from this study because VX-970 and/or gemcitabine are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with VX-970 and/or gemcitabine, breastfeeding should be discontinued if the mother is treated with VX-970 and/or gemcitabine.
- 3.2.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with VX-970 and/or gemcitabine. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Members of all races and ethnic groups are eligible for this trial. This study is design for female patient only.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the **CTEP Investigator Registration Help Desk** by email at pmbregpend@ctep.nci.nih.gov.

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (*i.e.*, all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (*i.e.*, all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the **CTEP Associate Registration Help Desk** by email at ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office

before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

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

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9944 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to <https://www.ctsu.org> and log in using your CTEP IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MA036, and protocol 9944.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Submitting Regulatory Documents

Requirements For 9944 Site Registration:

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

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

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

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

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

4.2.3 Checking Site Registration Status

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

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

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

4.3 **Patient Registration**

4.3.1 OPEN / IWRS

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

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

Once a slot reservation request has been made, the following source documentation

should be faxed to the Lead Institution or designee for confirmation of eligibility.

- Copy of required laboratory tests:
 - CBC with differential
 - Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, total protein)
 - PT or INR with PTT
 - CA125
 - B-HCG pregnancy test, if applicable
- Signed informed consent form
- HIPAA authorization form (if separate from the informed consent document)
- EKG
- CT scan
- Pathology report
- Screening or most recent clinic visit note (including documentation of oncologic history, past medical history, concomitant medications)

The Lead Institution or designee may then approve the slot reservation to allow completion of enrollment.

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- To approve slot reservations or access cohort management: Be identified to Theradex as the “Client Admin” for the study.
- Have regulatory approval for the conduct of the study at their site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: <http://theradex.com/CTMS/Downloads.aspx>. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Other issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

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

Premedication with anti-emetics (excluding aprepitant [Emend]) is allowed according to standard practice guidelines. Hematopoietic growth factors may be used to treat neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) or Institutional guidelines.

Gemcitabine Administration

Gemcitabine should be administered by IV infusion at a dose of 1000 mg/m² alone or at a dose of 1000 mg/m² in combination with VX-970 over 30 minutes (study sites may follow standard of care dosing windows) on days 1 and 8 of a 21 day cycle (or until toxicity necessitates reducing or holding a dose). The gemcitabine dose will be individually calculated for all infusion visits according to the subject's current weight. In calculating the dose, there will be no downward adjustment to "ideal" body weight unless institution policy requires it. Treatment regimen is described in the tables below

VX-970 Administration

VX-970 should be administered 24 hours (+/- 4 hour) after Gemcitabine by IV infusion at a dose of 210 mg/m² over 1 hour on days 2 and 9 of a 21 day cycle. The VX-970 dose on Day 2 will be calculated using the weight on Day 1 or Day 2 (i.e. weight assessment on day 2 is optional, and VX-970 dose may be calculated based on weight taken on Day 1). Similarly, the VX-970 dose on Day 9 will be calculated using the weight on Day 8 or Day 9 (i.e. weight assessment on day 9 is optional, and VX-970 dose may be calculated based on weight taken on Day 8). In calculating the dose, there will be no downward adjustment to "ideal" body weight unless institution policy requires it. VX-970 should not come in contact with 0.9% Sodium Chloride due to incompatibility. 5% dextrose in water solution must be used for IV line priming and

flushing. Infuse using an infusion set containing low-sorption or non-PVC, DEHP-free tubing and an in-line 0.2 micron filter. Treatment regimen is described in the tables below:

Regimen Description: gemcitabine alone arm					
<i>Agent</i>	<i>Premedications; Precautions</i>	<i>Dose</i>	<i>Route</i>	<i>Schedule</i>	<i>Cycle Length</i>
Gemcitabine	Per institutional guidelines	1000 mg/m ² in NS per institutional guidelines	IV over 30 minutes or according to institutional standards	Days 1 and 8	21 days (3 weeks)

Regimen Description: VX-970 plus gemcitabine arm					
<i>Agent</i>	<i>Premedications; Precautions</i>	<i>Dose</i>	<i>Route</i>	<i>Schedule</i>	<i>Cycle Length</i>
VX-970	Steroid and antihistamine combination (Section 5.1.1)	210 mg/m ² in D5W to a final concentration between 0.075 mg/ml and 1 mg/ml	IV over 1 hour	Days 2 and 9	21 days (3 weeks)
Gemcitabine	Per institutional guidelines	1000 mg/m ² in NS per institutional guidelines	IV over 30 minutes or according to institutional standards	Days 1 and 8	

Patients on the gemcitabine/VX-970 arm will receive: Based on Study 001 Part A, which was a dose escalation study of VX-970 in combination with gemcitabine, gemcitabine is administered on Days 1 and 8 and VX-970 on Days 2 and 9 of a 21 day cycle. VX-970 has been escalated up to 210mg/m² on Days 2 and 9 of a 21 day cycle (the predicted human dose of VX-970 to achieve exposure with maximum activity in mouse = 120 mg/m²). Gemcitabine was escalated to 1000mg/m² on Days 1, 8 of a 21 day cycle with VX-970 given at 210mg/m² on days 2 and 9 of a 21 day cycle and was tolerated well. Therefore in the combination arm we will treat according to the table above with 1000mg/m² of gemcitabine on days 1 and 8, and 210mg/m² of VX-970 on days 2 and 9 of a 21 day cycle.

Treatment will continue until disease progression or intolerable toxicity and patients who progress on weekly gemcitabine alone will be allowed to crossover to the experimental gemcitabine/VX-970 arm.

5.1.1 VX-970 (preparation and recommendations)

VX-970 absorbs in the UV-visible radiation spectrum and is widely distributed including to the skin, so subjects should be cautioned to minimize exposure to the sun and other sources of visible and UV radiation and to take protective measures when necessary. Furthermore:

(1) VX-970 will be supplied as 20 mg/mL VX-970 (in betadex sulfobutyl ether and acetate buffer) to be diluted in D5W before intravenous infusion. VX-970 solution will be constituted into the individual dosing containers by a qualified pharmacist.

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

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

Based on the observation of acute hypersensitivity in 3 subjects at various doses of VX-970 and of pruritus in 2 subjects at 480 mg/m² of VX-970, pre-medication with a corticosteroid and an antihistamine will be performed for all subjects receiving VX-970 and gemcitabine to prophylax against possible acute hypersensitivity.

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

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

5.1.2 Gemcitabine

Please refer to gemcitabine package insert for additional information.

5.2 **General Concomitant Medication and Supportive Care Guidelines**

Because there is a potential for interaction of VX-970 and/or gemcitabine with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug

interactions. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients. Because VX-970 is primarily metabolized by CYP3A4, concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients. Patients receiving any medications or substances that are inhibitors or inducers of cytochrome P450 3A (CYP3A4 enzyme) are ineligible. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

5.3 Duration of Therapy

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

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

Patients with CA125 elevation alone may continue on study as long as they have not developed progressive disease by RECIST.

Patients who develop disease progression by RECIST 1.1 on weekly gemcitabine alone will be allowed to crossover to the experimental gemcitabine/VX-970 arm; in that case, treatment will continue until one of the above criteria stated in this section applies. Importantly, patients on weekly gemcitabine alone arm are not allowed to cross over to the combined gemcitabine/VX-970 arm based on CA125 elevation alone; Progressive disease by RECIST must be documented before cross over is allowed to the combined gemcitabine/VX-970 arm.

5.4 Duration of Follow Up

Participants will be followed for 3 years after removal from study treatment or until death, whichever occurs first. They will be followed up for survival status every 3 months (+/- 2 weeks) for one year after stopping study treatment; and every 6 months (+/- 2 weeks) thereafter until death. Subjects may withdraw from study treatment but still continue study follow-up procedures. Date and cause of death should be provided for participants who become deceased

within the 3 year interval following removal from the study treatment.

Participants removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study Treatment

Patients will be removed from study treatment when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed from study treatment must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Toxicity will be assessed utilizing the NCI CTCAE v4.0 (<http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE>), unless otherwise specified.

Brief treatment or visit delays (± 3 days) for public holidays or weather conditions do not constitute a protocol violation but should be recorded.

Any patient requiring a toxicity-related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Principal Investigator for the patient to continue.

The VX-970 and gemcitabine dose level reductions for both treatment Arms are presented in the tables below.

VX-970 Dose Level Reductions for Toxicity			
Arm	VX-970 Starting dose	VX-970 -1 level	VX-970 -2 level
gemcitabine/VX-970 ^a	210 mg/m ²	165 mg/m ²	120 mg/m ²

^a VX-970 once daily for 2 days on Days 2 and 9 of a 21 day cycle

gemcitabine Dose Level Reductions for Toxicity			
Arm	gemcitabine Starting dose	gemcitabine -1 level	gemcitabine -2 level
gemcitabine alone	1000 mg/m ²	750 mg/m ²	500 mg/m ²

gemcitabine^a /VX-970	1000 mg/m2	750 mg/m2	500 mg/m2
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^a gemcitabine once daily for 2 days on Days 1 and 8 of a 21 day cycle

Cross Over

For patients on the gemcitabine alone arm who cross over to the gemcitabine/VX-970 arm and their gemcitabine dose was already reduced, then the dose of gemcitabine in the combined arm will be the same as the reduced dose they were receiving on the gemcitabine alone arm (i.e. if it was dose reduced to 750mg/m2, they will get 750mg/m2 in the combined gemcitabine/VX-970 arm).

6.1 Dose Modifications due to Non-Hematologic Toxicity

- In case of Grade 3 nausea/vomiting/diarrhea despite adequate supportive and prophylactic antiemetic and/or antidiarrheal coverage, both VX-970 and gemcitabine will be dose reduced by 1 dose level. Furthermore, treatment will be interrupted and may be resumed when all toxicities (nausea/vomiting/diarrhea) have returned to Grade 2 or less at the discretion of the investigator. If adequate supportive and prophylactic antiemetic and/or antidiarrheal coverage had not been provided, then the investigators may continue with the same dosing as long as maximum antiemetic and/or antidiarrheal coverage is provided.
- In case of Grade 3 or higher non-hematologic toxicity (excluding nausea/vomiting/diarrhea), treatment will be interrupted and may be resumed when all toxicities have returned to Grade 2 or less, at the discretion of the investigator.
 - For the following non-hematologic toxicities, once the toxicity has returned to Grade 2 or less, dosing can be resumed at a lower dose level of gemcitabine (gemcitabine and not VX-970 is dose reduced). If any of the below drug-related toxicity is subsequently observed with the reduced dose of gemcitabine, VX 970 dose will then be reduced by one dose level:
 - a) Grade 3 non-hematologic toxicity
 - b) Any Grade 2 or lower non-hematologic toxicity requiring dose delay of more than 2 weeks
 - For Grade 4 non-hematologic toxicities, treatment will be interrupted and may be resumed at a lower dose when toxicity has returned to Grade 2 at less. Both gemcitabine and VX-970 will be reduced by one dose level.
- For infusion reactions, hypersensitivity or allergic reactions related or possibly related to VX-970 then please refer to section 5.1.1 for management with prophylactic steroids and H1-blockers. If an infusion reaction/hypersensitivity or allergic reaction related or possibly related to VX-970 occurs despite prophylactic steroids and H1-blockers then protocol treatment will be discontinued.

- If any toxicity not described above results in delay in dosing in any Part of the Study and the subject may be benefitting from therapy, then at the discretion of the investigator, the dose of VX 970 or chemotherapy may be reduced by one dose level.
- For toxicities that lead to a dose reduction, the dose will not be re-escalated during subsequent cycles.
- If both drugs have been dose reduced by 2 dose levels and another dose reduction is required then VX-970 can be continued alone (i.e. -2 dose level).

If drug must be held, particularly on days 8 and 9, the dose will be omitted. The study clock does not stop for these dose holds.

6.2 Dose Modifications due to Hematologic Toxicity

- Complete blood counts (CBC) will be obtained for all patients at Days 1 and 8 of each cycle. In case of Grade 3 or higher hematologic toxicity, treatment will be interrupted and ANC and platelets should be monitored weekly until recovery. If hematologic parameters do not recover within 28 days, the patient should be removed from the study treatment. Treatment may be resumed when all toxicities have returned to Grade 2 or less, at the discretion of the investigator.
- The following hematologic dose modifications and management guidelines will be followed:

Day 1 of any cycle

ANC		PLT	Action
≥1000	AND	≥75,000	No dose modification. Proceed with treatment with gemcitabine on Day 1 and VX-970 on Day 2
<1000	OR	<75,000	Delay by 1 week intervals until recovery

Day 8 of any cycle

ANC		PLT	Action
>750	AND	>75,000	No dose modification. Proceed with treatment with gemcitabine on Day 8 and VX-970 on Day 9
500-750	OR	50,000-75,000	Hold gemcitabine on Day 8 and VX-970 on Day 9; Consider G-CSF
<500	OR	<50,000	Hold gemcitabine on Day 8 and VX-970 on Day 9; Dose

	reduce gemcitabine by one level; Consider G-CSF
--	---

- For the following hematologic toxicities, once the toxicity has returned to Grade 2 or less, dosing can be resumed with one dose level reduction in gemcitabine dose (except if gemcitabine has already been dose reduced in the same cycle). If, after reduction of gemcitabine dose, any of the below drug-related hematologic toxicities is subsequently observed, then the dose of VX-970 will be reduced by one level.
 - a) Grade 4 thrombocytopenia
 - b) Febrile neutropenia (growth factor support, per site protocol, may be used in lieu of dose reduction)
 - c) Grade 4 neutropenia lasting more than 7 days (growth factor support, per site protocol, may be used in lieu of dose reduction)

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with **bold** and *italicized* text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

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

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

7.1.1 CAEPR for VX-970

Comprehensive Adverse Events and Potential Risks list (CAEPR)

**for
VX-970 (NSC 780162)**

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

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

Version 1.2, August 9, 2016¹

Adverse Events with Possible Relationship to VX-970 (CTCAE 4.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	<i>Anemia (Gr 2)</i>
GASTROINTESTINAL DISORDERS	
Diarrhea	
Nausea	<i>Nausea (Gr 2)</i>
Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	<i>Fatigue (Gr 2)</i>
Infusion related reaction	
IMMUNE SYSTEM DISORDERS	
Immune system disorders (acute hypersensitivity reactions)	
INFECTIONS AND INFESTATIONS	
Urinary tract infection	
INVESTIGATIONS	
Alanine aminotransferase increased	
Creatinine increased	
NERVOUS SYSTEM DISORDERS	
Headache	
Lethargy	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Pruritus	
Rash maculo-papular	
VASCULAR DISORDERS	
Flushing	

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

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

GASTROINTESTINAL DISORDERS - Abdominal pain; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever
IMMUNE SYSTEM DISORDERS - Allergic reaction
INVESTIGATIONS - Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Anorexia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression)
NERVOUS SYSTEM DISORDERS - Dizziness
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hypohidrosis
VASCULAR DISORDERS - Hypotension

Animal Data: The following toxicities have been observed in animal studies with VX-970:

Dogs

GASTROINTESTINAL DISORDERS - salivation
HEPATOBIILIARY DISORDERS - bile duct hyperplasia; cachexia secondary to liver toxicity; cholestasis; periportal vacuolation in the liver
INVESTIGATIONS - increases in alkaline phosphatase; increases in eosinophils; increases in phosphorus; increases in sorbitol dehydrogenase; increases in urine bilirubin
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - pale mucous membranes

Dogs and Rats

GASTROINTESTINAL DISORDERS - fecal abnormalities
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - hunched posture
INVESTIGATIONS - decrease in RETIC, decreases in reticulocytes; increase in reticulocytes
METABOLISM AND NUTRITION DISORDERS - dehydration
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - degeneration/atrophy of the seminiferous tubules of the testes, testicular degeneration/atrophy of seminiferous tubules

Rats

BLOOD AND LYMPHATIC SYSTEM DISORDERS - extramedullary hematopoiesis in liver and spleen; increase in spleen organ weight; inflammation and/or necrosis in spleen
ENDOCRINE DISORDERS - increase in adrenal organ weight
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - material around the nose/muzzle
HEPATOBIILIARY DISORDERS - inflammation and/or necrosis in liver
IMMUNE SYSTEM DISORDERS - decrease in thymus organ weight
INVESTIGATIONS - decrement in eosinophils; increase in MCV; increase in neutrophils; increase in platelets, increase in PLT; organ weight changes
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - decrease in ovary organ weight; decrease in prostate organ weight; decrease in seminal vesicle organ weight; decrease in testes organ weight; decrease in uterus organ weight; stained anogenital area
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - inflammation and/or necrosis in lung
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - loss of skin elasticity

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

7.1.2 **Adverse Event List(s) for gemcitabine**

The following adverse events have been associated with gemcitabine:

i) Schedule-dependent Toxicity

In clinical trials evaluating the maximum tolerated dose of Gemcitabine, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life of Gemcitabine is influenced by the length of the infusion).

ii) Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with Gemcitabine as a single agent and the risks are increased when Gemcitabine is combined with other cytotoxic drugs. In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of patients receiving single-agent Gemcitabine. The frequencies of Grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in patients receiving Gemcitabine in combination with another drug.

iii) Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of Gemcitabine.

iv) Hemolytic Uremic Syndrome

Hemolytic uremic syndrome, including fatalities from renal failure or the requirement for dialysis, can occur in patients treated with Gemcitabine. In clinical trials, HUS was reported in 6 of 2429 patients (0.25%).

v) Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs. Administration of Gemcitabine in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency.

vi) Embryofetal Toxicity

Gemcitabine can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits.

vii) Exacerbation of Radiation Therapy Toxicity

Gemcitabine is not indicated for use in combination with radiation therapy.

viii) Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving Gemcitabine as a single agent or in combination with other chemotherapeutic agents.

ix) Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving Gemcitabine as a single agent or in combination with other chemotherapeutic agents. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances.

Please refer to the package insert for the comprehensive list of adverse events.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. The investigator must determine and record the severity of all serious and non-serious AEs. The CTCAE Version 4.0 (Cancer Therapy Evaluation Program website; available at: <https://evs.nci.nih.gov/ftp1/CTCAE/About.html>) should be used for grading the severity of AEs. AEs of CTCAE Grades 4 and 5 should be documented as “life-threatening”.
- **For expedited reporting purposes only:**
 - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
 - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.
- **Attribution** of the AE:
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

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

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

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

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

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

Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) - Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
 An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not Applicable

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported**

expeditiously through CTEP-AERS must also be reported in routine study data submissions.

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

7.5 Secondary Malignancy

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

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

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

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

7.6 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

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

8.1 VX-970 (NSC # 780162)

8.1.1 Pharmaceutical Information for VX-970 (NSC # 780162)

Other Names: VRT-0768079, VE-822

Classification: ATR inhibitor

Molecular Formula: C₂₄H₂₆ClN₅O₃S

M.W.: 500.01 Da

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

Description: The drug substance for VX-970 is the HCl salt.

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

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

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

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

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

Route of Administration: Intravenous (IV) infusion.

Method of Administration: Prior to administration the solution should be given one hour at ambient temperature to warm up if stored refrigerated following preparation. Infuse over 60 minutes using an infusion set containing low-sorption or non-PVC, DEHP-free tubing and an in-line 0.2

micron filter. 5% dextrose in water solution must be used for IV line priming and flushing. VX-970 should not come in contact with 0.9% Sodium Chloride due to incompatibility. The infusion time may be extended beyond 60 minutes (as tolerated) but no more than 90 minutes if standard procedures to limit symptoms of an infusion reaction are insufficient or if the total volume of the infusion exceeds 600 mL. To minimize the possibility of phlebitis, VX-970 should be administered through a large bore catheter into a large caliber peripheral vein or via a standard intravenous catheter or port/port-a-cath. .

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

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

Availability

VX-970 (NSC # 780162) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

VX-970 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment

of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

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

8.1.2.4 Useful Links and Contacts

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

8.2 Gemcitabine (NSC 613327)

8.2.1 Pharmaceutical Information for Gemcitabine (NSC 613327)

8.2.1.1 Description/How Supplied/Storage

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

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

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

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

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

8.2.1.2 Preparation for Intravenous Infusion Administration and Stability

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

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

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

8.2.1.3 Agent Source

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

In the exploratory endpoints of our study, we hypothesize that tumors with high replicative stress may be associated with enhanced sensitivity to VX-970/gemcitabine. Therefore, we propose to explore whether baseline alterations associated with high replicative stress such as:

- i) mutations in HR and NER pathway genes,
 - ii) mutations in TP53, ATM and ATR,
 - iii) Amplification of CCNE1, ATR or MYC,
 - iv) homozygous deletion of PTEN
 - v) loss of ATM expression by immunohistochemistry
- are predictive of clinical outcome after gemcitabine/VX-970.

Regarding TP53 mutations, although TP53 mutations are found almost universally in high grade serous ovarian cancers, not all TP53 mutations abrogate TP53 function; a small fraction of TP53 mutations (approximately 10%) are not deleterious. Furthermore, in high grade serous ovarian cancer, approximately one third of TP53 mutations are truncating mutations leading to no expression of TP53 by immunohistochemistry. The remaining two thirds of TP53 mutations are

missense mutations or in-frame deletions leading to increased expression of TP53 by immunohistochemistry. Given that the functional consequence of the heterogeneous TP53 mutations in terms of ATR inhibition is not known, we will explore their association with response to gemcitabine/VX-970. For these reasons, we propose to sequence TP53 and to perform TP53 immunohistochemistry. Of note, TP53 IHC is a standard test that is routinely performed and should be available for most patients prior to enrollment in our trial. Finally, given that Alternative Lengthening of Telomeres (ALT) has been shown to be associated with response to ATR inhibition, we propose to evaluate whether ALT at baseline is predictive of clinical outcome after gemcitabine/VX-970.

9.1 Exploratory/Ancillary Correlative Studies

The following assays will be performed to evaluate the aforementioned proposed exploratory biomarkers:

1. Multigene next generation sequencing assay (Oncopanel Assay)

At Dana Farber Cancer Institute, in the Department of Pathology Center for Advanced Molecular Diagnostic at Brigham and Women's Hospital, we have developed a cancer genomic assay to detect somatic mutations, copy number variations and structural variants in tumor DNA extracted from fresh, frozen or formalin-fixed paraffin-embedded samples (Wagle et al. High-throughput detection of actionable genomic alterations in clinical tumor samples by targeted, massively parallel sequencing. *Cancer Discovery* 2012). The OncoPanel assay surveys exonic DNA sequences of 275 cancer genes and 91 introns across 30 genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. The Oncopanel assay assesses genes including mutations and copy number variations in TP53, CCNE1, MYC, ATR, ATM, PTEN and HR pathway and NER pathway genes. This assay will be performed in archival FFPE specimens if has not already been performed (it is now standard for patients at Dana Farber Cancer Institute).

2. TP53 and ATM Immunohistochemistry (IHC)

This will be performed in archival FFPE specimens using standard IHC protocols for TP53 IHC. TP53 IHC is a standard diagnostic test that is performed in most ovarian cancers to establish the diagnosis; the test will be performed only if it was not previously performed. TP53 IHC will be performed in the Department of Pathology at Brigham and Women's Hospital.

3. Detection of Alternative Lengthening of Telomeres (ALT)

Fluorescent in-situ hybridization (FISH) in archival FFPE samples with telomere specific probes will be performed in our institution in the Center of DNA Damage and Repair (CDDR).

4. Whole Exome Sequencing (WES)

In addition to the Oncopanel assay, archival FFPE samples will be submitted to Dr Levi Garraway's Lab in collaboration with the Broad Institute Genomics Platform for WES. WES allows evaluation of additional potential exploratory biomarkers of replicative stress that are not captured by Oncopanel. The Broad Genomics Platform has made a series of technological innovations that maximize the quality and speed of WES data generation, even when limiting or

degraded FFPE starting material is used. As a result the platform is capable of generating WES data using as little as 20ng of genomic DNA. This assay will be performed on an individual basis, i.e. depending on findings from the Oncopanel assay and availability of FFPE tissue.

5. Pharmacokinetic Drug Level Monitoring

Blood samples will be collected from all patients enrolled in the clinical trial to monitor the concentration of VX-970 in plasma achieved at the end of the 60 min i.v. infusion of the drug for the doses given on days 2 and 9 of cycles 1 and 2. The pre-dose PK blood draw should be done 5 to 1 minute before infusion start. There is no time window for the post-infusion PK collection. Blood should be drawn at the same time that the infusion ends. At each sample time, collect 3 mL of blood from a vein in the arm not receiving the infusion of drug by direct venipuncture in a lavender top Vacutainer plastic tube with spray dried K₂EDTA (Becton Dickinson, product no. 367835 or 367856). Gently invert the tube 5-times to thoroughly mix the blood and with the anticoagulant. Insert the blood collection tube in a container of wet ice until centrifuged for 10 min at 1,300 g and 4°C within 30 min after collection. Using a disposable pipette, carefully remove the plasma without disturbing the packed blood cells and transfer approximately equal volumes into two self-standing, 2.0 mL, polypropylene cryovials with external threads (e.g. Thermo Fisher Scientific, product no., 5000-0020). Attach a preprinted label to each cryovial with the following information: protocol no., patient entry no., sample no., sample collection date, sample collection time, Aliquot A or Aliquot B. Wrap the label with protective cryogenic freezer tape (Fisher Scientific, product no. 11-867B). Be sure not to allow the label or tape to cover any part of the vial cap. Place the tube on crushed dry-ice until stored in a freezer maintained at ≤ -70°C until packaged for shipment

The samples in the vials labeled "Aliquot A" must be shipped separately from the "Aliquot B" vials. Place the sample tubes in a fiberboard freezer box sealed in a zip lock plastic bag. Put at least three inches of crushed dry ice in a seamless styrofoam container. Place the plastic bag containing the samples in the box, on top of the crushed dry ice, and cover with an additional three inches or more of dry ice. Seal the styrofoam container within a tight-fitting cardboard shipping box. Send the samples on a Monday, Tuesday, or Wednesday by overnight courier for next day delivery by 10:00 a.m. to:

Dr. Jeffrey G. Supko
Massachusetts General Hospital
55 Fruit St., GRJ 1025
Boston, MA 02114
Tel: 617-724-1970

Notification of the shipment, the name of the courier service, and the courier tracking no. must be made by sending an e-mail to alitman@partners.org and jsupko@partners.org. Attach files for the Shipping Manifest and the Pharmacokinetic Sample Time Form for each set of samples to the email.

9.1.1 Collection, Shipping and Sites performing exploratory assays.

As a part of the eligibility criteria, only patients with available archival FFPE tissue (either one paraffin embedded tissue block OR 10 5-micron unstained slides from the block on regular (non-plus) slides and 1 H&E slide) will be accrued onto this study. This archival FFPE tissue specimen will be analyzed with the aforementioned assays (section 9.1). FFPE block or unstained slides will be batch shipped upon trial completion to Dana-Farber Cancer Institute.

Sarah Farooq, MPH
Dana-Farber Cancer Institute
450 Brookline Ave, Boston, MA 02215

All studies will be performed at the DFCI/Brigham and Women’s hospital. Specifically, the Oncopanel assay and TP53 IHC will be performed at the Department of Pathology at Brigham and Women’s Hospital. ALT assay will be performed at the Center of DNA Damage and Repair (CDDR) at DFCI. WES will be performed at Dr Levi Garraway’s Lab at DFCI in collaboration with the Broad Institute of Genomics.

10. STUDY CALENDAR

The physical examination, medical history, concomitant medications recorded ≤ 14 days prior to trial entry; EKG, ECOG PS, complete blood count with differential and platelets, and clinical chemistry should be done ≤ 14 days prior to initiation of treatment. However, if these initial examinations are obtained within 3 days prior to the initiation of treatment they do not have to be repeated. Scans to document evaluable disease (i.e., tumor measurement) should be performed ≤ 28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

Assessments must be performed prior to administration of any study agent.

A +/- 3 day window will be allowed for Day 1 of Cycle 2 and subsequent treatment cycles. If Day 1 is moved, then Day 8 can be moved. Please note that Day 2 and Day 9 should occur 24 hours (+/- 4 hours) after Day 1 and Day 8 respectively.

	Pre Study	Screen	Day 1	Day 2	Day 8	Day 9	Off Study treatment ⁸
VX-970 ¹²				X		X	
Gemcitabine			X		X		
Informed consent	X						
Archival FFPE sample	X						
Demographics		X					
Medical history		X					

Physical exam		X	X				X
Concomitant Medications		X	X		X		
Vital signs ¹		X	X	X	X	X	X
Height		X					
Weight ¹³		X	X	X	X	X	
ECOG Performance status		X	X		X		X
Coagulation (PT, PTT, INR) ³		X					
CBC w/diff, plts		X	X ¹¹		X		X
Clinical chemistry ²		X	X ¹¹		X		X
CA125 ⁹		X	X				X
Adverse event evaluation			X		X		X
CT or MRI scan (chest, abdomen, pelvis) and Tumor assessments (RECIST 1.1) ^{5, 6, 7}		X	CT scan and tumor assessment should be performed every 9 weeks . Documentation (radiologic) must be provided for patients removed from study for progressive disease.				
B-HCG ⁴		X					
EKG		X					
PK ¹⁰				X		X	

¹ Vital signs will include resting heart rate, blood pressure, temperature and weight at the screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to chemotherapy administration according to institutional practice.

² Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST, ALT, total bilirubin, total protein, and albumin.

³ Coagulation studies will be performed at baseline only (PT or INR with PTT); they will be repeated beginning of every cycle if patient on coumadin.

⁴ Pregnancy tests will only be performed in women of childbearing potential within 14 days prior to first dose of study treatment.

⁵ Patients will be restaged after every 3 cycles (every 9 weeks [± 7 days]). Patients with unacceptable toxicity should be discontinued from the study; patients with SD or response to therapy will continue treatment. Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy. If a patient on the gemcitabine alone arm is removed for clinical progression a CT scan may be done to prove RECIST progression. Patients with progressive disease per RECIST 1.1 on the gemcitabine alone arm are allowed to cross over to the gemcitabine/VX-970 arm. Patients with progressive disease per RECIST 1.1 on gemcitabine/VX-970 arm will be discontinued from the study.

⁶ CT scans of the chest and abdomen and pelvis are required at baseline and every 3 cycles (9 weeks). The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures.

⁷ Patients continuing study treatment for a minimum of 1 year may have the tumor imaging assessments expanded to every 4 cycles (12 weeks [± 7 days]).

⁸ The End of Study Treatment Visit will be performed within 30 days from the last treatment dose. Reassessments for toxicity, disease progression, and survival will be performed 30 days from last treatment dose. Follow up of patients after removal from study treatment will be as described in Section 5.4.

⁹ CA-125 serum sample collected at baseline, Day 1 of each cycle and at the end-of-study treatment visit.

- ¹⁰ PK: Blood samples will be collected from patients enrolled on the gemcitabine + VX-970 arm of the clinical trial to monitor the concentration of VX-970 in plasma achieved at the end of the 60 min i.v. infusion of the drug for the doses given on days 2 and 9 of cycles 1 and 2. The pre-dose PK blood draw should be done 5 to 1 minute before infusion start. There is no time window for the post-infusion PK collection. Blood should be drawn at the same time that the infusion ends. Please refer to section 9 for more details.
- ¹¹ Patients do not need to re-meet eligibility criteria on Cycle 1 Day 1 in order to be treated.
- ¹² Only patients being treated on the gemcitabine + VX-970 arm need to come in on Day 2 and Day 9.
- ¹³ Weight assessment on day 2 and 9 are optional, and VX-970 dose may be calculated based on weight taken on day 1 and 8, respectively.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans should also be obtained within 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with VX-970.

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

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

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

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

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

PET-CT At present, the low dose or attenuation correction CT portion of a combined

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

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

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

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

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

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

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

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-

PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must

normalize for a patient to be considered in complete clinical response.

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

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Confirmatory scans will be required for response (PR or CR) *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p>				

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

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

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

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

PFS is defined as the number of days from the date the subject was randomized to the date of documented progressive disease (PD) by RECIST version 1.1 or death (regardless of cause).

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

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

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

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

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

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (<https://eapps-ctep.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

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

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

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: <http://www.theradex.com/CTMS>. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

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

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

An End of Study CRF is to be completed by the PI, and is to include the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (<http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models>). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent

possible to promote data integrity.

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

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

12.3 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. The DSMC will provide the Overall PI an outcome of the review, which will be forwarded to all sites, and discussed on regular teleconferences if needed.

12.4 Collaborative Agreements Language

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

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

(an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

- a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
 4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
 5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
 6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release.

Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

We propose a randomized open label, Phase 2 trial of VX-970 and gemcitabine versus gemcitabine alone in patients with recurrent platinum resistant high grade serous ovarian or primary peritoneal or fallopian tube cancers. Specifically, patients with platinum resistant high grade serous ovarian or primary peritoneal or fallopian tube cancer will be randomized 1:1 to either gemcitabine alone or gemcitabine/VX-970. There is no limit in the number of previous chemotherapy regimens, but patients are not eligible if they have received more than 1 prior regimen in the platinum resistant setting. Treatment will continue until disease progression and patients who progress on weekly gemcitabine alone will be allowed to crossover to the experimental gemcitabine/VX-970 arm. Only patients with available archival FFPE tissue (either one paraffin embedded tissue block OR 10 5-micron unstained slides from the block on regular (non-plus) slides and 1 H&E slide) will be eligible to participate in this study.

The primary endpoint of the study is to compare the PFS between gemcitabine/VX-970 and gemcitabine alone arms. PFS is defined as the number of days from the date the subject was randomized to the date of documented progressive disease (PD) by RECIST version 1.1 or death (regardless of cause).

The secondary endpoints include to determine and compare overall response rate (ORR) by RECIST, PFS at 6 months, CBR, DOR, CA125 reduction by 50% and OS between gemcitabine/VX-970 and gemcitabine alone arms. Furthermore, we will determine and compare the safety profile of gemcitabine/VX-970 and gemcitabine alone regimens.

We will perform a modified intent-to-treat analysis that includes all patients who are randomized and initiate protocol therapy. Patients who go off treatment for reasons unrelated to progression will be included in the analysis regardless of non-protocol therapy. Patients who will be included in the analysis who start another non-protocol treatment prior to progression will be censored at the time they start the non-protocol therapy.

Finally, another secondary objective of our study is to enable the investigation of the efficacy (ORR) of the gemcitabine/VX-970 after crossover following disease progression after single agent gemcitabine. In this regard, we hypothesize that addition of VX-970 to gemcitabine will be

clinically effective for patients who develop disease progression on gemcitabine alone. Specifically, if there is significant response observed in patients who cross over to gemcitabine/VX-970 after progression on gemcitabine alone, then this would be a clinically important observation. These patients are platinum resistant (we allow unlimited lines in platinum sensitive setting and up to 1 line in the platinum resistant setting) and would have progressed on gemcitabine already. Therefore, a significant ORR of the gemcitabine/VX-970 combination in this very resistant and heavily pretreated population would be clinically important. In this regard, ORR was the endpoint used for the recent approval of olaparib in ovarian cancer and is also consistent with the consensus statement of the SGO white paper (Herzog et al. Gyn Onc, 2013) stating that ORR is a valid endpoint for heavily pretreated patients. Furthermore, given that many ovarian cancer patients receive a combination of gemcitabine with carboplatin in the platinum sensitive setting (either after first or second recurrence), evidence of response to gemcitabine/VX-970 after progression on gemcitabine alone, would support use of this combination in patients who have already received gemcitabine in the past, either alone or in combination with carboplatin.

In this exploratory trial, in order to have 80% power to detect improvement of median PFS (primary endpoint) from 15 weeks with gemcitabine alone to 27.3 weeks with gemcitabine/VX-970 (HR=0.55) using a stratified log-rank test with the platinum free interval as the stratification factor with a one-sided alpha level of 0.1, 64 patients would be randomized (32 patients on each arm). Final analysis would occur when 50 PFS events are to be observed. This assumes a constant accrual over 1 year with 6 months of additional follow-up, and a constant hazard of PFS and dropout such that 5% of patients are lost-to-follow-up at 1 year. Although the target number of evaluable patients is 64, it is anticipated that 10% of subjects will not be evaluable and thus the maximum total number of patients to be enrolled will be 70. An interim analysis will be planned at 25 PFS events to stop for futility only.

ORR will be the endpoint for the patients who crossover to gemcitabine/VX-970 after progression on gemcitabine alone. Based on this design, there will be about 32 evaluable patients on single agent gemcitabine arm. Assuming 75% (n=24) of the these 32 patients elect to switch to combination agents arm after progression, the following table provides the effect sizes to reject a null hypothesis of 5% ORR with at least 80% power and one-sided alpha of 0.1 or lower. For example, if 21 patients on single agent arm elect to switch to combination agents arm after progression, and if the true ORR is 20%, 3 or more responses are needed to reject the null hypothesis of 5% ORR with 82% power and one-sided alpha of 0.08.

Table: Effect sizes for which there will be 80% power to reject a null of a 5% ORR (one-sided alpha = 0.1)

Actual Sample Size	True ORR that yields 80% power	Obs ORR to reject the null (N)	Obs ORR to reject the null (%)	Power	One-sided Alpha
21	20%	≥ 3	14.3%	0.82	0.08
24	22%	≥4	16.7%	0.81	0.03
27	20%	≥4	14.8%	0.82	0.04

13.2 Sample Size/Accrual Rate

In order to have 80% power to detect improvement of median PFS (primary endpoint) from 15 weeks with gemcitabine alone to 27.3 weeks with gemcitabine/VX-970 (HR=0.55) using a stratified log-rank test with the platinum free interval as the stratification factor with a one-sided alpha level of 0.1, 64 patients would be randomized (32 patients on each arm). Final analysis would occur when 50 PFS events are to be observed. This assumes a constant accrual over 1 year with 6 months of additional follow-up, and a constant hazard of PFS and dropout such that 5% of patients are lost-to-follow-up at 1 year. Although the target number of evaluable patients is 64, it is anticipated that 10% of subjects will not be evaluable and thus the maximum total number of patients to be enrolled will be 70. An interim analysis will be planned at 25 PFS events (50% information) to stop for futility only. The stopping boundary is defined as a Z-statistic from the logrank test less than 0 (i.e. observed HR of 1.0 or greater under a univariable Cox proportional hazard model). No early stopping for efficacy is allowed, and the nominal alpha at final analysis will not be increased according to the planned futility analysis (i.e. non-binding).

We anticipate that between 4-5 patients are enrolled per month to this study.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	10	0	0	0	10
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	0	2	0	7
White	46	0	7	0	53
More Than One Race	0	0	0	0	0
Total	61	0	9	0	70

13.3 Stratification Factors

One stratification factors will be included: i) platinum free interval (PFI) ≤ 3 months vs < 6 months.

13.4 Analysis of Secondary Endpoints

Subject demographic and baseline characteristics will be summarized by mean, standard deviation, median, minimum, and maximum for continuous variables; and by counts and percentages for categorical variables. Summaries will be provided separately for each treatment group.

The analysis population for all secondary efficacy and exploratory endpoints will be the modified intention to treat which includes all patients to receive protocol therapy, including those with measurable disease that were not assessable for objective response due to early discontinuation of protocol therapy.

Overall survival is the number of days from the date the subject was randomized until date of death (regardless of cause). PFS and OS will be summarized using Kaplan-Meier analyses and compared between the two arms using a stratified log-rank test with the platinum free interval as the stratification factor. PFS and OS will additionally be analyzed using a Cox Proportional Hazards Model, including the stratification factor, and will be used to estimate the Hazard Ratio (HR) of the gemcitabine/VX-970 arm relative to the gemcitabine alone arm and the associated 90% CI.

Objective response rate (ORR) is defined as the percentage of subjects achieving a response rating of complete response (CR) or partial response (PR) by RECIST guideline v1.1 during the study. **Clinical benefit rate (CBR)** is defined as the percentage of subjects achieving a response rating of stable disease (SD) ≥ 4 months, PR, or CR during the study. These rates and 95% confidence intervals will be determined for both gemcitabine/VX-970 and gemcitabine alone arms. Percent of subjects with **at least 50% reduction in CA-125** will be evaluated and presented with 95% confidence intervals and compared across the two groups using z-test for independent proportions. Treatment group comparisons in ORR, CBR and CA-125 50% reduction will be evaluated using logistic regression and expressed as odds ratios with associated 90% CIs. In the event that rates are low, comparisons will be based on Fisher's Exact test.

Duration of response (DOR) will be computed with "start" of response being:

- for subjects whose best response is SD, the day protocol therapy was first administered;
- for subjects whose best response is CR or PR, the earliest assessment of CR or PR.

Duration of best response will not be estimated for subjects who leave the study prior to a first assessment of response (scheduled at the end of treatment Cycle 2), subjects whose best response is progressive disease, and subjects who leave the study prior to an assessment of progressive disease.

“End” of response is the earliest assessment of progressive disease or death or last follow up where the subject has not yet progressed from her prior response. For DOR, informational summaries and Kaplan Meier plots, without formal statistical comparisons, will be produced. The following minimum data summaries will be presented by treatment arm for safety assessments:

- Treatment-emergent adverse events (TEAEs) of any CTCAE grade – summarized by system organ class and CTCAE grade
- SAEs
- Deaths summarized by primary cause
- Laboratory parameters (hematology and chemistry), vital signs, ECG data and concomitant medications will be summarized appropriately.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Gemcitabine and VX-970.

13.5.2 Evaluation of Response

The analysis population for all secondary efficacy and exploratory endpoints will be the modified intention to treat which includes all patients to receive protocol therapy, including those with measurable disease that were not assessable for objective response due to early discontinuation of protocol therapy.

Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.] Patients in response categories 4-9 should be considered to have a treatment failure (disease progression).

14. PUBLICATION PLAN

The results should be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug **VX-970**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

VX-970 interacts with a specific enzyme in the liver.

- The enzyme in question is **CYP3A4**. **VX-970** is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

VX-970 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

VX-970 must be used very carefully with other medicines that need certain **liver enzymes to be effective or to be cleared from your system**. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of **CYP3A4**."

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

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **VX-970**. This clinical trial is sponsored by the NCI. **VX-970** may interact with drugs that are **processed by your liver**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

VX-970 interacts with a specific liver enzyme called **CYP 3A4**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **“strong inducers/inhibitors of CYP 3A4”**
- Before prescribing new medicines, your regular prescribers should go to [a frequently-updated medical reference](#) for a list of drugs to avoid, or contact your study doctor.
- Your study doctor’s name is _____
and can be contacted at _____.

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1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (<i>e.g.</i> , 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.
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- The enzyme in question is **CYP3A4**. **VX-970** is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

VX-970 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

VX-970 must be used very carefully with other medicines that need certain **liver enzymes to be effective or to be cleared from your system**. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of **CYP3A4**."

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

_____ and he or she can be contacted at

_____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **VX-970**. This clinical trial is sponsored by the NCI. **VX-970** may interact with drugs that are **processed by your liver**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

VX-970 interacts with a specific liver enzyme called **CYP 3A4**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **“strong inducers/inhibitors of CYP 3A4”**
- Before prescribing new medicines, your regular prescribers should go to [a frequently-updated medical reference](#) for a list of drugs to avoid, or contact your study doctor.
- Your study doctor’s name is _____ and can be contacted at _____.