Abbreviated Title: Taxol-Tasigna
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Title: Phase II Study of Intravenous and Intraperitoneal Paclitaxel and Oral Nilotinib for Peritoneal Carcinomatosis from Colorectal, Appendiceal, Small Bowel, Gastric, Cholangiocarcinoma, Breast, Ovarian, or Other Gynecologic Primary Cancer

NCI Principal Investigator: Andrew M. Blakely, M.D.
Surgical Oncology Program (SOP), CCR, NCI, NIH
9000 Rockville Pike
Building 10, Room 4-3760
Bethesda, MD 20892
Phone: 240-760-7647
Email: andrew.blakely@nih.gov

Commercial Agents: Paclitaxel (Taxol®), Nilotinib (Tasigna®)

PRÉCIS

Background:

- Peritoneal carcinomatosis is uniformly fatal if untreated; despite advances in systemic chemotherapy, cytoreductive surgery, and intraperitoneal chemotherapy, survival remains poor for the majority of patients
- The combination of oral nilotinib and intravenous paclitaxel has demonstrated pre-clinical and clinical synergism in the treatment of solid tumors, with an ongoing Phase I trial at the NIH
- The synergy of oral nilotinib with intraperitoneal paclitaxel remains to be characterized
- This study involves the combination of intravenous and intraperitoneal paclitaxel and oral nilotinib for unresectable peritoneal carcinomatosis from colorectal, appendiceal, small bowel, gastric, cholangiocarcinoma, breast, ovarian, or other gynecologic primary histologies

Objective:

- To evaluate efficacy of bidirectional chemotherapy using intraperitoneal and intravenous paclitaxel and oral nilotinib by calculating the rate of downstaging of peritoneal disease burden to become resectable, based on Peritoneal Carcinomatosis Index (PCI)

Eligibility:

- Participants ≥ 18 years of age with histologically confirmed peritoneal carcinomatosis of colorectal, appendiceal, small bowel, gastric, cholangiocarcinoma, breast, ovarian, or other gynecologic primary histology
- Demonstrated resistance or lack of response to at least one line of already approved and available systemic chemotherapy
- No history of allergic reactions attributed to compounds of similar chemical or biologic composition to study drugs
- No intraperitoneal chemotherapy within the last six months
- Deemed unable to undergo complete cytoreduction

Design:

- Phase II open-label, non-randomized study
- After confirmation of eligibility, at the time of diagnostic laparoscopy, biopsies will be taken, and an intraperitoneal catheter will be placed for subsequent chemotherapy administration
- Up to 6 cycles will be planned, with restaging laparoscopy and biopsies after Cycles 3 and 6

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Participants Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

- To evaluate efficacy of bidirectional chemotherapy using intraperitoneal and intravenous paclitaxel and oral nilotinib by calculating the rate of downstaging of peritoneal disease burden to become resectable, based on Peritoneal Carcinomatosis Index (PCI)

1.1.2 Secondary Objectives

- To assess clinicopathologic response to therapy by assessing response rate by RECIST 1.1 and/or by Peritoneal Carcinomatosis Index (PCI)
- To evaluate the safety and tolerability of intraperitoneal and intravenous paclitaxel and oral nilotinib
- To determine peritoneal progression-free survival (pPFS) after therapy
- To evaluate the peritoneal progression-free survival (pPFS) probability and the percentage of participants who become resectable by individual histologies
- To measure overall survival (OS) and overall progression-free survival (PFS) for up to 3 years post therapy
- To evaluate participants' quality of life using FACT-C (Functional Assessment of Cancer Therapy-Colorectal) and EQ-5D-5L (EuroQol Group 5-Dimension 5-Level Health Survey) (refer to **Appendix D** and **Appendix E**)

1.1.3 Exploratory Objectives

- To assess the rate and etiology of adverse events related to therapy
- To assess difference in response to *ex vivo* paclitaxel exposure between nilotinib-naïve versus nilotinib-exposed tumor-derived organoid tissue
- To assess the synergy (PK and PD) between intraperitoneal paclitaxel and oral nilotinib compared to intravenous paclitaxel and oral nilotinib
- To assess whether oral nilotinib is delivered to peritoneal tumor tissue and ascites at measurable concentrations
- To evaluate serum and intraperitoneal circulating tumor cells and immune subsets, to determine their association with clinical response and with progression-free survival (PFS)
- To evaluate the clinical benefit of additional cycles of IV paclitaxel and PO nilotinib after completion of bidirectional therapy for participants who remain unresectable

1.2 BACKGROUND AND RATIONALE

1.2.1 Background

Peritoneal metastasis is uniformly lethal, characterized by a relentlessly aggressive clinical course leading to significant morbidity (1). Peritoneal carcinomatosis is largely a result of regional spread

of ovarian (50-60%) and gastrointestinal (GI) cancers (30-40%), or may develop from the peritoneum itself (mesothelioma) (2). Management is primarily palliative, involving systemic chemotherapy and/or cytoreductive surgery (CRS) with the goal of locoregional disease control. However, survival outcomes with systemic chemotherapy or CRS alone have remained dismal (median survival: 24 months) (3, 4).

More recently, Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has demonstrated encouraging results, especially after CRS (median survival ~40 months among highly selected patients) (5, 6). The procedure involves laparotomy and optimal tumor debulking followed by intraperitoneal delivery of heated chemotherapy to treat any small residual or microscopic disease. Complete cytoreduction to tumor deposits no more than 2.5 mm in diameter is required for HIPEC to be utilized, as its depth of tissue penetration is limited (7). Across essentially all histologic etiologies of peritoneal carcinomatosis, completeness of cytoreduction has been recognized as a primary driver of outcomes (4, 8-11). Cytoreduction and HIPEC is highly invasive, requiring intensive care unit monitoring and extended inpatient stays (~10 days or more) resulting in significant morbidity (~70%) and mortality (~5%) (12). This procedure can therefore only be offered to a fraction of patients with peritoneal carcinomatosis (PC) (13). In addition, repeat intraperitoneal treatment in an adjuvant approach is made more difficult by often robust intra-abdominal adhesion formation following cytoreduction and HIPEC. Alternative, neoadjuvant approaches that can repeatedly deliver the localized therapy with enhanced tolerability and minimal morbidity may potentially impact the durability of local disease control as well as allow a larger pool of patients to benefit from an aggressive cytoreductive approach.

1.2.2 Rationale for Intraperitoneal Chemotherapy Administration

The rationale for administration of intraperitoneal chemotherapy is based on its regional treatment effect (8, 14, 15). The peritoneal surface has been characterized as similar to a dialysis membrane in its activity in drug transport between the peritoneal cavity and plasma, resembling a two-compartment model (16). Peritoneal implants are thought to be less well-vascularized than metastatic deposits in the liver or lung, decreasing their relative susceptibility to systemic chemotherapy. Intra-peritoneal administration of the same chemotherapeutic agent can achieve significantly higher peritoneal cavity drug concentrations than systemic administration (17). This is characterized by the drug's area under the curve (AUC) of peritoneal versus plasma concentrations, with a higher value indicating a relatively higher achievable peritoneal drug level (18). In this way, therapeutic doses of chemotherapy agents may be used, with less systemic uptake and resultant toxicity.

1.2.3 Selection of Intraperitoneal Chemotherapeutic Agent

Chemotherapeutic agents are either considered to be either agnostic or specific to the cell cycle (19). Agents that are cell cycle-specific have limited utility in HIPEC, since only a susceptible portion of the tumor tissue will respond to the chemotherapy. These drugs have greater utility in repeated dosing in the setting of intra-peritoneal treatment. Agents that affect cancer cells irrespective of cell cycle are generally preferred for use in HIPEC. Other major characteristics to consider include the agent's pharmacokinetics and AUC, the depth of tissue penetration, and the relative enhancement provided by elevated temperatures (**Table 1**) (20).

Table 1: Summary of Chemotherapy Agents Used for Intraperitoneal Administration

Drug	Molecular weight	Type	AUC Ratio	T ½ (mins)	T 80% (mins)	Dose	Carrier Solution	Incompatibility in solution	Heat synergy	Heat stability	Depth of penetration
Doxorubicin	579.99	Antitumor antibiotic	230	20	80	15 mg/m^2	1.5% dextrose dialysis solution	Heparin, fluorouracil	Yes	42 ℃	4-6 cell layers
DOXIL (liposomal doxorubicin)	579.99	Antitumor antibiotic	1,040	180	NA	100mg/m^2	1.5% dextrose dialysis solution	Heparin, fluorouracil	Yes	42 ℃	4-6 cell layers
Etoposide	588.58	Antitumor antibiotic	65	NA	NA	25-350 mg/m^2	5% dextrose	Plastic devices; acrylics; antibiotics	Yes	42 ℃	NA
5-fluorouracil	130.08	Anti-metabolite	280	75	75	650mg/m^2 (x5 days)	0.9% sodium chloride; 1.5% dextrose dialysis solution; Icodextrin	Doxorubicin daunorubicin idaurubicin cisplatin diazepam icytarabine	Minimal	43 ℃	0.2mm
Floxuridine (FUDR)	246.2	Anti-metabolite	75	NA	NA	500mg/m^2 (x3 days)	0.9% sodium chloride	NA	Minimal	42.5 ℃	NA
Gemcitabine	299.5	Pyrimidine antagonist	205	75	75	1000 mg/m^2	0.9% sodium chloride	NA	At 48 hours	42.5 ℃	NA
Irinotecan	677.19	Antitumor antibiotic	NA	NA	NA	200mg/m^2	1.5% dextrose dialysis solution	NA	No	44 ℃	NA
Melphalan	305.2	Alkylator	56	69	69	70 mg/m^2	0.9% sodium chloride	NA	Marked	42 ℃	NA
Mitomycin C	334.3	Antitumor antibiotic	27	90	90	15 mg/m^2	1.5% dextrose dialysis solution	Bleomycin	Yes	42.5 ℃	2,000 μm
Mitoxantrone	517.41	Antitumor antibiotic	115-255	NA	NA	28 mg/m^2	0.9% sodium chloride; lactated Ringer's solution	Heparin	Yes	43 ℃	5-6 cell layers
Pemetrexed	471.4	Multitargeted antifolate	70	260	260	500mg/m^2	1.5% dextrose dialysis solution	NA	NA	NA	NA

Drug	Molecular weight	Type	AUC Ratio	$T_{½}$ (mins)	$T_{80\%}$ (mins)	Dose	Carrier Solution	Incompatibility in solution	Heat synergy	Heat stability	Depth of penetration
Carboplatin	371.25	Alkylator	10	NA	NA	300mg/m^2	0.9% sodium chloride	NA	Yes	41.5 ℃	0.5mm
Cisplatin	300.1	Alkylator	10	90	90	90 mg/m^2	0.9% sodium chloride	NA	Yes	41.5 ℃	1-3 mm
Oxaliplatin	397.3	Alkylator	16	60	60	460 mg/m^2	5% dextrose	Aluminum alkaline or NaCl solutions	Yes	46 ℃	1-2 mm
Paclitaxel	853.9	Antimitotic	1,000	NA	NA	120-180 mg (total dose)	1.5% dextrose dialysis solution; 6% hetastarch	Plastic containers and tubes	No	42.5 ℃	>80 cell layers
Docetaxel	861.9	Antimitotic	552	NA	NA	45 mg/m^2	0.9% sodium chloride	Plastic containers and tubes	No	NA	NA
AUC, area under the curve; $T^{80\%}$, time for 80% clearance of drug from peritoneal space; NA, data not available. (20)											

1.2.4 Intraperitoneal Paclitaxel

Based on these factors, paclitaxel is an ideal intraperitoneal chemotherapeutic agent, characterized by high molecular weight and hydrophobic properties (21). These features in turn allow for prolonged intraperitoneal retention, as evidenced by high AUC, compared to other agents (20, 22).

Paclitaxel acts by inducing polymerization of tubulin, thereby impairing microtubule function, leading to arrest of mitosis and cell death (23). Cellular distress is evidenced several hours after intraperitoneal administration, with elevated intraperitoneal drug levels persisting for at least 72 hours (24, 25). Since its mechanism of action is cell cycle-specific and depth of penetration is limited to approximately 100 μm, repeated administration is required to achieve maximal treatment benefit (26).

1.2.5 Bidirectional Therapy

The rationale for bidirectional therapy is to provide a hematogenous drug gradient, thereby concomitantly treating peritoneal tumors from two approaches. A proposed mechanism of the relative resistance of peritoneal surface implants to systemic administration of chemotherapy is leakage of the agent from extensive tumoral microvasculature into the intraperitoneal space (27). Intraperitoneal administration of drug may oppose that gradient and injure or collapse the microvascular network, thereby improving tissue penetration. Prior Phase I and II studies of the addition of intraperitoneal paclitaxel to standard intravenous chemotherapy regimens have suggested an added benefit of intraperitoneal therapy compared to historical controls of intravenous-only chemotherapy (25, 28).

1.2.6 Dosing Rationale

Previous Phase I studies of intraperitoneal paclitaxel as monotherapy established a dose of 60 mg/m^2 as safe in terms of toxicity, with a small amount of systemic uptake (8, 29, 30). A subsequent series of concomitant intravenous and intraperitoneal paclitaxel suggested that a dose of 20 mg/m^2 was associated with high intraperitoneal concentrations even at the reduced dose (31). The toxicity of combined intraperitoneal and intravenous paclitaxel was assessed in a subsequent Phase II study; rates of Grade 3 and 4 adverse events were 40% and 15%, respectively, most commonly being neutropenia (38%), leukopenia (18%) and anemia (10%) (25). Intraperitoneal dosing in these studies has largely been every 3 weeks, with concurrent or staggered intravenous dosing.

Intravenous paclitaxel has been used as first-line and subsequent therapy for various malignancies, including ovarian cancer. Intravenous paclitaxel is dosed at 80-100 mg/m^2 on a weekly basis (32).

Nilotinib is a BCR-Abl kinase inhibitor approved by the FDA for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase and the treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib. The recommended dose is 300 mg orally twice daily for newly diagnosed Ph+ CML-CP and 400 mg orally twice daily for resistant or intolerant Ph+ CML-CP and CML-AP.

1.2.7 Combination of Paclitaxel and Nilotinib

1.2.7.1 Preclinical and Mechanism of Action Studies

Within the NCI, DCTD initiated a systematic *in vitro* combination drug screen of FDA-approved anticancer drugs in the NCI-60 tumor cell line panel. The objective was to obtain data about novel drug combinations that potentially have promising anticancer activity (33). Within DCTD, promising combinations are being evaluated in human tumor xenografts to elucidate both the therapeutic index and the mechanism(s) of action of the agents being studied, and to identify potential markers of drug resistance and response.

One combination identified from this screening initiative is nilotinib plus paclitaxel. Selection criteria included a greater than additive effect of the two drugs on growth inhibition for cell lines (combination score) where 0 indicates an additive effect of the drug combination and positive scores indicate more than additive effect of growth inhibition. Regressions were measured in the MDA-MB-468 breast (**Figure 1**), RXF-393 renal, and OVCAR-3 ovarian adenocarcinoma xenograft models following co-administration of nilotinib and paclitaxel in studies performed at the NCI.

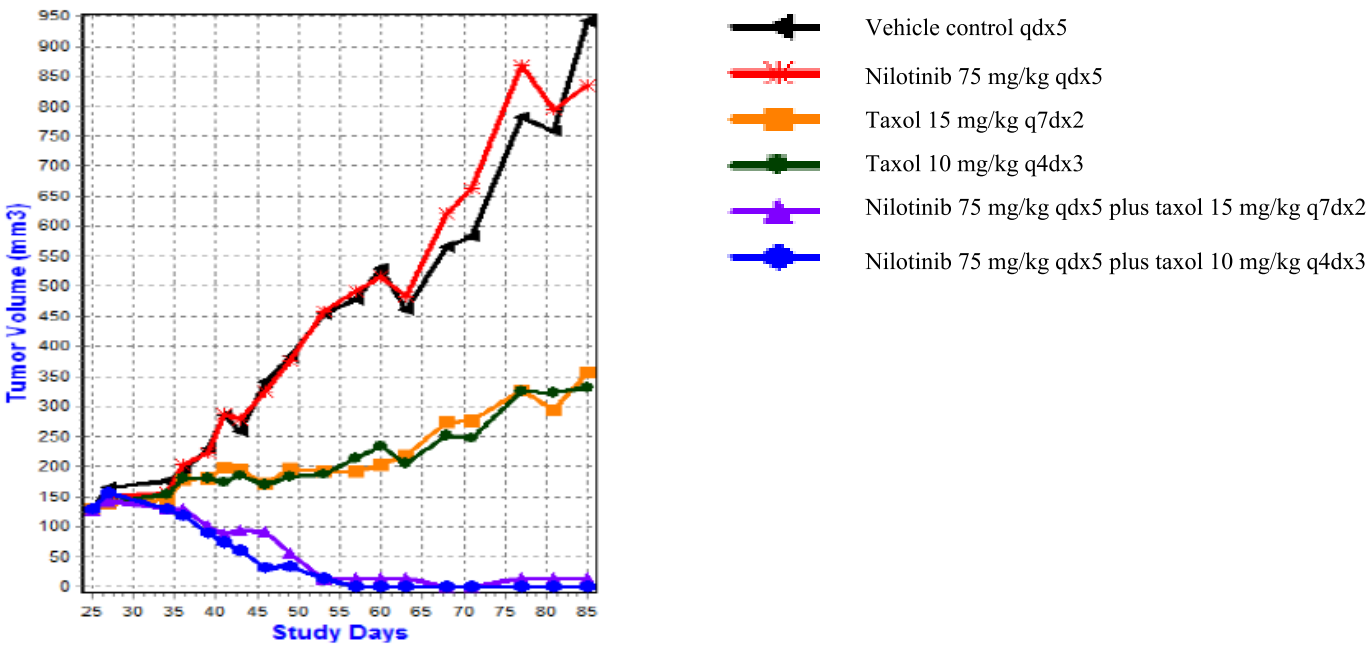

Figure 1: Tumor regressions were measured in the MDA-MB-468 adenocarcinoma xenograft model following co-administration of nilotinib and taxol.

DCTD conducted a confirmatory preclinical efficacy study in the MDA-MB-468 model to compare the activity of the nilotinib plus paclitaxel combination with that of another BCR-Abl kinase inhibitor, imatinib (**Figure 2**). The imatinib plus paclitaxel combination is more active than paclitaxel alone, but the nilotinib plus paclitaxel combination is the most active in this model.

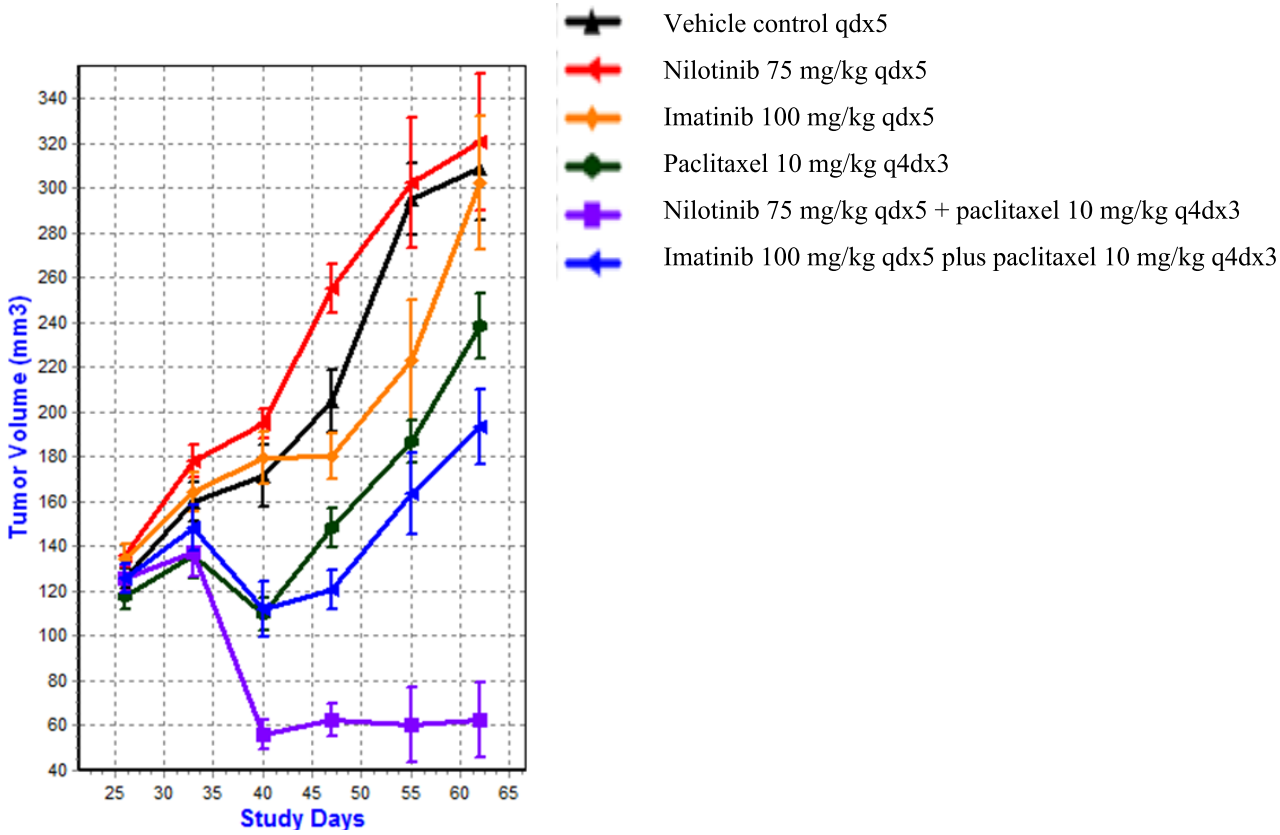

Figure 2: Efficacy in the MDA-MB-468 adenocarcinoma xenograft model following co-administration of nilotinib and paclitaxel.

Intriguingly, *in vitro* activity of the nilotinib plus paclitaxel combination did not correlate with expression or mutation of known targets for nilotinib, suggesting a novel mechanism accounting for the observed efficacy and synergism between the two agents.

One possible mechanism is modulation of CYP2C8, a major paclitaxel-metabolizing enzyme that catalyzes paclitaxel 6α-hydroxylation and is known to be inhibited by nilotinib in vitro. Kim et al. showed that nilotinib is a strong and selective CYP2C8 inhibitor in human liver microsomes, with a paclitaxel 6α-hydroxylation IC_{50} value at least 23-fold lower than those of 5 other TKIs (imatinib, dasatinib, gefitinib, erlotinib, sunitinib). Nilotinib inhibits CYP2C8 selectively, with an IC_{50} value at least 13 to 100-fold lower than other CYP isoforms, i.e., CYP3A4, 2C9, 2D6 (34). In addition, nilotinib is a potent modulator of ABCB1-, ABCG2-, and ABCC10-mediated multidrug resistance (MDR) and can synergistically enhance the antitumor response of paclitaxel in multidrug-resistant cell lines and xenograft models (35, 36). Nilotinib plus paclitaxel combination regimens did not result in increased toxicity; instead, the agents uniformly improved the efficacy of paclitaxel in the ABCB1-, ABCG2- and ABCC10-overexpressing xenograft models compared to paclitaxel treatment alone (**Figure 3**) (36).

However, in a tumor pharmacokinetics study in MDA-MB-468 breast cancer xenograft models, DCTD investigators found comparable intratumoral paclitaxel concentrations in animals treated with the nilotinib plus paclitaxel combination and those treated with paclitaxel alone, indicating that inhibition of ABC transporter-mediated paclitaxel export or CYP2C8-mediated paclitaxel metabolism does not account for the impressive antitumor activity of the combination in this model

(33); therefore, nilotinib-mediated modulation of intratumoral paclitaxel levels is unlikely to be the mechanism underlying the observed synergism of this combination. In collaboration with the Biometric Research Program, DCTD is currently conducting exploratory analyses of baseline and post-treatment RNA-seq data from multiple patient-derived xenograft models to identify transcriptional signatures associated with combination activity.

Though the primary mechanism of greater-than-additive activity for this combination is still being investigated, preclinical analysis of MDA-MB-468 breast cancer xenograft models using the epithelial-mesenchymal transition immunofluorescence assay (EMT-IFA) developed by the Pharmacodynamic Assay Development and Implementation Section (PADIS) at NCI Frederick found that the nilotinib-paclitaxel combination induced a significant shift toward a more mesenchymal-like phenotype, coincident with pronounced anti-tumor activity (37). This shift in EMT phenotype also coincided with an increase in cancer stem cell (CSC) markers, suggesting that monitoring of EMT phenotype changes in response to nilotinib-paclitaxel treatment may be valuable as an indication of the emergence of CSC characteristics, including therapeutic resistance.

In addition, the mechanism of tumor cell death following nilotinib-paclitaxel treatment remains unknown. Preclinical pharmacodynamic analyses have revealed that nilotinib-paclitaxel–mediated cell death is caspase-3–independent, suggesting that alternative, non-apoptotic mechanisms of cell death account for the antitumor activity of this combination. For example, the elevated levels of endoplasmic reticulum–associated BAX–Bcl-2 following *in vivo* nilotinib-paclitaxel treatment suggest necroptosis as a potential cell death mechanism (33). Additional preclinical work on the underlying mechanisms of action for this combination is ongoing.

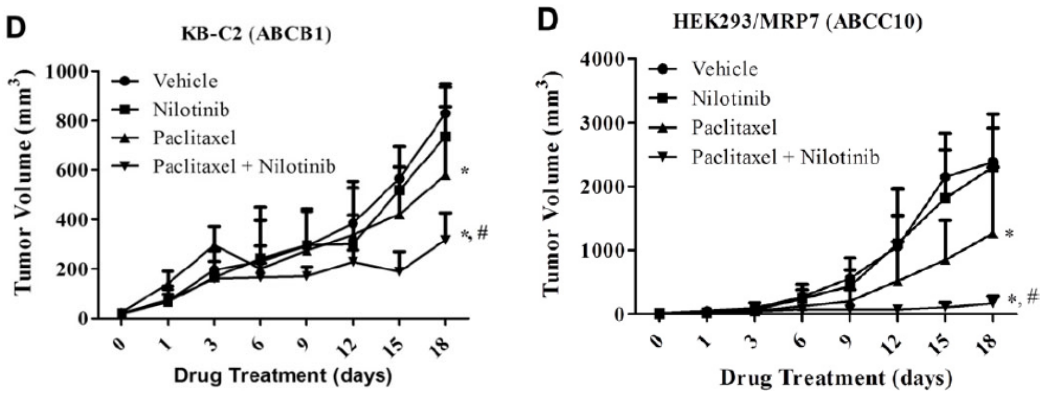

Figure 3: Left: Potentiation of antitumor effects of paclitaxel by nilotinib in ABCB1-overexpressing oral epidermoid carcinoma (KB-C2) xenograft model. Right: human embryonic kidney (HEK293) cells transfected with ABCC10 in the MRP7-xenograft model (36).

1.2.7.2 Clinical Status of the Phase 1 Nilotinib + IV Paclitaxel Combination Study (15-C-0086)

Thirty-two participants have been accrued to this study at the Clinical Center as of May 2020 (diagnosis, best response, and number of cycles of treatment are included in **Table 2** for the dose escalation and expansion phases). Dose-limiting toxicities consisted of Grade 4 rash and Grade 4 neutropenia; Dose Level 2 was selected as the expansion cohort dose (Nilotinib 300 mg orally BID, paclitaxel IV at 80 mg/m^2 on Days 1, 8, and 15; 28-day cycles). Fourteen participants have been enrolled on the expansion phase. There have been 3 confirmed partial responses (PR) and 15 participants with a best response of stable disease (SD), including 7 participants with SD for ≥ 8 cycles.

Table 2: Patient Clinical Status From 15-C-0086

Participant	Dose Level	Diagnosis	Best Response	Cycles Completed
ESCALATION COHORT				
1010001	1	NSCLC	SD	8
1010002	1	Unknown primary	PD	2
1010003	1	Anal cancer	PR*	1
1010004	1	Unknown primary	PD	2
1010005	1	Pleural mesothelioma	PD†	1
1010006	1	Bladder	PD	2
1010007	2	Small cell unknown primary	SD	14
1010008	2	Endometrial	PR	11
1010009	2	Thyroid disorder	PD	1
1010010	2	Granulosa cell ovarian cancer	PR	46‡
1010011	2	Adenocarcinoma	NA	0
1010012	3	Granulosa cell ovarian cancer	PR	43‡
1010013	3	Lung cancer	SD	2
1010014	3	Ovarian carcinoma	SD	4
1010015	2	Pancreatic cancer	NP	1
1010016	2	Ovarian cancer	SD	28
1010017	2	Breast cancer	PD	2
1010018	2	Breast cancer	SD	16
EXPANSION COHORT				
1010019	2	Juvenile granulosa ovarian	NP	1
1010020	2	Breast cancer	SD	2
1010021	2	Neuroendocrine, prostate	PD	2
1010022	2	NSCLC	PD	1
1010023	2	Peritoneal sarcoma	SD	18‡
1010024	2	Leiomyosarcoma	PD	2
1010025	2	Adenocarcinoma, endometrium	SD	10
1010026	2/NIL-1	Adenocarcinoma, bladder	SD	12‡
1010027	2	Pancreatic cancer	SD	6
1010028	2	Chondrosarcoma	NP	0
1010029	2	Uterine sarcoma	PD	2
1010030	2	Endometrial cancer	SD	3
1010031	2	Adenocarcinoma, bladder	SD	4
1010032	2	Cholangiocarcinoma	SD	3

SD = stable disease; PR = partial response; NP = not applicable per protocol;
PD = progression of disease; * = unconfirmed PR; ‡ = participant still on study

These preliminary response data are promising, especially considering that all three responding participants had undergone prior paclitaxel-based therapy and experienced a best response of only stable disease (participant 1010008) or progressive disease (participants 1010010 and 1010012) to carboplatin/paclitaxel or paclitaxel monotherapy, respectively, suggesting that the nilotinib-paclitaxel combination has superior efficacy to paclitaxel monotherapy in some patients.

In addition, adverse event data from this study indicate that the nilotinib-paclitaxel combination may offer improved tolerability relative to paclitaxel monotherapy. No Grade ≥ 3 peripheral neuropathy has been observed in this study to date, as compared to rates of 8-30% in prior studies of 80-100 mg/m^2 weekly paclitaxel monotherapy in patients with metastatic breast cancer (38). There were three incidences of Grade 1 and two incidences of Grade 2 peripheral neuropathy, all reversible with dose reduction and gabapentin. Our findings are consistent with recent preclinical data suggesting a reduced incidence of peripheral neuropathy for this combination relative to paclitaxel monotherapy (39).

Table 3: Adverse Effect Profile and Incidences in 15-C-0086

Toxicity	No. Events (Gr. 3 & 4)	Toxicity	No. Events (Gr. 3 & 4)
Hematologic		***Gastrointestinal***	
Anemia	7	Constipation/Flatulence	2
Lymphopenia	11	Hyperbilirubinemia	1
Neutropenia*	9	Transaminase increase	4
Leukopenia	9	Alkaline phosphatase increase	2
Skin		***Electrolytes***	
Rash*	1	Hyponatremia	3
Constitutional		Hypomagnesemia	1
Fatigue	2	Hypophosphatemia	9
Flank pain	1	***Genitourinary***	
Cardiovascular		Proteinuria	1
Atrial fibrillation	1	Urinary tract obstruction	1
Hypertension	1	***Neurologic***	
		Photosensitivity	1

*dose-limiting toxicity

1.2.8 Study Rationale

Management of advanced peritoneal carcinomatosis remains a challenge, both because many patients will not be able to undergo cytoreductive surgery and because the efficacy of intravenous chemotherapy alone is limited. Improved treatment strategies are needed to potentially afford more patients the survival benefit of cytoreduction. The combination of intravenous paclitaxel and oral nilotinib has demonstrated synergy and improved efficacy compared to either agent alone, with the suggestion of the activation of an as-yet unidentified cell death pathway. The relative synergy of intraperitoneal paclitaxel and oral nilotinib remains to be elucidated; likewise, the additional benefit of oral nilotinib to bidirectional paclitaxel is unknown.

This is a Phase II study to evaluate the efficacy of this drug combination in terms of rate of downstaging to become resectable. An important secondary objective is to assess peritoneal progression-free survival following protocol treatment.

The National Cancer Institute represents the ideal institution in which to further evaluate the combination of bidirectional paclitaxel and oral nilotinib within a Phase II trial setting. This combination was identified as a direct result of a drug exploration initiative based out of the NCI/DCTD. Furthermore, the NCI has a long history of novel treatment approaches to peritoneal

surface malignancies in addition to the access to multiple research cores, uniquely positioning the institute to improve the treatment and care of this challenging patient population.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria.

2.1.1.1 Histological confirmation of peritoneal carcinomatosis from colorectal, appendiceal, small bowel, gastric, cholangiocarcinoma, breast, ovarian, or other gynecologic (i.e., endometrial, fallopian tube, primary peritoneal, cervical) primary by the Laboratory of Pathology, NCI.

2.1.1.2 Participants must have been treated with at least one line of approved systemic chemotherapy, with demonstrated resistance or lack of response.

2.1.1.3 Measurable or evaluable disease as defined by RECIST v1.1. criteria in Section **6.3.1** and/or by Peritoneal Carcinomatosis Index (PCI) in **Appendix B**.

2.1.1.4 Participants must be assessed to not be candidates for cytoreductive surgery, with laparoscopically assessed PCI score (see **Appendix B**) thresholds as indicated below:

Primary Histology	**PCI Cutoff for Eligibility**
Gastric	Total Score ≥ 10 (out of 39 possible points)
Others	Total Score ≥ 20 (out of 39 possible points)
Any	Jejunoileal Score ≥ 4 (out of 12 possible points)

2.1.1.5 Age ≥ 18 years.

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

2.1.1.7 Participants must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,000/mcL
- Platelets ≥ 100,000/mcL
- Total bilirubin within ≤ 1.5x institutional upper limit of normal (ULN)
- AST (SGOT)/ ALT (SGPT) ≤ 3x institutional ULN, **or** ≤ 5.0x ULN in participants with liver metastases (only)
- Serum potassium and magnesium greater than institutional lower limit of normal
- Creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal calculated using eGFR

2.1.1.8 Nursing (including breastfeeding) participant must agree to discontinue nursing.

2.1.1.9 Individuals of child-bearing potential (IOCBP) 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 for 90 days after last study treatment. Should an

individual of child-bearing potential suspect to be pregnant while participating in this study, the individual should inform the treating physician immediately.

2.1.1.10 Ability of participant to understand and the willingness to sign a written informed consent document.

2.1.1.11 Participants must agree to co-enrollment on the tissue collection protocol 13C0176, "Tumor, Normal Tissue and Specimens from Patients Undergoing Evaluation or Surgical Resection of Solid Tumors."

2.1.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study.

2.1.2.1 Participants who are receiving any other investigational agents or who have received an investigational agent within 30 days prior to the start of study treatment.

2.1.2.2 Participants with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to study drugs.

2.1.2.3 Participants who have received systemic (i.e., oral or intravenous) chemotherapy or other anti-cancer therapy (i.e., immunotherapy) within either 5 half-lives or within 30 days of the last dose of individual agent(s) administered prior to the start of study treatment, whichever is shorter.

2.1.2.4 Participants who have undergone major abdominal surgery within the last 12 weeks prior to the start of study treatment.

Note: Exclusion of participants who have undergone major abdominal surgery within the last 12 weeks prior to start of study treatment is to allow for scar tissue formation from that surgery to stabilize. Participant ECOG performance status will be checked (refer to **2.1.1.6**) to account for prolonged or difficult recoveries from other types of major surgery that would appropriately influence eligibility assessment.

2.1.2.5 Participants who have received previous intraperitoneal chemotherapy within the last 6 months prior to the start of study treatment.

2.1.2.6 Participants requiring the use of drugs known to prolong the QT interval (**Appendix F**) or known to strongly inhibit CYP3A4, 2C8 (**Appendix G**). Participants on such agents at the time of screening are permitted on study if an alternative that does not have the same pharmacokinetic interactions can be found.

2.1.2.7 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. Note: No subject will be excluded based on a social situation prior to consultation with the Department of Social Work.

2.1.2.8 Pregnant individuals are excluded from this study.

2.1.2.9 Participants with HIV who have detectable viral load, or whose ART contains a drug listed in **Appendix F** and **Appendix G** regardless of viral load. (NOTE: Participants with

HIV who have an undetectable viral load and have been on stable doses of ART that does not prolong the QT interval or is a strong CYP3A4, 2C8 inhibitor are eligible).

2.1.2.10 QTcF interval of ≥ 450 msec at study entry, or congenital long QT syndrome.

2.1.2.11 More than 3 liters of ascites present at initial laparoscopy, or history of more than two therapeutic paracentesis procedures, each yielding at least 1.5 liters of fluid, in the 30 days prior to initial laparoscopy, or confirmation of predominantly mucinous ascites at the time of screening laparoscopy.

2.1.2.12 Advanced hepatic failure, as indicated by Child-Pugh Class C cirrhosis.

2.1.2.13 Sensory/motor neuropathy ≥ Grade 2

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement and will be posted on NIH websites, such as the CCR website and clinicaltrials.gov, as well as on NIH social media forums following IRB approval, when appropriate.

2.2 SCREENING EVALUATION

2.2.1 Screening Activities Performed Prior to Obtaining Informed Consent

Minimal risk activities that may be performed before the participant has signed a consent include the following:

- Email, written, in-person or telephone communications with prospective participants
- Review of existing medical records, including H&P, laboratory studies, etc.
- Review of existing x-ray, CT, or MRI images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.2.2 Screening Activities Performed After a Consent for Screening Has Been Signed

Assessments and procedures to confirm study eligibility should be completed within 6 weeks prior to the start of treatment (i.e., loading dose of nilotinib prior to laparoscopy# 2), unless otherwise noted regardless of where they are or have been performed.

Part 1: Procedures That May Be Abstracted From Medical Records

After the participant has signed the 000237 study consent the following screening procedures will be performed, or results of the screening procedures abstracted from the medical records from outside sites/other NIH protocols:

- Medical history and physical exam including vital signs and performance status
- Laboratory assessments:
    - CBC with differential
    - Serum chemistries: albumin, total bilirubin, total calcium, bicarbonate, chloride, creatinine, eGFR, glucose, alkaline phosphatase, potassium, total protein, sodium, ALT, AST, BUN, magnesium
    - PT/INR

  - Urinalysis
  - HIV antibody (within 3 months)
  - Pregnancy test (urine or serum); individuals of childbearing potential must have a negative pregnancy test within 7 days prior to laparoscopy #1
- Electrocardiogram (ECG)
- Cross-sectional imaging: CT scan chest/abdomen/pelvis (CAP)
- Pathologic confirmation of organ of origin for peritoneal carcinomatosis by NCI Lab of Pathology. Note: If there is no available tumor sample, or if the participant has an available tumor sample but the screening CT (above) did not have any radiographically apparent disease for an interventional radiology (IR) biopsy, a biopsy will be performed during diagnostic laparoscopy to confirm the diagnosis.

Part 2: Procedures That Must Be Completed As Part Of The 000237 Screening Visit And Cannot Be Abstracted From Medical Records

- Diagnostic laparoscopy with PCI scoring
- Co-enrollment on the tissue collection protocol 13C0176

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

2.3.2 Treatment Assignment Procedures

2.3.2.1 Cohorts

Number	Name	Description
1	Peritoneal Carcinomatosis	Eligible participants with peritoneal carcinomatosis from colorectal, appendiceal, small bowel, gastric, cholangiocarcinoma, breast, ovarian, or other gynecologic primary histology

2.3.2.2 Arms

Number	Name	Description
1	IP Catheter Placement and Bidirectional Chemotherapy	Repeat laparoscopy with intraperitoneal catheter placement and bidirectional chemotherapy of intraperitoneal and intravenous paclitaxel and oral nilotinib

2.3.2.3 Arm Assignment

All participants in Cohort 1 will be directly assigned to Arm 1.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a single-arm, Phase II study of intraperitoneal and intravenous paclitaxel and oral nilotinib in participants with peritoneal carcinomatosis from colorectal, appendiceal, small bowel, gastric, cholangiocarcinoma, breast, ovarian, or other gynecologic primary cancer. At the time of screening diagnostic laparoscopy (#1), participants will be assessed for ability to undergo complete cytoreduction (PCI scoring). Those who are candidates for cytoreductive surgery will be taken off study.

Interim analysis will be performed per Section **8.2**.

3.1.1 Part A of Protocol Therapy

Those who are not candidates for cytoreductive surgery will continue on study, and intra-operatively will have initial tumor biopsies (during laparoscopy #1). Some of the resected tumor biopsy tissue may be utilized for *ex vivo* organoid research purposes (refer to Section **5**).

Please refer to **Figure 4** for the study schema. Following screening during laparoscopy #1, eligible participants will then be counseled for diagnostic laparoscopy #2 with concomitant intraperitoneal catheter placement. The participants will be given a loading dose regimen of nilotinib, 300 mg twice daily, starting 4 days (i.e., Days -4, -3, -2, -1) prior to laparoscopy #2 (i.e., Day 0). At the time of diagnostic laparoscopy #2, additional tumor biopsies will be taken for research purposes (refer to Section **5**).

The day after intraperitoneal catheter placement, intraperitoneal paclitaxel will be given at a dose of 60 mg/m^2 (Cycle 1 Day 1). Intravenous paclitaxel will be given at 1 day and 7 days after intraperitoneal paclitaxel administration (Cycle 1 Day 2 and Cycle 1 Day 8, respectively). The Cycle 1 Day 2 dose of intravenous paclitaxel will be 60 mg/m^2 to ensure tolerability (refer to Section **3.3** for dose modification, as applicable), and thereafter the dose will be 80 mg/mg^2 starting on Cycle 1 Day 8. Oral nilotinib will be administered from the loading dose leading up to laparoscopy #2 onward, throughout the study time. Participants will undergo up to six 21-day cycles, with repeat laparoscopic assessment after Cycles 3 and 6. Please refer to **Table 4** for the chemotherapy dosing schema. **Note:** Oral nilotinib will be held on the day of any planned procedures involving general anesthesia (e.g., laparoscopy) and only to be given at least 4 hours after the procedure has been completed (i.e., the participant's morning dose of oral nilotinib will be held the on each day in which laparoscopy is performed).

During Week 3 of Cycle 3, participants will undergo diagnostic laparoscopy #3 for repeat biopsies and for restaging of disease (see **Appendix B**). Tumor biopsies from diagnostic laparoscopy #3 will be fixed and then evaluated and scored by an intramural pathologist to evaluate the response to protocol therapy.

At laparoscopy #3, response to treatment will be assessed as indicated in Section **6.3.9**. Participants who demonstrate disease progression will come off protocol treatment. Participants who demonstrate disease stability or response but who are still deemed unable to undergo complete cytoreduction will undergo three additional 21-day cycles. Participants with disease stability who

have tolerated the 60 mg/m^2 dose of intraperitoneal paclitaxel for Cycles 1 through 3 will have a planned dose increase to 80 mg/m^2; this increase will be optional for participants who have disease response, based on participant counseling and PI discretion. Participants who demonstrate an exceptional treatment response and are deemed able to undergo complete cytoreduction at laparoscopy #3 will be counseled to either continue with an additional three cycles of protocol treatment or to come off treatment and consider undergoing cytoreductive surgery.

Participants who receive the additional 3 cycles of nilotinib/paclitaxel will undergo diagnostic laparoscopy #4 during Cycle 6 Week 3 for repeat biopsies and for restaging of disease. Tumor biopsies will be fixed and then evaluated and scored by an intramural pathologist to evaluate the response to protocol therapy.

3.1.2 Part B of Protocol Therapy

Participants who demonstrate disease stability but remain unresectable after 6 cycles of treatment will be able to continue with 4-week cycles of IV paclitaxel and PO nilotinib (paclitaxel dosing once weekly for Weeks 1 through 3, with continuous oral nilotinib dosing) until disease progression or intolerable toxicity, or for up to one year – whichever occurs first. Those who demonstrate disease progression or treatment toxicity will come off treatment. Those who demonstrate radiographic response or stability may be offered repeat staging laparoscopy to reassess resectability.

This protocol will focus on evaluations of the rate of downstaging of disease to be deemed appropriate for cytoreduction as well as treatment response and peritoneal progression-free survival following therapy. Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy would be performed on a separate treatment protocol.

Figure 4: Study Schema

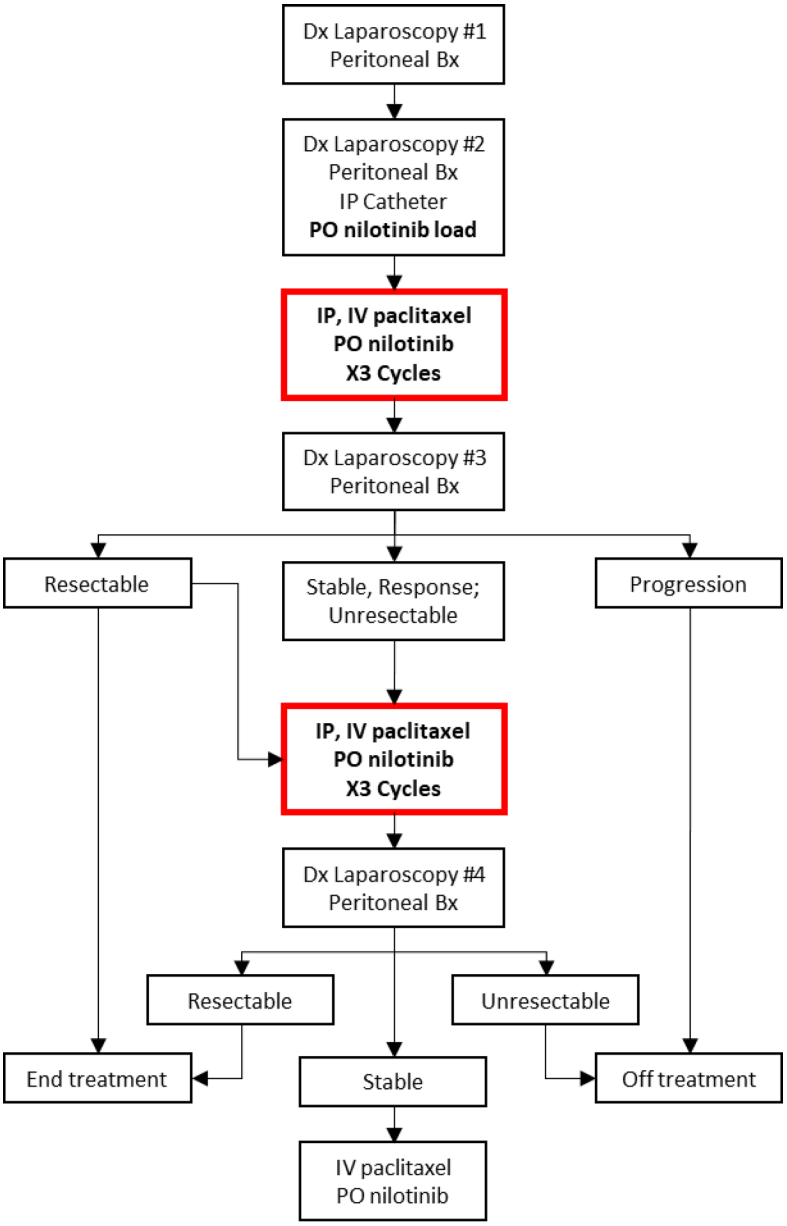

Table 4: Chemotherapy Schema for Cycles 1-3

PRIOR TO INTRAPERITONEAL CATHETER PLACEMENT

	Day -6		Day -5		Day -4		Day -3		Day -2		Day -1		Day 0	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Week 0					✓	✓	✓	✓	✓	✓	✓	✓		✓
					Diagnostic laparoscopy, biopsies, IP catheter placement (Day 0)									

AFTER INTRAPERITONEAL CATHETER PLACEMENT

	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Week 1	✓	✓,*	✓	✓,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 2	✓	✓,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 4	✓	✓,*,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 5	✓	✓,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 7	✓	✓,*,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 8	✓	✓,#	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Week 9	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Diagnostic laparoscopy, biopsies (between Days 1 and 7); hold AM dose of nilotinib on the corresponding day													

✓ = PO nilotinib; * = IP paclitaxel; # = IV paclitaxel

3.2 Drug Administration

Please refer to Section **1.2.8** for dose rationale. Body surface area will be calculated at each cycle for each participant.

3.2.1 Intraperitoneal Paclitaxel

Intraperitoneal paclitaxel will be dosed at 60 mg/m^2 and will be diluted in 500 mL of 0.9% NS. The solution will then be infused via intraperitoneal catheter over 1 hour ± 15 minutes on Day 1 of each 3-week cycle. In instances of participant abdominal discomfort appearing to be related to the infusion, the infusion will be treated by first pausing the infusion and then by slowing the rate of administration for up to a total of 3 hours of infusion time. Upon completion of drug infusion,

the participant will be instructed to adjust position every 15 minutes for 2 hours. Participants with a cardiac history must be monitored during first infusion due to reported conduction abnormalities resulting in AV block and ventricular tachycardia.

Participants who have tolerated the 60 mg/m^2 and have stable or responding disease but remain unresectable after Cycles 1 through 3 of treatment will undergo a dose increase to 80 mg/m^2 for Cycles 4 through 6. Participants who convert to resectable will have the option to pursue Cycles 4 through 6 of treatment, with the option to undergo a dose increase to 80 mg/m^2 for Cycles 4 through 6. This will be diluted in 500 mL of 0.9% NS. Toxicities that manifest during Cycles 4 through 6 that are specifically attributed to the IP paclitaxel will prompt return to the 60 mg/m^2 dose for the remaining cycles.

Dose-reduced intraperitoneal paclitaxel will be diluted in 500 mL of 0.9% NS as well (-1: 40 mg/m^2, -2: 20 mg/m^2).

Participants who are concurrently receiving or requiring any agents which may increase the risk for paclitaxel-related toxicities will have all medications reconciled by an NIH Clinical Center clinical pharmacist.

Starting in Cycle 2, intraperitoneal and intravenous paclitaxel will be given sequentially on the same day (in order to best delineate immediate adverse effects attributable to one agent or the other). The Pharmacy will be asked to affix a brightly colored label indicating "**NOT for IV use**" to the intraperitoneal paclitaxel bag so that intraperitoneal and intravenous paclitaxel is not incorrectly administered.

3.2.2 Intravenous Paclitaxel Administration

Intravenous paclitaxel will be dosed at 60 mg/m^2 for Week 1 of Cycle 1 to ensure tolerability. In the absence of infusion reactions or toxicities, IV paclitaxel will subsequently be dosed at 80 mg/m^2. Paclitaxel will be diluted in 100 to 250 ml of 0.9% NS. The solution will be administered over 1 hour ± 15 minutes, on Day 2 of the first week of Cycle 1, followed by Day 1 of the subsequent treatment weeks (i.e., Cycle 1 Week 2 Day 1, Cycle 2 Week 1 Day 1, Cycle 2 Week 2 Day 1, etc.). Prior to Cycle 1 treatment with paclitaxel, all participants will receive primary prophylaxis against hypersensitivity reactions with:

- **Dexamethasone** administered orally at least 60 minutes before starting paclitaxel, or intravenously 30–60 minutes before starting paclitaxel (10 mg per administration during Week 1; 4 mg per administration during Week 2; 2 mg per administration during Week 3; and then optionally at 2 mg per administration from Week 4 onwards), ***plus***
- **Diphenhydramine** 25–50 mg orally approximately (at least) 60 minutes before starting paclitaxel, or intravenously 30–60 minutes before starting paclitaxel (or an equivalent dose of another H_1 antihistamine), ***plus***
- **Famotidine** 20 mg intravenously (or equivalent H2 receptor antagonist) approximately 2 hours after the morning nilotinib dose (on days when nilotinib is administered) and 30-60 minutes before starting paclitaxel (or an equivalent dose of another H_2 antihistamine).

If a participant does not experience a hypersensitivity reaction during Cycle 1 treatment with paclitaxel, premedication doses with dexamethasone and H_1- and H_2-selective antihistamines may be decreased or discontinued prior to subsequent paclitaxel doses at the discretion of medically responsible clinicians treating the participant.

If a participant experiences a hypersensitivity reaction in association with any dose of paclitaxel, then prior to all subsequent paclitaxel doses, hypersensitivity prophylaxis will be given. If a participant experiences nausea, anti-emetics may be added.

Participants with a cardiac history must be monitored during first infusion due to reported conduction abnormalities resulting in AV block and ventricular tachycardia.

3.2.3 Nilotinib Administration

Nilotinib will be dosed at 300 mg twice daily, exempting the days in which laparoscopy is performed (refer to Section **3.1.1** for details). Nilotinib will be administered continually from the loading dose leading up to laparoscopy #2 onward. Nilotinib will be taken on an empty stomach, at least 2 hours after or 1 hour before a meal, with 8 ounces of water, approximately 12 hours apart; i.e., no food should be consumed within 2 hours before or 1 hour after taking nilotinib. For participants who are unable to swallow whole capsules, the capsules may be opened and their contents dispersed in one teaspoonful of applesauce (puréed apple). The mixture should be taken immediately (within 15 minutes) and should not be stored for future use. A missed or vomited dose will not be replaced. Participants will be instructed to take the next scheduled dose at the regularly scheduled time. After Cycle 2, a cycle will be considered completed if 90% of the prescribed nilotinib doses are administered.

Participants will also be asked to maintain a Study Medication Diary (**Appendix C**) and record each dose of medication, and they will be given instructions for completing the medication diary; they will be asked to return it to the clinic staff at the end of each cycle. Participants will also be told to avoid drugs known to prolong the QT interval (**Appendix F**) in addition to drugs and foods that are known to inhibit CYP3A4, 2C8 strongly (**Appendix G**).

3.3 DOSE MODIFICATIONS

Non-hematologic toxicities (at least possibly related to therapy) should have resolved to ≤ Grade 2 or baseline prior to starting the next cycle or receiving the next dose of nilotinib or paclitaxel within a cycle.

Hematologic toxicities (at least possibly related to therapy) should have resolved to ≤ Grade 1 for thrombocytopenia, ≤ Grade 2 for neutropenia and anemia prior to resuming therapy. Any grade lymphopenia, leucopenia in the absence of Grade 3 neutropenia will not require delay or reduction in therapy.

Start of next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. Dose modifications are intended for within-cycle and start-of-next-cycle changes.

3.3.1 Dose Reduction

A maximum of two dose reductions for IV paclitaxel and/or PO nilotinib will be allowed before participant is taken off treatment. Participants who require a dose reduction will not have the dose re-escalated. Dose reductions may occur to a single compound independent of the other compound if toxicity necessitating a dose reduction is attributed to a single agent in the opinion of the study Principal Investigator (see table below).

One dose level reduction due to nilotinib-associated toxicities such as clinical diagnosis of pancreatitis with biochemical confirmation, and electrolyte disturbances means that nilotinib should be reduced without change in paclitaxel dose. Similarly, one dose level reduction due to

paclitaxel-associated toxicities such as infusion reaction or neuropathy means that paclitaxel should be reduced without changes in nilotinib.

Dose Reduction Schedule (21-Day Cycle)		
Dose Level	PO Nilotinib	IV Paclitaxel
-2	300 mg once daily D1-21	60 mg/m^2 D1, 8
(-1) IV Paclitaxel	300 mg BID D1-21	60 mg/m^2 D1, 8
(-1) Nilotinib	400 mg once daily D1-21	80 mg/m^2 D1*, 8
1	300 mg BID D1-21	80 mg/m^2 D1*, 8

* The dose of IV paclitaxel for Cycle 1 will be 60 mg/m^2 and will be administered on Day 2; thereafter, the dose will be 80 mg/m^2 given on Days 1 and 8.

A maximum of two dose reductions for IP paclitaxel will be allowed before IP therapy is discontinued. For IP paclitaxel dose reduction, the toxicity must be temporally related to IP paclitaxel administration and referable to the abdomen; this would most commonly be manifested as abdominal discomfort, pain, or inflammation. Each dose reduction will be in increments of 20 mg/m^2 (e.g., (-1) IP paclitaxel = 40 mg/m^2, (-2) IP paclitaxel = 20 mg/m^2), to be given on D1 of each 3-week cycle. Participants who require a dose reduction of IP paclitaxel will not have the dose re-escalated. Participants who experience disease stability or response and come off IP paclitaxel therapy will have to option to continue on IV paclitaxel and nilotinib.

Grade 2 Drug-related toxicities: No changes will be made to the dose for Grade 2 toxicities except QTc. For a QTcF > 480 msec (Grade 2), hold both study drugs and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. Resume at same dose as soon as QTcF returns to < 450 msec and to within 20 msec of baseline. If QTcF is between 450 msec and 480 msec, reduce the dose to 400 mg once daily. If, following dose-reduction to 400 mg once daily, QTcF returns to > 480 msec, nilotinib should be discontinued and the participant will be removed from protocol therapy. An ECG should be repeated approximately 7 days after any dose adjustment.

Grade 3-4 Drug-related non-hematologic toxicities (except alopecia): Doses of nilotinib/paclitaxel will be held until toxicities recover to ≤ Grade 2 prior to re-initiating treatment at the lower dose level. Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment (see Section **4.2.2**).

Grade 3-4 Drug-related thrombocytopenia: Doses of study drugs will be held until it has resolved to ≤ Grade 1 prior to re-initiating treatment at the lower dose level.

Grade 3-4 Drug-related neutropenia: Dose of study drugs will be held until it has resolved to ≤ Grade 2 prior to re-initiating treatment. Growth factors may be used per ASCO guidelines. Dose will be reduced if Grade 3-4 neutropenia recurs despite supportive measures. If dose reduction of either agent is not indicated for other toxicities, paclitaxel will be reduced by one dose level. If Grade 3-4 drug related neutropenia recurs, nilotinib will be reduced by one dose level.

A drop in Hgb ≥ 3.0 g/dL over one week: Dose of study drugs will be held until it has resolved to ≤ Grade 2 prior to re-initiating treatment at the lower dose level.

Any grade lymphopenia, leucopenia in the absence of at least Grade 3 neutropenia: Dose of study drugs will not be held or modified.

For clinical diagnosis of pancreatitis with biochemical confirmation, only nilotinib dose will be reduced to the next lower level.

For infusion reaction and neuropathy, only the paclitaxel dose will be reduced to the next lower level. If the infusion reaction toxicity is not severe, paclitaxel infusion will be held while diphenhydramine (25-50 mg IV/PO) and famotidine (IV) are administered, after which, infusion will resume at a slower rate, with paclitaxel administered over 3-6 hours; if the infusion reaction toxicity is severe, 20 mg dexamethasone will be administered the evening before and morning of paclitaxel infusion, and paclitaxel will be administered over 3-6 hours.

Specific surgical considerations that would preclude intraperitoneal paclitaxel administration include bowel obstruction, bowel perforation, or catheter malfunction. Subsequent treatment administration following recovery from such complications would be at the discretion of the PI.

3.4 ON STUDY ASSESSMENTS/EVALUATIONS

Participants who demonstrate disease stability but remain unresectable after 6 cycles of treatment will be able to continue with IV paclitaxel and PO nilotinib per Section **3.1.2**.

3.4.1 Timing of Procedures

The following describes all tests and procedures to be conducted on study and during treatment. Refer to **Appendix I: Study Calendar** for timing and applicable windows.

For each time period, consider the following order of assessments:

- **Screening**: Refer to Section **2.2**. If treatment does not start within 6 weeks after enrollment, screening evaluations will be repeated.
- **Baseline:** All baseline assessments must be completed within 6 weeks prior to the start of treatment (i.e., loading dose of nilotinib prior to laparoscopy #2).
- **Study Drug Administration:** Participants will have up to 6 cycles of study therapy comprising IP paclitaxel, IV paclitaxel, oral nilotinib. Each cycle is 21 days. Study therapy will be discontinued in cases of disease progression, unacceptable toxicity, or other criteria listed in Section **3.8.1**. Nilotinib administration begins 5 days prior to C1D1 (i.e., Days -4, -3, -2, -1, and Day 0). Note: Hold AM dose of nilotinib on laparoscopy days. Dose administration can be delayed by no more than 1 week to accommodate scheduling conflicts.
- **Week -1:** Assessments to be completed within 1 week prior to the start of treatment (i.e., loading dose of nilotinib prior to laparoscopy #2). If results of assessments (excluding laparoscopy) performed within this timeframe are available from screening, they do not need to be repeated. Note: Medical history and physical exam done during Week-1 will count for pre-anesthesia purposes prior to the laparoscopy and port placement (i.e., C1D1), as well as for protocol research endpoints as applicable.
- **Cycle 1:** Assessments to be completed within 1 week prior to the start of treatment (i.e., loading dose of nilotinib starting on Day -4 prior to laparoscopy #2).

- **Cycles 2-6:** After Cycle 1, assessments may be performed up to 3 days prior to Day 1 of a cycle, except where otherwise noted. The results from all procedures/tests must be reviewed prior to initiation of each cycle of treatment for consideration of dose modifications.
- **Unscheduled Visits:** In the event of an unscheduled/unplanned visit (e.g., additional clinical assessment(s) due to toxicity), the investigator should use best clinical judgement as to the necessary assessments. In the event that the decision is made to continue treatment, all tests/assessments as required by the next visit on the Study Calendar (**Appendix I**) should still be conducted (or repeated) within the applicable windows. If a decision is made to discontinue treatment, the participant should move to the 4-8 weeks post therapy visit with tests/assessments completed (or repeated) within the applicable windows.
- **4-8 Weeks Post Treatment Visit (Safety Visit):** The safety visit will be conducted at 6 weeks (±2 weeks) after treatment discontinuation at NIH CC. For participants proceeding to Part B, treatment will be discontinued if there is disease progression or participant experiences adverse event that requires removal.
- **Follow Up Visits:** Follow-up will consist of a physical visit at NIH CC every 3 months (±2 weeks) for up to 3 years total. If the participant is unable to travel then follow-up will be conducted by phone or virtually with results of CBC, serum chemistries, and cross-sectional imaging (performed by a local oncologist) sent in.

3.4.2 Description of Procedures

- Medical history: a review of treatment history, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
- Physical exam: standard assessments including exams of cardiovascular, nervous and respiratory systems; height, weight, and vital signs (i.e., temperature, pulse, respirations, blood pressure and oxygen saturation). After initiation of study drug, symptom-directed physical examinations will be performed as clinically indicated in the investigator's judgment. Prior to start of every cycle height and weight will be taken.
- Performance status (ECOG): an assessment of activities of daily living; see **Appendix A**.
- Laboratory assessments: the following comprises the required tests/analytes. These may be performed outside NIH and results forwarded to the study team for review and management. As the assessments include standard analyses which in general use the same methodology across all laboratories, no significant variability is expected and there is no anticipation that study data will be affected.
    - CBC with differential: includes Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, WBC, RBC, Hemoglobin, Hematocrit, RBC Indices, MCV, RDW, Platelet.
    - Serum Chemistries: Albumin, Total Bilirubin, Total Calcium, Bicarbonate, Chloride, Creatinine, eGFR, Glucose, Alkaline Phosphatase, Potassium, Total Protein, Sodium, ALT, AST, BUN, magnesium
    - HIV antibody
    - Pregnancy test: Urine or serum HCG for individuals of child-bearing potential
    - Urinalysis
- Laparoscopy and PCI scoring, see Section **3.6** and **Appendix B**

- CT scans: chest, abdomen and pelvis; may be adjusted to assess additional known sites of disease, as needed. Scans will be performed per standard of care, including pregnancy testing if applicable.
- Electrocardiogram (ECG)
- Pre-op consults: Anesthesia consult; cardiology, pulmonology and/or neurology consults may also be ordered when clinically indicated.
- Study drug administration schedule; refer to Section **3.2**
- Adverse events and concomitant medication review: Adverse events and concomitant medication will be continuously monitored throughout the study until disease progression or end of treatment visit. Adverse events that occur beyond 30 days after the last administration will be recorded per Section **6.1**.
- Correlative studies; refer to Section **5**
- QOL Surveys

  The FACT-C and EQ-5D-5L questionnaires (see **Appendix D** and **Appendix E**) assess participants' physical and mental health-related quality of life (QOL). These surveys have been validated in surgical participant populations. The questionnaires will be provided to the participant in an electronic application-based format to be filled out at baseline, and immediately prior to Cycles 3 and 6 and in follow-up (see Study Calendar **Appendix I**). It is anticipated that filling out the surveys will take approximately 10 minutes. Information collected from the surveys will be encrypted and stored electronically in a data capture system provided by the NCI CCR as part of the protocol information for each enrolled participant.

3.5 STUDY CALENDAR

See **Appendix I: Study Calendar**

3.6 SURGICAL GUIDELINES

3.6.1 Preoperative Participant Management

Participants will receive standard preoperative care as appropriate to the planned surgical intervention and the participant's underlying health status.

3.6.2 Participant Management in the Operating Room

3.6.2.1 Diagnostic Laparoscopy

- Standard techniques will be used to achieve insufflation
- Sampling of ascites if present or peritoneal lavage will be performed
- PCI scoring will be performed (**Appendix B**)
- Representative biopsies will be obtained
- Intraperitoneal catheter will be placed using standard techniques

3.6.3 Postoperative Care

3.6.3.1 Participant Monitoring

- The participants will be monitored in post-anesthesia recovery per routine if same-day discharge is planned.
- The participants will be further monitored on the surgical ward per routine if staying overnight.

3.6.4 Discharge

- Total hospitalization may be approximately 3-4 days for the visit involving intraperitoneal catheter placement and 2-3 days for other visits.

3.7 COSTS AND COMPENSATION

3.7.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all participants complete a safety visit 6 weeks ± 2 weeks following the last dose of study therapy.

3.8.1 Criteria for Removal from Protocol Therapy

Participants who meet the following criteria should be discontinued from protocol therapy:

- Completion of Part A of protocol therapy if not proceeding to Part B
- Progressive disease
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicities as listed in Section **3.3**
- Clinical need to remove the intraperitoneal port prior to completion of protocol therapy
- Surgical complication that precludes intraperitoneal chemotherapy administration
- Participant's request to withdraw from protocol therapy
- Investigator's decision
- Participant's non-compliance
- Pregnancy

3.8.2 Off-Study Criteria

- Participant experiences an exceptional response to treatment as assessed on laparoscopy after Cycle 3 and desires to pursue cytoreductive surgery, which is not part of this protocol and will be performed outside of the bounds of this protocol
- Completed study follow-up period
- Participant requests to be withdrawn from study
- Participant fails to complete first cycle of treatment for reasons other than toxicity
- Participant is lost to follow-up
- Death
- Screen failure

At PI discretion, a participant who is taken off therapy because the participant 1) completed the planned therapy or 2) was unable to complete the planned therapy, may be counseled for cytoreductive surgery with or without additional intra-peritoneal chemotherapy. For those who completed the planned therapy, cytoreductive surgery would be considered no earlier than Week 18.

3.8.3 Lost to Follow-Up

A participant will be considered lost to follow-up if the participant fails to return for 4 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 SUPPORTIVE CARE

Participants should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.

4.2 PRIOR AND CONCOMITANT THERAPY

Participants would have been on prior systemic chemotherapy. All concurrent medications should be documented prior to initiation of treatment and be periodically reviewed with the participant. Particular attention must be paid to medications which may prolong the QTc interval (**Appendix F**) and agents that interact with CYP450 isoenzymes (**Appendix G**).

No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biologic response modifiers, hormone therapy, immunotherapy, or radiotherapy.

4.2.1 Blood Products and Growth Factors

Starting at Week -1, blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of Smith et al, 2015 (WBC) (40) and Rizzo et al, 2010 (darbepoetin/epoetin) (41).

4.2.2 Nausea/Vomiting

Antiemetics may be used at the discretion of the attending physician. Anti-emetics will not be administered routinely prior to study drugs. However, if a participant develops nausea/vomiting, anti-emetics such as but not limited to prochlorperazine, metoclopramide, 5-HT3 antagonists, or aprepitant may be given. In the event that use of a 5-HT3 antagonist is required to manage nausea/vomiting, ganesetron will be the drug of choice, with close monitoring of the EKG for QTc prolongation. In addition, if a participant develops nausea and/or vomiting that is Grade 2 or greater, anti-emetics may be instituted prophylactically at the discretion of the investigator. Nausea and vomiting will be considered refractory if it does not resolve to ≤ Grade 1 with treatment with a combination of at least 2 of the anti-emetics within 24 hours.

4.2.3 Diarrhea

If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep). No more than 16 mg of loperamide should be taken in during a 24-hour period. This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours ≤ to Grade 2 with the above regimen (16 mg, or less if there is resolution of the symptoms, of loperamide in a 24-hour period).

4.2.4 Neutropenia

Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. Growth factors to prevent neutropenia will not be administered prophylactically. If necessary, they may be administered according to accepted American Society of Clinical Oncology (ASCO) guidelines to allow re-treatment.

4.2.5 Anemia

Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. Use of erythropoietin will follow ASCO guidelines.

4.2.6 Thrombocytopenia

Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤10,000/mm^3. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above 50,000/mm^3.

4.2.7 QTc Prolongation

Caution should be exercised when administering nilotinib to participants with a history of QTc interval prolongation, in participants taking anti-arrhythmics or other medications that may prolong the QTc interval, and those with relevant pre-existing cardiac disease. A list of medications that may cause QTc interval prolongation are listed in **Appendix F**, and should be avoided by participants on this study. Dose reduction will be performed as described in Section **3.3.1**.

4.2.8 Acid Reflux

Avoid the concomitant use of PPIs with nilotinib. As an alternative to PPIs, H2 blockers can be administered approximately 10 hours before or approximately 2 hours after the dose of nilotinib. Alternatively, antacids can be administered approximately 2 hours before or approximately 2 hours after the dose of nilotinib.

4.2.9 CYP450 Interactions

4.2.9.1 Concomitant Strong CYP3A4 Inhibitors

Avoid grapefruit products since they may also increase serum concentrations of nilotinib. Avoid the concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Should treatment with any of these agents be required, therapy with nilotinib should be interrupted. If participants must be co-administered a strong CYP3A4 inhibitor, consider a dose reduction to 300 mg once daily. However, there are no clinical data with this dose adjustment in participants receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period should be allowed before the nilotinib dose is adjusted upward to the indicated dose. For participants who cannot avoid use of strong CYP3A4 inhibitors, monitor closely for prolongation of the QTc interval.

4.2.9.2 Concomitant Strong CYP3A4 Inducers

Avoid the concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). Also inform participants not to take St. John's Wort since these agents may reduce the concentration of nilotinib. Based on the nonlinear pharmacokinetic profile of nilotinib, increasing the dose of nilotinib when co-administered with such agents is unlikely to compensate for the loss of exposure.

4.2.10 Gastrointestinal Dysmotility

For participants with persistent gastroesophageal reflux, suspected or confirmed gastric dysmotility, or adynamic ileus or other intestinal dysmotility, management with metoclopramide and/or prucalopride as appropriate is permitted prior to or after initiation of study treatment. Fungal esophagitis may be treated with isovuconazole. Gastroenterology consultation and upper endoscopy should be obtained as clinically indicated.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 SUMMARY

Tissue, blood, and ascites samples are tracked at the participant level and can be linked to all protocols on which the participant has been enrolled, as all participants must enroll on 13-C-0176 (Tumor, Normal Tissue and Specimens from Participants Undergoing Evaluation or Surgical Resection of Solid Tumors).

Tumor tissue will also be collected for analysis of molecular determinants of response or resistance to the combination (via RNA sequencing [RNA-seq] and whole-exome sequencing [WES]), as well as pharmacodynamic (PD) biomarkers that may be associated with the mechanism of action for this combination, including markers of cell death, cell cycle disruption, and epithelial-mesenchymal transition (EMT) phenotype. In addition, blood and, when present, peritoneal ascites will be collected for analysis of treatment-induced changes in EMT phenotype of serum and peritoneal circulating tumor cells, respectively. Blood will also be collected for analyses of circulating tumor DNA (ctDNA) by the Molecular Characterization (MoCha) Laboratory at NCI Frederick to examine genomic alterations that may be associated with response or resistance to the combination. An additional baseline blood specimen will be collected for WES to identify somatic variants within the tumor WES data.

Finally, blood, peritoneal ascites (when present), and tumor tissue will be collected for pharmacokinetic analyses (PK) of nilotinib and paclitaxel concentrations. PK samples will be collected from the first 10 participants, after which, an interim PK analysis will be conducted to determine whether measurable nilotinib concentrations are detected in the peritoneal tumor tissue and ascites following oral nilotinib administration.

5.2 BIOSPECIMEN COLLECTION

5.2.1 Sample Collection Specific to Part A of this Study Include the Following

Test/Assay	Vol	Tube & Storage*	Timing	Location of Specimen Analysis
Tumor tissue for *ex vivo* organoid (cell culture) development and assessment	Tumor tissue	N/A	Intra-op at laparoscopies #1 and #2, ± laparoscopy #3	Dr. Muthuswamy's Lab (in LCBG), THEN Lab of Path
Tumor tissue for pharmacodynamic analyses	Tumor tissue	N/A	Intra-op at laparoscopies #1, #2, #3, and #4	PADIS Lab, NCI at Frederick
Tumor tissue for molecular analyses	Tumor tissue	N/A	Intra-op at laparoscopies #1, #2, #3, and #4	MoCha Lab, NCI at Frederick
Blood for ctDNA analysis	2 x 7.5 mL blood per time point	2 Streck tubes (7.5 mL blood each)	Within 24 hours after laparoscopy #1; within 24 hours before laparoscopies #2, #3, and #4	MoCha Lab, NCI at Frederick
Blood for germline WES analysis	2 x 7.5 mL blood	2 Streck tubes (7.5 mL blood each)	Within 24 hours after laparoscopy #1	MoCha Lab, NCI at Frederick
Blood for pharmacodynamic analysis of circulating serum tumor cells (CTCs)	7.5 mL blood per time point	Streck tube	Within 24 hours after laparoscopy #1; within 24 hours before laparoscopies #2, #3, and #4	PADIS Lab, NCI at Frederick
Peritoneal ascites for pharmacodynamic analysis of circulating serum tumor cells (CTCs)	7.5 mL peritoneal ascites per time point	Streck tube	Intra-op at laparoscopies #1, #2, #3, and #4	PADIS Lab, NCI at Frederick

Test/Assay	Vol	Tube & Storage*	Timing	Location of Specimen Analysis
Blood for pharmacokinetic (PK) analyses (Section **5.3.2.2**)	2 mL blood per time point	EDTA tube	Baseline (prior to nilotinib loading); C1D1 prior to IP paclitaxel and at 90 min., 150 min., 5 hours, and 9 hours post–IP paclitaxel; C1D2 prior to IV paclitaxel and at 90 min., 150 min., 5, 9, and 24 hours post–IV paclitaxel	Lab of Dr. Larry Anderson, DTP, NCI at Frederick
Peritoneal ascites for pharmacokinetic (PK) analyses (Section **5.3.2.2**)	2 mL peritoneal ascites per time point	EDTA tube	Intra-op at laparoscopy #1; C1D1 prior to IP paclitaxel and at 150 min. and 5 hours post–IP paclitaxel; C1D2 prior to IV paclitaxel and at 150 min., 5 hours, and 24 hours post–IV paclitaxel	Lab of Dr. Larry Anderson, DTP, NCI at Frederick
Tumor tissue for pharmacokinetic (PK) analyses (Section **5.3.1.4**)	Tumor tissue	N/A	Intra-op at laparoscopies #1, #2, and #3	Lab of Dr. Larry Anderson, DTP, NCI at Frederick
Peripheral blood for immune subset analysis	Peripheral blood, 16 mL	BD Vacutainer® CPT™ tube-sodium citrate (Cat no. 362761) (2 x 8 mL tubes)	Within 24 hours after laparoscopy #1; within 24 hours before laparoscopies #2, #3, and #4	DTB Clinical Translation Unit (or per PI discretion)
Peritoneal ascites for immune subset analysis	Peritoneal ascites, ≥10 mL OR Peritoneal washings, ≥50 mL	Specimen Cup with Anticoagulant (Heparin)	Intra-op at laparoscopies #1, #2, #3, and #4	DTB Clinical Translation Unit (or per PI discretion)
* Tubes/media may be adjusted at time of collection based upon materials available and/or to ensure best samples are collected for analyses per PI discretion.				

5.2.2 Sample Collection Specific to Part B of this Study Include the Following:

Test/Assay	Vol	Tube & Storage*	Timing	Location of specimen analysis
Blood for ctDNA analysis	2 x 7.5 mL blood per time point	2 Streck tubes (7.5 mL blood each)	At the end of each 4-week cycle	MoCha Lab, NCI at Frederick
Blood for pharmacodynamic analysis of circulating serum tumor cells (CTCs)	7.5 mL blood per time point	Streck tube	At the end of each 4-week cycle	PADIS Lab, NCI at Frederick
Peritoneal ascites for pharmacodynamic analysis of circulating serum tumor cells (CTCs)	7.5 mL peritoneal ascites per time point	Streck tube	Intra-op at repeat staging laparoscopy, if performed	PADIS Lab, NCI at Frederick
Tumor tissue for pharmacodynamic analyses	Tumor tissue	N/A	Intra-op at repeat staging laparoscopy, if performed	PADIS Lab, NCI at Frederick
Tumor tissue for molecular analyses	Tumor tissue	N/A	Intra-op at repeat staging laparoscopy, if performed	MoCha Lab, NCI at Frederick
* Tubes/media may be adjusted at time of collection based upon materials available and/or to ensure best samples are collected for analyses per PI discretion.				

5.3 SAMPLE COLLECTION AND PROCESSING

Note: As also above, tubes/media may be adjusted at time of collection based upon materials available and/or to ensure best samples are collected for analyses per PI discretion. Similarly, the number/volume of aliquots, vials, and procedures, etc., noted in the following sub-section may be adjusted at the time of processing and analysis to ensure analyses are performed as needed, per PI discretion. In addition, analysis platforms and procedures may be adjusted based upon current technology and/or collaborations in place at the time of actual analyses per PI discretion.

5.3.1 Tumor Tissue Collection

Tumor and normal tissue samples will be collected at the time of surgery. Tissue will only be taken for research purposes after it is removed as part of the standard operation, as viable tissue that will otherwise be removed as part of the operation.

Note: Resected tumor tissue sent to the Blood Processing Core (BPC) will be by BPC-indicated processes.

5.3.1.1 Tumor Tissue for *Ex Vivo* Modeling

Tissue samples may be sent to the Laboratory of Dr. Senthil Muthuswamy (see Section **5.4.4**) for the purposes of tumor cell culture (organoid) development. Successfully cultivated organoids, both the *ex vivo* nilotinib-naive and nilotinib-exposed tumor tissue cell cultures, will be exposed to

paclitaxel and results qualitatively compared by an intramural pathologist in the Laboratory of Pathology.

5.3.1.2 Tumor Tissue for Pharmacodynamic Analyses

Tumor tissue for PD analysis will be collected per summary tables in Section **5.2**. Note: The required PD tissue specimen size is between 2x2x2 to 5x5x5 mm. A minimum of two specimens per timepoint of this size would be preferred.

Tumor tissue for PD analysis will be immediately (within 2 minutes) flash-frozen in liquid nitrogen; detailed instructions for tumor tissue collection and processing can be found in SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). The frozen tumor specimens should be transferred to PADIS on dry ice, where the tumor tissue is stored at -80°C until processing.

Labeling:

Tumor tissue specimens should be labeled with:

- Sample type (e.g., resected tumor tissue)
- Time point (e.g., C01D01 pre dose)
- Collection date and time
- Sample ID, containing:
  - NIH Clinical Center protocol number
  - Unique patient ID (Do NOT include patient name, medical record number, or initials)
  - 500-series sample collection number (e.g., 500, 501, 502, etc.)
  - Pass/Core/Fragment identifier (e.g., A, B, C, etc.)

  For example, the sample ID for the first core of a baseline sample collected on study 10005 for NCI DTC patient #004 should be: 10005_NCIDTC_004_500A.

The sample shipping manifest and batch record, both of which are included in NCI DCTD SOP340507, should be completed and included with the shipment.

Tumor tissue samples for <u>PD analyses</u> will be shipped on dry ice to:

Attn: PADIS IQC Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 425, Room 105
Frederick, MD 21702
Phone: 301.846.7292
NCI_PD_Support@mail.nih.gov

Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893. The Clinical Center should notify NCIPDSupportPADIS@mail.nih.gov with sample information.

PADIS Contacts for Tumor Tissue for PD Analysis

Please contact Amy Pantella (office: 301.846.6747, cell: 301.401.8070) or Rachel Andrews (office: 301.846.1951, cell: 240.344.5697) (email: NCI_PD_Support@mail.nih.gov) to ask any questions regarding storage or shipment of these specimens.

NIH Clinical Center Laboratory Contact for Tumor Tissue for PD Analysis

At least 24 hours prior to tumor tissue collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov, Pager (preferred): 102-12798, Phone: 240-858-3963, Fax: 301-480-5871. Initial processing and shipping of the samples will be completed as described above.

Testing and data analysis will be performed by PADIS, NCI at Frederick.

5.3.1.3 Tumor Tissue for Molecular Analyses

Tumor tissue for molecular analysis will be collected per summary tables in Section **5.2**. The required tissue specimen size for genetics/genomics is between 2x2x2 to 5x5x5 mm.

Tumor tissue for molecular analysis will be immediately (within 2 minutes) flash-frozen in liquid nitrogen; detailed instructions for tumor tissue collection and processing can be found in SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). The frozen tumor specimens should be transferred to MoCha on dry ice, where the tumor tissue is stored at -80°C until processing

Labeling:

Tumor tissue specimens should be labeled with:

- Sample type (e.g., resected tumor tissue)
- Time point (e.g., C01D01 pre dose)
- Collection date and time
- Sample ID, containing:
  - NIH Clinical Center protocol number
  - Unique patient ID (Do NOT include patient name, medical record number, or initials)
  - 500-series sample collection number (e.g., 500, 501, 502, etc.)
  - Pass/Core/Fragment identifier (e.g., A, B, C, etc.)

  For example, the sample ID for the first core of a baseline sample collected on study 10005 for NCI DTC patient #004 should be: 10005_NCIDTC_004_500A.

Tumor tissue samples for <u>molecular analyses</u> will be shipped on dry ice to:

Attn: Gloryvee Rivera
MoCha Histology Lab
Frederick National Lab for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room 107
Frederick, MD 21702
Phone: 301-846-6349

MoChaSampleReceiving@nih.gov

Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893. The Clinical Center should notify MoChaSampleReceiving@nih.gov with sample information.

Contacts for Tumor Tissue for Molecular Analysis

Please contact Tom Forbes, thomas.forbes@nih.gov (phone: 301.228.4685) to ask any questions regarding storage or shipment of these specimens.

NIH Clinical Center Laboratory Contact for Tumor Tissue for Molecular Analysis

At least 24 hours prior to tumor tissue collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov, Pager (preferred): 102-12798, Phone: 240-858-3963, Fax: 301-480-5871. Initial processing and shipping of the samples will be completed as described above.

Testing and data analysis will be performed by MoCha, NCI at Frederick.

5.3.1.4 Tumor Tissue for Pharmacokinetic Analysis

Tumor tissue samples will be sent to Dr. Larry Anderson's laboratory (Developmental Therapeutics Program, NCI at Frederick) for analysis of intratumoral nilotinib and paclitaxel concentrations. See Section **5.3.2.2** for shipping details.

5.3.2 Blood and Peritoneal Ascites Collection

5.3.2.1 Blood and Peritoneal Ascites Collection for Circulating Tumor Cell Analysis

Whole blood (7.5 mL per collection) will be collected aseptically by venipuncture or from a venous port into one 10-mL Streck tube at the timepoints listed in Section **5.2**. When present, peritoneal ascites for CTC analysis (7.5 mL per collection) will also be collected into one 10-mL Streck tube. Tubes must be inverted 8 times to ensure adequate mixing of the additive that preserves the CTCs at the timepoints listed in Section **5.2**. Blood samples for CTC analysis should be shipped as soon as possible so they can be analyzed within 48 hours of collection (preferably, within 24 hours of collection). Because of the 48-hour window of CTC sample stability, CTC samples should be shipped to arrive when specified below:

Collection Day	Day/time samples **must** arrive at PADIS
Monday	Wednesday (early morning)
Tuesday	Thursday (early morning)
Wednesday	Friday (early morning)
Thursday	Friday (early morning)
Saturday	Monday (early morning)
Sunday	Tuesday (early morning)

CTC samples may not be collected on Fridays, due to shipment and processing requirements. Scheduled CTC collections that fall on a Friday are waived.

Shipping address for CTC specimens:

Attn: PADIS CTC Laboratory
Frederick National Laboratory for Cancer Research

Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 425, Room 102
Frederick, MD 21702
Phone: 301.228.4711

Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893. The Clinical Center should notify NCIPDSupportPADIS@mail.nih.gov with sample information.

PADIS Contacts for CTC Samples

Please contact Amy Pantella (office: 301.846.6747, cell: 301.401.8070) or Rachel Andrews (office: 301.846.1951, cell: 240.344.5697) (email: NCI_PD_Support@mail.nih.gov) to ask any questions regarding storage or shipment of these specimens.

NIH Clinical Center Laboratory Contact for CTC Samples

At least 24 hours prior to blood or peritoneal ascites sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov, Pager (preferred): 102-12798, Phone: 240-858-3963, Fax: 301-480-5871. Initial processing and shipping of the samples will be completed as described above. Samples for CTC analysis should be shipped as soon as possible so they can be analyzed within 48 hours of collection (preferably, within 24 hours of collection).

5.3.2.2 Blood and Peritoneal Ascites Collection for Pharmacokinetic Analysis

PK samples will be collected from the first 10 participants, after which an interim PK analysis will be conducted to determine whether measurable nilotinib concentrations are detected in the peritoneal ascites following oral nilotinib administration.

All liquid PK samples will be collected in lavender-top (EDTA) tubes, with 2 mL of blood or peritoneal ascites per sample and stored refrigerated (2-8°C).

Blood samples for PK analysis will be collected on baseline prior to the nilotinib loading, Cycle 1 Day 1 prior to IP paclitaxel administration and at 90 (± 15) minutes), 150 (± 15) minutes, and 5 (± 1) hours, and 9 (± 1) hours post–IP paclitaxel administration; and on Cycle 1 Day 2 prior to IV paclitaxel administration and at 90 min (± 15) minutes, 150 min (± 15) minutes, and 5 (± 1), 9 (± 1), and 24 (± 4) hours post–IV paclitaxel administration. Blood samples will be centrifuged, and plasma will be stored at -70°C for analysis.

Samples of peritoneal ascites (when present) for paclitaxel and nilotinib PK analysis will be collected at the time of laparoscopy #1; on Cycle 1 Day 1 prior to IP paclitaxel administration and at 150 (± 15) minutes and 5 (± 1) hours post–IP paclitaxel administration; and on Cycle 1 Day 2 prior to IV paclitaxel administration and at 150 (± 15) minutes, 5 (± 1) hours, and 24 (± 4) hours post–IV paclitaxel administration.

Based on results from initial measurements, sampling times may be adjusted, but neither the total number of samples nor the total amount of blood or peritoneal ascites drawn per participant will be increased. Samples will be analyzed using a validated LC-MS or LC-MS/MS method.

PK Sample Shipping information

Send PK samples to the following lab contact:

Tracy W. Webb
Office of the Associate Director/DTP/NCI
FNLCR
Boyles Street
Building 1047, Room 8
Frederick, MD 21702
301-846-7402; webbtw@mail.nih.gov

Laboratory Contact for PK Sample Collection

At least 24 hours prior to blood or peritoneal ascites sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov, Pager (preferred): 102-12798, Phone: 240-858-3963, Fax: 301-480-5871. Initial processing and shipping of the samples will be completed as described above.

5.3.2.3 Blood Collection for ctDNA and WES Analysis

For ctDNA analysis, 2 whole blood samples of ≥ 7.5 mL each will be collected into 10-mL Streck tubes at the timepoints listed in Section **5.2** and shipped to MoCha within 3 days.

For WES analysis, 2 whole blood samples of ≥ 7.5 mL each will be collected into 10-mL Streck tubes at the time of the pre-treatment laparoscopy and shipped to MoCha within 3 days.

Blood samples for ctDNA and WES analysis should be labeled with only the unique participant ID. **Do NOT include participant identifiers (e.g., medical record number, participant name, or initials) with the samples.**

Ship blood specimens at ambient temperature to:

Attn: Gloryvee Rivera
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room 107
Frederick, MD 21702
Phone: 301.846.1718
MoChaSampleReceiving@nih.gov

Shipment should be by CSP Courier and may be arranged by contacting Jenn Bangh, FNLCR, Tel.: 301-846-5893.

5.3.2.4 Immune Subset Analysis

For blood samples and peritoneal ascites or peritoneal washings collected for immune subset analyses; contact the Developmental Therapeutics Branch (DTB) Clinical Translation Unit per Section **5.4.6** or per PI discretion as applicable.

5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.4.1 General

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

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

Access to specimens and associated data will only be granted to researchers not named in the protocol following OHSRP/IRB approval of an additional protocol, granting the rights to use the material/data. Samples/data that is not identifiable to the recipients may be shared without approvals if determined to be not human subjects' research.

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

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

5.4.2 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not placed in paraffin blocks is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the participant was enrolled.

5.4.3 Procedures for Storage and Tracking of Tumor Tissue, Blood, and Peritoneal Ascites Specimens for Pharmacokinetic, Pharmacodynamic, and Molecular Analyses

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and participant confidentiality pursuant to informed consent provisions. Information about each specimen (per specific protocol) will be recorded on a PK/PD collection worksheet included in **Appendix H**.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory

system. To ensure participant confidentiality, only containers used for the initial specimen collections will be labeled with participant identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no participant information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without participant identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: protocol number, unique participant accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three participants will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:

- 000 series: peritoneal ascites for PK
- 200 series: blood for PK
- 400 series: blood for circulating tumor cells (CTCs)
- 500 series: tumor tissue from laparoscopy
- 700 series: peritoneal ascites for CTCs
- 800 series: blood for genetic analysis (ctDNA and WES)
    - 899 indicates specimens for germline WES

The inventory process contains other security provisions sufficient to safeguard participant privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only participant information available in the inventory system will be the participant sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a participant and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested), and reported as such to the IRB.

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

5.4.4 Procedures for Storage of Specimens in the Laboratory of Dr. Muthuswamy

All research samples acquired under this protocol for Dr. Senthil Muthuswamy's Lab will be labeled with a unique deidentified sample identifier and entered into the lab's secure data capture system provided by the NIH, secured on the NIH secure server. All access to the provided participant research samples, and associated data, are limited to Dr. Muthuswamy and his laboratory's research team. All data associated with the participant clinical research samples and generated cell line records will be entered into the lab's secure data capture system. Access is

limited to Dr. Muthuswamy and his laboratory's research team, requiring individual login and password.

Received participant research samples will be stored in freezers designated for human research specimens only. The freezers are maintained at -80°C (e.g., sera, plasma, tissue samples) or under liquid nitrogen (e.g., cells) according to stability requirements of the specific specimens. Access to the laboratory's freezers is maintained under lock and key accessible only to Dr. Muthuswamy and the designated laboratory research personnel. Access to samples from the protocol for research purposes will be by permission of the Principal Investigator. All use of the participant research samples and associated generated cell lines in Dr. Muthuswamy's lab will be only per approved IRB research as specifically indicated in the appropriate human research protocol.

5.4.5 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

5.4.5.1 BPC Contact Information

Please e-mail Figg's Lab at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

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

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.4.5.2 Sample Data Collection

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

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the NIH Clinical Center (i.e., NIH CC generated) Patient Number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.4.5.3 Sample Storage and Destruction

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

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples

must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

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

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed or returned to the participant, if so requested. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

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

5.4.6 Procedures for Processing and Storage of Specimens in the Developmental Therapeutics Branch (DTB) Clinical Translation Unit

5.4.6.1 DTB Clinical Translation Unit Contact Information

Contact by email (Min-Jung Lee at leemin@mail.nih.gov and Sunmin Lee at lees@pop.nci.nih.gov) when the participant is scheduled and by phone as soon as the blood is drawn at 240-760-6330.

If a lab member does not pick up the phone, please leave a message including the time, protocol, and where to pick up the blood or other samples and a lab member will be there as soon as possible.

Please keep blood at ambient temperature.

5.4.6.2 Sample Data Collection, Storage, and Destruction

Members of the lab will enter the samples into a secure, password-protected CCR approved participant sample database and process the samples.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. Specimen labels will indicate: protocol number, type of sample, and date as appropriate. The inventory process contains other security provisions sufficient to safeguard participant privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved.

SOPs ensure that any changes in informed consent made by a participant and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

5.5 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.5.1 Description of the Scope of Genetic/Genomic Analysis

The research correlates for this study may include DNA/RNA sequencing of tumors. For any genetic studies performed, the results will be deposited in a database such as dbGaP per NIH requirements. Although there is controlled access to such a database, such a submission carries theoretical risks of revealing the identity of the participant. This is discussed in the consent.

5.5.2 Description of How Privacy and Confidentiality of Medical Information/Biological Specimens Will Be Maximized

As stated in Section **5.4.3** unique database generated identifiers are attached to samples and are linked through the database to medical record information, with the key available to investigators on the approved study. Samples/data may be shared with investigators not named on this protocol per Section **5.4** and data will also be shared per the GDS policy. Therefore, potential identification would only occur in the event of a data breach or improper sharing of a key. We do not plan to publish pedigrees; therefore, this is not a potential source of identification. In addition, a Certificate of Confidentiality has been obtained for this study.

5.5.3 Management of Results

Participants will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

5.5.4 Genetic Counseling

Participants will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the participant will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the participant does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

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

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency, and timeliness. The principal investigator, associate investigators/research nurses, and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual participant.

All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded.

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

Document AEs from the first study intervention (Day -4), through 30 days after last dose of study drug was administered. After 30 days, only adverse events which are serious and related to the study intervention need to be recorded.

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

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

6.1.1 Data Collection/Recording Exceptions

6.1.1.1 Abnormal Laboratory Values

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

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

The PI evaluation of each AE not captured in the clinical database determining that it meets the criteria above will be documented in the source documents.

6.2 DATA SHARING PLAN

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in another public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center).

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: ClinicalTrials.gov, dbGaP.

- BTRIS (automatic for activities in the Clinical Center).
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

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

6.3 RESPONSE CRITERIA

For the purpose of this study, participants will be re-evaluated for response after each 9-week course of treatment and then every 3 months (±2 weeks) for up to 3 years.

Response and progression will be evaluated in this study primarily using the Peritoneal Carcinomatosis Index (PCI; see **Appendix B**), as well as, if radiographically measurable disease is present at study inclusion, the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (42).

6.3.1 Response Evaluation Criteria in Solid Tumors (RECIST) Disease Parameters

Measurable disease: Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

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

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

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 in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

Note: RECIST guidelines have defined measurability of lesions based on assumption that slice thickness of CT or MRI is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Derivation or calculation of outcome variable: To assess objective response of future progression it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only participants with measurable disease at baseline will be included in the study since objective tumor response is a primary endpoint.

6.3.2 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant 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 (43, 44). 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 (45).

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

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

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

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

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

6.3.3 Evaluation of Target Lesions

- Complete Response (CR) – disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm
- Partial Response (PR) – At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD) – At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on available studies. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD) – Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.4 Evaluation of Non-Target Lesions

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

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

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

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

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

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

For Participants 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	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
Any	Any	Yes	PD	

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

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

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

Note: Participants 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 Participants with Non-Measurable Disease (i.e., Non-Target Disease)

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

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

6.3.6 Duration of Response

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for Complete Response (CR) or Partial Response (PR) (whichever is first recorded) until the first date that recurrent or Progressive Disease (PD) 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 PD is objectively documented.

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

6.3.7 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from the start of the treatment until time of disease relapse from CR, disease progression, or death, whichever occurs first, for up to 3 years after completion of therapy.

6.3.8 Overall Survival

Overall Survival (OS) is defined as the time from the start of the treatment until time of death from any cause, for up to 3 years after completion of therapy.

6.3.9 Peritoneal Carcinomatosis Index (PCI)

Determination of Peritoneal Carcinomatosis Index (PCI; see **Appendix B**) will be made at the time of initial and subsequent laparoscopy, or MRI and/or CT imaging if laparoscopy is not planned. Peritoneal disease burden will be considered to be stable when the PCI score at laparoscopy #3 is < 4 points higher or lower compared to the PCI score at laparoscopy #2. Disease progression will be defined as an increase in PCI score by ≥ 4 points, while disease response will be defined as a decrease in PCI score by ≥ 4 points.

Derivation or calculation of outcome variable: Concordance between the PCI scores calculated by different surgeons is high (~90%) (46). We will apply the following definitions for macroscopic determination of tumor response during laparoscopy:

- Complete Response (CR) – PCI ≤ 5 with negative histology of at least 3 peritoneal biopsies of suspect nodules and washings with negative cytology.
- Partial Response (PR) – At least 4 points decrease in PCI.
- Progressive Disease (PD) – At least 4 points increase in PCI. The appearance of one or more new lesions is also considered progression.
- Stable Disease (SD) – Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the PCI.

In order to document PCI scoring for each participant, the rubric will be completed following each laparoscopy. In addition, photo or video documentation of peritoneal disease will be captured for each participant at each laparoscopy. In this way, independent review of the scoring would be possible (47).

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site ((http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802: Non-Compliance Human Participants Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

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

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

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when participants are being actively treated on the trial to discuss each participant.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meting requirements for expedited reporting as described in Section

7.2.1 will be submitted within the appropriate timelines.

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

8 STATISTICAL CONSIDERATIONS

8.1 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate efficacy of bidirectional chemotherapy using intraperitoneal and intravenous paclitaxel and oral nilotinib by calculating the rate of downstaging of peritoneal disease burden to become resectable, based on Peritoneal Carcinomatosis Index (PCI)	Rate of downstaging- i.e., the fraction of participants who are successfully downstaged to resectable based on PCI and PI discretion, assessed every 9 weeks while on treatment and then every 3 months (±2 weeks) for 3 years.	This is the most immediate endpoint of such a study, with the goal of specifically targeting peritoneal disease burden to facilitate subsequent cytoreduction to optimize regional cancer treatment and disease control.
Secondary		
To assess clinicopathologic response to therapy by assessing response rate by RECIST 1.1 and/or by PCI	Response rate by RECIST 1.1 and/or by PCI, assessed every 9 weeks while on treatment and then every 3 months (±2 weeks) for 3 years.	Standard endpoints for cancer clinical trials. Success of regimen will be determined by this endpoint.
To evaluate the safety and tolerability of intraperitoneal and intravenous paclitaxel and oral nilotinib	Adverse events (AEs) will be assessed using CTCAE v.5.0 and documented from Day 1 of protocol therapy until end of treatment, at the defined study visits and at standard of care visits, see also Section **6.1.1** and **Appendix I**	Standard for cancer clinical trials, collecting information on all major organ function and observed toxicity, if any, to determine prominent toxicity to advise safety and tolerability.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To determine peritoneal progression-free survival (pPFS) after therapy	Peritoneal progression-free survival (pPFS) is defined as the duration of time from the start of the treatment until time of peritoneal disease relapse from CR or peritoneal disease progression, for up to 3 years after completion of therapy, assessed every 3 months (±2 weeks).	Clinical trial-specific endpoint given the metastatic disease of interest. Success of regimens will be determined by these endpoints.
To evaluate the peritoneal progression-free survival (pPFS) probability and the percentage of participants who become resectable by individual histologies	- Peritoneal progression-free survival (pPFS) is defined as the duration of time from the start of the treatment until time of peritoneal disease relapse from CR or peritoneal disease progression, for up to 3 years after completion of therapy, assessed every 3 months (±2 weeks). - The fraction of participants who are able to be down-staged to resectable will be reported for each histology	Protocol-specific endpoints to assess peritoneal relapse separate from overall disease relapse and to assess therapy efficacy in facilitating subsequent cytoreductive surgery.
To measure overall survival (OS) and overall progression free survival (PFS) for up to 3 years post therapy	- Progression-free survival (PFS) is defined as the duration of time from the start of the treatment until time of disease relapse from CR, disease progression, or death, whichever occurs first, for up to 3 years after completion of therapy, assessed every 3 months (±2 weeks). - Overall survival (OS) is defined as the time from the start of the treatment until time of death from any cause, for up to 3 years after completion of therapy, assessed every 3 months (±2 weeks).	Standard endpoints for cancer clinical trials. Success of regimens will be determined by these endpoints.
To evaluate participants' quality of life using FACT-C and EQ-5D-5L	Quality of life as measured by FACT-C and EQ-5D-5L, (**Appendix D** and **Appendix E**). Assessed baseline, every 9 weeks while on treatment, then every 3 months (±2 weeks) for 3 years after completion of study therapy.	Standard component of clinical trial participant assessment to capture QOL data and outcomes before, during, and after protocol therapy.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
To assess the rate and etiology of adverse events related to therapy	Each of these will be evaluated using descriptive methods and reported as exploratory results. If any statistical tests are performed in these analyses, the results will be presented without adjustment for multiple comparisons but reported in the context of the number of tests performed. See Section for **5.2** collection timepoints.	Exploratory analysis
To assess difference in response to *ex vivo* paclitaxel exposure between nilotinib-naïve versus nilotinib-exposed tumor-derived organoid tissue		
To assess the synergy (PK and PD) between intraperitoneal paclitaxel and oral nilotinib compared to intravenous paclitaxel and oral nilotinib		
To assess whether oral nilotinib is delivered to peritoneal tumor tissue and ascites at measurable concentrations		
To evaluate serum and intraperitoneal circulating tumor cells and immune subsets, to determine their association with clinical response and with progression-free survival (PFS)		
To evaluate the clinical benefit of additional cycles of IV paclitaxel and PO nilotinib after completion of 6 cycles of bidirectional therapy for participants who remain unresectable		

8.2 SAMPLE SIZE DETERMINATION

This trial is designed to provide an estimate of the percentage of participants who are able to have peritoneal disease burden be successfully down-staged to become resectable with reasonable precision. All participants enrolled on the trial will be primarily evaluated together.

With 43 total evaluable participants, and a projected fraction of 20% of participants being successfully down-staged, a two-sided 95% confidence interval for the fraction will extend ± 0.12 from the expected proportion of 0.20.

As an early stopping rule, after approximately 1/3 of participants (14) have been enrolled and treated, if 0/14 are able to be successfully down-staged, then no further participants will be enrolled since the one-sided 90% upper confidence bound on 0/14 is 15.2%, which would be below the desired 20%. At the time the 14th evaluable participant has been restaged during follow-up after

completion of IP and IV treatment (Part A), accrual will be paused to allow for an analysis by the study statistician. A brief memo will be created by the study statistician to document the number of participants down-staged to resectable, and to be reviewed by the PI and study team.

It is reasonably expected that 15 participants per year may be evaluated with laparoscopy on this protocol, of whom 10 will not be able to undergo complete cytoreduction. With up to 43 evaluable participants necessary, as well as planning for a small number for inevaluable participants (5), we intend to initiate intervention in up to 48 (43+5=48) participants. It is expected that they can be accrued within 4-5 years. Note: To allow for up to 22 screen failures, a total of 70 (43+5+22=70) participants will be set for the purposes of the NIH accrual ceiling.

8.3 POPULATIONS FOR ANALYSES

8.3.1 Modified Intention to Treat

Any participants who enroll onto the trial, provide consent, and undergo intraperitoneal catheter placement and subsequent chemotherapy administration will be included in the efficacy and safety evaluations as appropriate. All participants will be evaluated for safety with respect to CTCAE version 5.0 events, and all evaluable participants will be included in the efficacy evaluation.

8.4 STATISTICAL ANALYSES

8.4.1 General Approach

The fraction of participants who are able to be down-staged will be determined and reported along with a confidence interval. The peritoneal PFS will be estimated and reported along with a confidence interval.

8.4.2 Analysis of the Primary Endpoints

- The fraction of participants who are successfully down-staged to resectable by use of chemotherapy will be reported along with a 95% confidence interval.

8.4.3 Analysis of the Secondary Endpoints

The following are the secondary evaluations to be performed and the intended method of analysis

- To assess clinicopathologic response to therapy by assessing response rate by RECIST 1.1 and/or by Peritoneal Carcinomatosis Index (PCI). The fractions with a clinical response will be reported for all participants along with a 95% confidence interval.
- Safety will be assessed by analyzing the type, grade and frequency of toxicities in addition to laboratory data and vital signs. Adverse events (AEs) will be assessed using CTCAE v.5.0 and documented from Day 1 of protocol therapy until week 21, at the defined study visits and at standard of care visits.
- To measure peritoneal progression-free survival (pPFS), the Kaplan-Meier method will be used, and the median peritoneal progression-free survival (pPFS) will be reported along with a 95% two-sided confidence interval. This will be done for all participants.
- To evaluate overall survival (OS) and overall progression-free survival (PFS) for up to 3 years after protocol treatment, the Kaplan-Meier method will be used; a 95% confidence

interval will be reported on the median OS and PFS.

- Peritoneal progression-free survival (pPFS) probability and the percentage of participants who become resectable will be evaluated by individual histologies; median peritoneal progression-free survival (pPFS) will be reported using the Kaplan-Meier method, along with a 95% confidence interval for each histology. The fraction who are able to be down-staged to resectable will be reported for each histology along with a 95% confidence interval.
- To evaluate participants' quality of life, the FACT-C and EQ-5D-5L instruments will be used (**Appendix D** and **Appendix E**). The outcomes from this instrument will be reported using descriptive statistics, as well as comparing the results from before to after treatment: physical and mental health-related quality of life.

8.4.4 Safety Analyses

The impact of nilotinib on participants with peritoneal carcinomatosis in terms of bowel obstruction requiring nasogastric tube compression or perforation are as yet undefined. This participant population may be expected to develop obstruction or perforation in the setting of active chemotherapy treatment. If the rate of these specific complication overall is above 25% after enrolling and treating every 12th patient, the study will be put on hold and assessed prior to continuing treatment or additional participant accrual.

8.4.5 Baseline Descriptive Statistics

Baseline demographic characteristics will be reported overall.

8.4.6 Planned Interim Analyses

An early evaluation for efficacy will take place after 14 evaluable participants have been treated. Further details are provided in Section **8.2**.

8.4.7 Sub-Group Analyses

Subsets of participants within histologic cohort and treatment arm may have their peritoneal progression free survival and *ex vivo* and *in vivo* chemotherapy response evaluated as an exploratory endpoint.

8.4.8 Tabulation of Individual Participant Data

None

8.4.9 Analysis of Exploratory Objectives

- To assess the rate and etiology of adverse events related to therapy; this will be done descriptively
- To assess difference in response to *ex vivo* paclitaxel exposure using organoids derived from resected tumor tissue that has not versus has been exposed to systemic nilotinib. The organoids will be fixed and qualitatively evaluated by an intramural pathologist.

- To assess the synergy (PK and PD) between intraperitoneal paclitaxel and oral nilotinib compared to intravenous paclitaxel and oral nilotinib. The evaluations will be done descriptively for the various measures obtained.
- To assess whether oral nilotinib is delivered to the peritoneal tumor tissue and ascites at measurable concentrations. PK samples will be collected for the first 10 participants, after which, an interim PK analysis will be conducted to determine whether measurable nilotinib concentrations are detected in the peritoneal tumor tissue and ascites following oral nilotinib administration. If 0 of the first 10 participants do not have measurable nilotinib, then the upper one-sided 90% confidence interval bound is 20.6%. This means that the probability of detecting nilotinib is likely to be <21%.
- To evaluate serum and intraperitoneal circulating tumor cells and immune subsets, to determine their association with clinical response and with progression-free survival. Two-group tests such as a Wilcoxon rank sum test may be used to assess association with response, while Kaplan-Meier curves and log-rank tests along with a Cox proportional hazards model may be used to assess association with peritoneal progression free survival.
- To evaluate the clinical benefit of additional cycles of IV paclitaxel and PO nilotinib after completion of 6 cycles of bidirectional therapy for participants who remain unresectable. This subset of participants will be evaluated separately from the entire cohort. The fraction of participants in the subset who are successfully down-staged to resectable by use of chemotherapy will be reported along with a 95% confidence interval. These participants' serum and intraperitoneal circulating tumor cells will be assessed while on treatment. Two-group tests such as a Wilcoxon rank sum test may be used to assess association with response, while Kaplan-Meier curves and log-rank tests along with a Cox proportional hazards model may be used to assess association with peritoneal progression free survival.

9 COLLABORATIVE AGREEMENTS

None

10 HUMAN PARTICIPANTS PROTECTIONS

10.1 RATIONALE FOR PARTICIPANT SELECTION

All participants from both sexes and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in the protocol and provide informed consent to protocol participation. Pregnant or nursing individuals are excluded because of the potential teratogenic effects of therapy.

10.2 PARTICIPATION OF CHILDREN

Because there is not yet adequate dosing or adverse event data on the combined administration of nilotinib and paclitaxel in participants < 18 years of age, children will not participate in this study.

10.3 RISK/BENEFIT ASSESSMENT

Peritoneal metastasis is a lethal disease, with an aggressive clinical course leading to significant morbidity. Survival outcomes with systemic chemotherapy or CRS alone have remained dismal. The combination of bidirectional paclitaxel and oral nilotinib is a novel therapeutic approach that

is minimally invasive, does not require cytoreduction (laparotomy) and can be repeatedly given.

Pre-clinical data from DCTD demonstrated synergy between nilotinib and paclitaxel. In addition, participants accrued in an ongoing Phase I study for the combination have experienced a more favorable side effect profile compared to historical controls, particularly in terms of paclitaxel-related neuropathy.

Participants will receive evaluation of their disease at the National Cancer Institute's Clinical Center. Participants may obtain direct benefit from treatment with bidirectional paclitaxel and nilotinib.

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. Participants will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of participants will be recorded in the participant chart. If participants suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland.

Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations. In all publications and presentations resulting from this trial, participants' anonymity will be protected to the maximum extent possible. Authorized personnel from the National Cancer Institute (NCI) and Food and Drug Administration (FDA) or other regulatory authorities may have access to research files in order to verify that participants' rights have been safeguarded.

10.3.1 Known Potential Risks

The primary risks of participation in this study include the possible occurrence of any of a range of side effects from chemotherapy administration. Furthermore, there may be complications from laparoscopy and/or intraperitoneal catheter placement. Procedure-related complications are usually low-grade.

10.3.1.1 Blood Collection

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting. No more than about 86.5 mL will be collected at a timepoint. No more than a potential of about 247 mL of blood maximum can be collected over a single 8-week period.

10.3.1.2 Electrocardiogram (ECG)

Side effects of ECG are skin irritation where ECG electrodes are placed.

10.3.1.3 Urine Collection

There are no physical risks associated with urine collection.

10.3.1.4 Questionnaire

Some of the questions in the questionnaire may be upsetting or make participants feel anxious.

10.3.1.5 Laparoscopy

The most common risks are bleeding, infection, and damage to organs in the abdomen. Less common risks include complications from general anesthesia, inflammation of the abdominal wall, and blood clots.

10.3.1.6 General Anesthesia

Risks of general anesthesia include temporary confusion and memory loss, although this is more common in the elderly, dizziness, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, sore throat due to the breathing tube.

10.3.1.7 Radiation

The study will involve additional radiation risk from the following sources:

Up to 6 CT scans per year during the first year of the study (four on treatment, one scheduled at screening, but which may be repeated.).

Participants in this study may be exposed to approximately 6.6 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 0.7 out of 100 (0.6%) and of getting a fatal cancer is 0.3 out of 100 (0.3%).

10.3.2 Known Potential Benefits

Refer to Section **1.2.7** of the Background Section.

10.3.3 Assessment of Potential Risks and Benefits

There are risks associated with intraperitoneal chemotherapy administration, however we believe the potential benefits outweigh the risks, as the participant population has limited treatment options.

10.4 Consent Process and Documentation

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the participant will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (Non-Electronic) Signature on Electronic Document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy IRB.

11.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

11.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH Clinical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local

level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

12 PHARMACEUTICAL/DEVICE INFORMATION

There will be no IND obtained for the use of any of the commercial agents used in this study.

This clinical investigation of these marketed agents is exempt from the IND requirements because all of the criteria for an exemption in 21CFR 312.2(b) are met; including using an alternative route of administration in an unapproved indication:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
- Additional information on clinical investigations is available on FDA's Web site at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

12.1 PACLITAXEL

Refer to the FDA approved package insert for complete product information.

12.1.1 Acquisition and Accountability

Commercial supplies of paclitaxel will be purchased by the NIH Clinical Center.

12.1.2 Toxicity

Paclitaxel has been well studied and toxicities are well defined in the package insert for this FDA approved drug. The most common severe adverse reactions are related to myelosuppression and result in neutropenia, leukopenia and anemia. Additionally, participants with a cardiac history must be monitored during first infusion due to reported conduction abnormalities resulting in AV block and ventricular tachycardia. Participants with known liver disease may experience hepatic enzyme elevation given the high degree of hepatic metabolism. In participants that have received oxaliplatin as previous therapy there is an increased risk of worsening of peripheral neuropathy. In participants who have received radiation therapy there is a risk for radiation recall reactions Less severe reactions such as alopecia, nausea and vomiting have also been noted. When given in an intraperitoneal formulation for gastric cancer the most commonly noted adverse effects were

neutropenia and anemia. In limited data no patients experienced abdominal pain due to intraperitoneal formulation. In geriatric patients there is an overall increase in adverse events.

Refer to the package insert for complete information about this product.

12.1.3 Formulation and Preparation

Please refer to package insert for formulation and see Section **3.2** for preparation instructions

12.1.4 Stability and Storage

Refer to the package insert for complete information about this product.

12.1.5 Administration Procedures

See Section **3.2**

12.1.6 Incompatibilities

Refer to the package insert for complete information about this product.

12.2 NILOTINIB

Refer to the FDA approved package insert for complete product information.

12.2.1 Acquisition and Accountability

Commercial supplies of nilotinib will be purchased by the NIH Clinical Center.

12.2.2 Administration Procedures

See Section **3.2**

13 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event/Adverse Experience
ALT	Alanine Transaminase
AP	Accelerated Phase
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
AUC	Area Under the Curve
BID	Twice Daily
BTRIS	Biomedical Translational Research Information System
BUN	Blood Urea Nitrogen
C	Cycle
CAP	Chest/abdomen/pelvis
CAP/JCAHO	College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations
CBC	Complete Blood Count
CBR	Clinical Benefit Ratio
CCR	Center for Cancer Research
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COV	Close-out Visit
CR	Complete Response
CRIS	Clinical Research Information System
CP	Chronic Phase
CRS	Cytoreductive Surgery
CSC	Cancer Stem Cell
CT	Computed Tomography
ctDNA	Circulating Tumor DNA
CTC	Circulating Serum Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DCTD	Division of Cancer Treatment and Diagnosis
DOXIL	Liposomal Doxorubicin
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	EuroQol Group 5-Dimension 5-Level Health Survey
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMT	Epithelial-Mesenchymal Transition
FACT-C	Functional Assessment of Cancer Therapy-Colorectal
FDA	Food and Drug Administration
FUDR	FUDR Floxuridine

GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HgB	Hemoglobin
HHS	Health and Human Services
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
IMV	Interim Monitoring Visit
IND	Investigational New Drug
IP	Intraperitoneal
IR	Interventional Radiology
IRB	Institutional Review Board
IRBO	Institutional Review Board Office
IV	Intravenous
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
N	Number (typically refers to subjects)
NA	Not Applicable
NaCl	Sodium Chloride
NCT	National Clinical Trial (number)
NIH	National Institutes of Health
OHSRP	Office for Human Subjects Research Protections
OS	Overall Survival
PC	Peritoneal Carcinomatosis
PCI	Peritoneal Carcinomatosis Index
PD	Progressive Disease
PD	Pharmacodynamics
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PO	Orally
PPI	Proton Pump Inhibitor
PR	Partial Response
PT/INR	Prothrombin Time/International Normalized Ratio
PS	Performance Status
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
QTc	Corrected QT interval

QTcF	Fridericia's Correction Formula
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
RECIST	Response Evaluation Criteria in Solid Tumors
RCA	Research Collaborative Agreement
RNA-seq	RNA Sequencing
SAE	Serious Adverse Event/Serious Adverse Experience
SAV	Site Assessment Visit
SIV	Site Initiation Visit
SD	Stable Disease
SOP	Standard Operating Procedure
TPRG	Translational Pharmacodynamics Research Group Participant Sample Management
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WES	Whole Exome Sequencing

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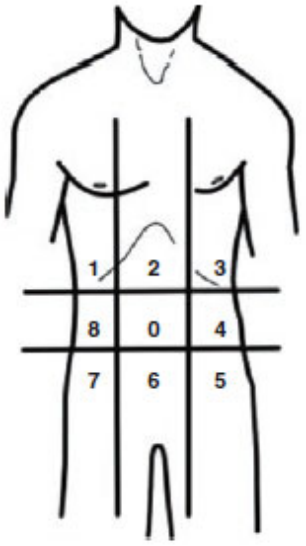
15 APPENDICES

15.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

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

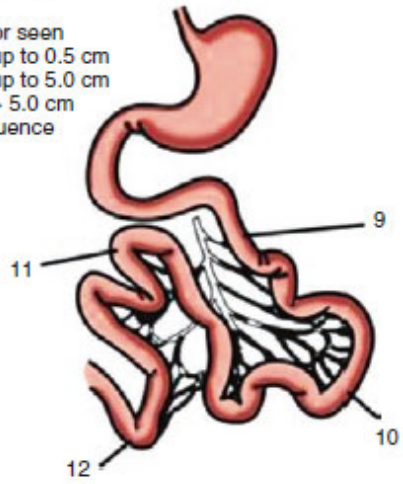
15.2 APPENDIX B: PERITONEAL CANCER INDEX (PCI)



Regions		Lesion Size
0	Central	
1	Right Upper	
2	Epigastrium	
3	Left Upper	
4	Left Flank	
5	Left Lower	
6	Pelvis	
7	Right Lower	
8	Right Flank	
9	Upper Jejunum	
10	Lower Jejunum	
11	Upper Ileum	
12	Lower Ileum	
PCI		

Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



15.3 APPENDIX C: PARTICIPANTS' MEDICATION DIARY

INSTRUCTIONS

1. Complete one form for each cycle of treatment.
2. Swallow nilotinib capsules whole with at least 8 ounces (1 measuring cup full) of water either 1 hour before or 2 hours after consuming food or beverages other than water. If you cannot swallow nilotinib capsules whole, you may open the capsules needed for a single dose and sprinkle the capsule contents in one teaspoonful of applesauce (puréed apple). Do not use more than one teaspoonful (TSP) of applesauce or sprinkle nilotinib on other foods. Swallow the mixture right away (within 15 minutes after sprinkling nilotinib on applesauce). Missed or skipped doses should not be taken later than 2 hours after the time you are scheduled to take them (no earlier than 10 hours and not later than 14 hours after a previously taken dose). Vomited doses should not be retaken. Record in the diary below if you vomited or missed taking capsules and inform the investigator or nurse that it happened. If a capsule is broken and the powder of the capsules gets on your skin, wash the exposed area with as much water as necessary. Inform the investigator or nurse if that occurs.
3. Record the date and time you took the drugs.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottle of drugs when you return for your appointment.
6. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.

Today's Date _____ Cycle #_____ Nilotinib Dose _____mg

Participant Study ID_____

Day	Date	Time of Dose		Number of Capsules		Comments
		AM	PM	AM	PM	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						

Day	Date	Time of Dose		Number of Capsules		Comments
		AM	PM	AM	PM	
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Participant's Signature: _____ Date: _____

15.4 APPENDIX D: FUNCTIONAL ASSESSMENT OF CANCER THERAPY-COLORECTAL (FACT-C)

See Study Instruments package

15.5 APPENDIX E: EUROQOL GROUP 5-DIMENSION, 5-LEVEL HEALTH SURVEY (EQ-5D-5L)

See Study Instruments package

15.6 APPENDIX F: QTC PROLONGING MEDICATIONS

The following table presents drugs that CredibleMeds has concluded either 1) have a risk of TdP, 2) prolong QT and therefore have a possible risk of TdP, or 3) have a risk of TdP under certain conditions such as overdose, drug-drug interactions or when administered to certain high-risk individuals (e.g., congenital long QT syndrome). Please note that this list is frequently updated. For the most current list of medications, please refer to http://crediblemeds.org/

Generic Name	Brand Name
Alfuzosin	Uroxatral®
Amantadine	Symmetrel® and others
Amiodarone	Cordarone® and others
Amisulpride	Solian® and others
Amitriptyline	Elavil® (Discontinued 6/13) and others
Amoxapine	Asendin® and others
Anagrelide	Agrylin® and others
Apomorphine	Apokyn® and others
Arsenic trioxide	Trisenox®
Atazanavir	Reyataz®
Azithromycin	Zithromax® and others
Bedaquiline	Sirturo®
Bortezomib	Velcade® and others
Bosutinib	Bosulif®
Chloral hydrate	Aquachloral® and others
Chloroquine	Aralen®
Chlorpromazine	Thorazine® and others
Ciprofloxacin	Cipro® and others
Citalopram	Celexa® and others
Clarithromycin	Biaxin® and others
Clomipramine	Anafranil®
Clozapine	Clozaril® and others
Cocaine	Cocaine
Crizotinib	Xalkori®
Dabrafenib	Tafinlar®
Dasatinib	Sprycel®
Desipramine	Pertofrane® and others
Dexmedetomidine	Precedex® and others
Dihydroartemisinin+piperaquine	Eurartesim®
Diphenhydramine	Benadryl® and others
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Dolasetron	Anzemet®
Doxepin	Sinequan® and others
Dronedarone	Multaq®
Droperidol	Inapsine® and others
Eribulin	Halaven®
Erythromycin	E.E.S.® and others
Escitalopram	Cipralex® and others
Famotidine	Pepcid® and others
Felbamate	Felbatol®
Fingolimod	Gilenya®
Flecainide	Tambocor® and others
Fluconazole	Diflucan® and others
Fluoxetine	Prozac® and others
Foscarnet	Foscavir®
Fosphenytoin	Cerebyx® and others
Furosemide (Frusemide)	Lasix® and others
Galantamine	Reminyl® and others
Gemifloxacin	Factive®
Granisetron	Kytril® and others
Halofantrine	Halfan®
Haloperidol	Haldol® (US & UK) and others
Hydrochlorothiazide	Apo-Hydro® and others
Ibutilide	Corvert®
Iloperidone	Fanapt® and others
Imipramine (melipramine)	Tofranil®
Indapamide	Lozol® and others
Isradipine	Dynacirc®
Itraconazole	Sporanox® and others
Ketoconazole	Nizoral® and others
Lapatinib	Tykerb® and others
Levofloxacin	Levaquin® and others
Lithium	Eskalith® and others
Methadone	Dolophine® and others
Mifepristone	Korlym® and others
Mirabegron	Myrbetriq®
Mirtazapine	Remeron
Moexipril/HCTZ	Uniretic® and others
Moxifloxacin	Avelox® and others
Nicardipine	Cardene®
Nilotinib	Tasigna®
Norfloxacin	Noroxin® and others
Nortriptyline	Pamelor® and others
Ofloxacin	Floxin®
Olanzapine	Zyprexa® and others
Ondansetron	Zofran® and others
Oxytocin	Pitocin® and others
Paliperidone	Invega® and others
Paroxetine	Paxil® and others
Pasireotide	Signifor®

15.7 APPENDIX G: POTENTIAL DRUG INTERACTIONS

Nilotinib is a substrate of CYP3A4; it also inhibits CYP2C8 moderately and induces CYP2C8 weakly. Inhibitors and substrates of these enzymes can increase nilotinib plasma concentrations while inducers of these enzymes can decrease nilotinib plasma concentrations. Please note that this list is frequently updated. For the most current list of medications, please consult the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table.

CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nafcillin	Pentobarbital	Primidone	Rifapentine
Carbamazepine	Nevirapine	Phenobarbital	Rifabutin	St. John's wort
Fosphenytoin	Oxcarbazepine	Phenytoin	Rifampin	

CYP3A4 Substrates

Albuterol	Docetaxel	Ketamine	Progesterone
Alfentanil	Doxepin	Ketoconazole	Quetiapine
Alprazolam	Doxorubicin	Lansoprazole	Quinidine
Amlodipine	Doxycycline	Letrozole	Rabeprazole
Amprenavir	Efavirenz	Levomethadyl acetate	Repaglinide
Aprepitant	Eletriptan	hydrochloride	Rifabutin
Aripiprazole	Enalapril	Levonorgestrel	Rifampin
Atazanavir	Eplerenone	Lidocaine	Ritonavir
Atorvastatin	Ergoloid mesylates	Losartan	Saquinavir
Benzphetamine	Ergonovine	Lovastatin	Sertraline
Bisoprolol	Ergotamine	Medroxyprogesterone	Sibutramine
Bortezomib	Erythromycin	Mefloquine	Sildenafil
Bosentan	Escitalopram	Mestranol	Simvastatin
Bromazepam	Estradiol	Methadone	Sirolimus
Bromocriptine	Estrogens, conj.,	Methylergonovine	Sufentanil
Buprenorphine	synthetic	Methysergide	Tacrolimus
Buspirone	Estrogens, conj., equine	Miconazole	Tamoxifen
Busulfan	Estrogens, conj.,	Midazolam	Tamsulosin
Carbamazepine	esterified	Miglustat	Telithromycin
Cerivastatin	Estrone	Mirtazapine	Teniposide
Chlordiazepoxide	Estropipate	Modafinil	Terbinafine
Chloroquine	Ethinyl estradiol	Montelukast	Tetracycline
Chlorpheniramine	Ethosuximide	Moricizine	Theophylline
Cisapride	Etoposide	Nateglinide	Tiagabine
Citalopram	Felbamate	Nefazodone	Ticlopidine
Clarithromycin	Felodipine	Nelfinavir	Tolterodine
Clobazam	Fentanyl	Nevirapine	Toremifene
Clonazepam	Flurazepam	Nicardipine	Trazodone
Clorazepate	Flutamide	Nifedipine	Triazolam
Cocaine	Fosamprenavir	Nimodipine	Trimethoprim
Colchicine	Fulvestrant	Nisoldipine	Trimipramine
Cyclophosphamide	Gefitinib	Nitrendipine	Troleandomycin
Cyclosporine	Halofantrine	Norethindrone	Vardenafil
Dantrolene	Haloperidol	Norgestrel	Venlafaxine
Dapsone	Ifosfamide	Ondansetron	Verapamil
Delavirdine	Imatinib	Paclitaxel	Vinblastine
Diazepam	Indinavir	Pergolide	Vincristine
Digitoxin	Irinotecan	Phencyclidine	Vinorelbine
Dihydroergotamine	Isosorbide dinitrate	Pimozide	Zolpidem
Diltiazem	Isosorbide mononitrate	Pioglitazone	Zonisamide
Disopyramide	Isradipine	Primaquine	Zopiclone
	Itraconazole		

CYP2C8/9 Inhibitors

Amiodarone	Felodipine	Modafinil	Sertraline
Amitriptyline	Fluconazole	Montelukast	Sildenafil
Amlodipine	Fluoxetine	Nateglinide	Simvastatin
Anastrozole	Fluphenazine	Nelfinavir	Sulconazole
Aprepitant	Flurbiprofen	Nicardipine	Sulfadiazine
Atazanavir	Fluvastatin	Nifedipine	Sulfamethoxazole
Azelastine	Fluvoxamine	Olanzapine	Sulfinpyrazone
Bortezomib	Gemfibrozil	Omeprazole	Sulfisoxazole
Candesartan	Ibuprofen	Ondansetron	Tamoxifen
Chloramphenicol	Imatinib	Orphenadrine	Teniposide
Cholecalciferol (Vitamin D_3)	Indinavir	Pantoprazole	Thioridazine
Cimetidine	Indomethacin	Paroxetine	Ticlopidine
Clopidogrel	Irbesartan	Pentamidine	Tioconazole
Clotrimazole	Isoniazid	Pioglitazone	Tolbutamide
Clozapine	Ketoconazole	Piroxicam	Tolcapone
Cyclosporine	Ketoprofen	Pravastatin	Tranylcypromine
Delavirdine	Lansoprazole	Progesterone	Tretinoin
Dexmedetomidine	Leflunomide	Propafenone	Triazolam
Diclofenac	Losartan	Propofol	Trimethoprim
Diltiazem	Lovastatin	Propoxyphene	Valdecoxib
Dimethyl sulfoxide	Mefenamic acid	Pyrimethamine	Valproic acid
Disulfiram	Meloxicam	Quinidine	Valsartan
Drospirenone	Methimazole	Quinine	Verapamil
Efavirenz	Methoxsalen	Ritonavir	Voriconazole
Entacapone	Metronidazole	Rosiglitazone	Warfarin
Eprosartan	Miconazole	Saquinavir	Zafirlukast
Etoposide	Midazolam	Selegiline	

CYP2C8/9 Inducers

Carbamazepine	Phenobarbital	Primidone	Rifapentine
Fosphenytoin	Phenytoin	Rifampin	Secobarbital

CYP2C8/9 Substrates

Alosetron	Losartan	Rifampin	Tolbutamide
Amiodarone	Mephenytoin	Rosiglitazone	Torsemide
Bosentan	Mestranol	Selegiline	Trimethoprim
Carvedilol	Montelukast	Sertraline	Voriconazole
Fluoxetine	Nateglinide	Sulfadiazine	Warfarin
Fosphenytoin	Paclitaxel	Sulfamethoxazole	Zafirlukast
Glimepiride	Phenytoin	Sulfinpyrazone	Zopiclone
Glipizide	Pioglitazone	Sulfisoxazole	
Ketamine	Propofol	Tamoxifen	

15.8 APPENDIX H: PK/PD SAMPLE COLLECTION WORKSHEETS

See Study Instruments package

15.9 APPENDIX I: STUDY CALENDAR

15.9.1 Calendar for Part A of Protocol Therapy

1 cycle = 3 weeks

Tests/Procedures	Screening	Baseline	Week -1	On Treatment (± 1 day)								Post-Treatment Follow-Up	
				Cycles 1 and 4			Cycles 2 and 5		Cycle 3 and 6			4-8 Weeks Post-Therapy (±2 weeks)	Every 3 Months (±2 weeks) for up to 3 Years Total
				D1 (± 3 days at start of cycle)	D2	D8	D1 (± 3 days at start of cycle)	D8	D1 (± 3 days at start of cycle)	D8	Wk3		
Informed Consent	X												
Confirmation of diagnosis	X												
Medical history and Physical exam (see Section 3.4.1)	X		X (i.e., C1D1)	Pre dosing (except C1)	X (C1 only)		Pre dosing		Pre dosing			X	X
Vital Signs	X		X	X		X	X	X	X	X		X	X
Pregnancy Test (serum or urine)	X		X								X		
CBC with differential	X		X	X		X	X	X	X	X		X	X
Serum Chemistries	X		X	X		X	X	X	X	X		X	X
PT/INR	X												
Urinalysis	X		X								X		
ECG	X		X	X			X		X			X	
Pre-Op Anesthesia Consult	X	X (only if ≥ 30 days from last)									X		
HIV Ab	X												
ECOG Performance Status	X										X	X	
QOL Surveys		X									X	X	
CT Scan CAP	X										X		X

Tests/Procedures	**Screening**	**Baseline**	**Week -1**	**On Treatment (± 1 day)**								**Post-Treatment Follow-Up**	
				Cycles 1 and 4			**Cycles 2 and 5**		**Cycle 3 and 6**			**4-8 Weeks Post-Therapy (±2 weeks)**	**Every 3 Months (±2 weeks) for up to 3 Years Total**
				D1 (± 3 days at start of cycle)	D2	D8	D1 (± 3 days at start of cycle)	D8	D1 (± 3 days at start of cycle)	D8	Wk3		
Laparoscopy	X		D0								X		
PCI Scoring	X		D0								X		
Nilotinib			Twice daily from 4 days prior to diagnostic laparoscopy #2 through end of treatment (hold AM dose of nilotinib on laparoscopy days)										
IP Catheter Placement			D0										
IP Paclitaxel				X			X		X				
IV Paclitaxel				C4 only	C1 only	X	X	X	X	X			
AE Assessment				C4	C1	X	X	X	X	X		X	
PK Samples (See Section **5.2.1** for timepoints)[1]		X		C1 only	C1 only								
Other Research Blood Samples[2]	X[3] (intra-op)		X (pre-lap)								X (pre-lap)		
Research Peritoneal Biopsies and Ascites/ Washing Samples[4]	X[5] (intra-op)		D0 (intra-op)								X (intra-op)		

[1] Required in 1st 10 participants. It will be determined if samples will be collected from additional participants; may be collected after interim analysis.
[2] Refer to Section **5** for more details.
[3] Collection as indicated in Section **5**. Note: Research blood will only be collected within 24 hours after laparoscopy #1 if the outcome of laparoscopy #1 indicates that the participant is eligible (i.e., laparoscopy #1 is the last screening procedure performed on the protocol to confirm eligibility and the outcome is known at the end of the procedure), see Section **2.2.2** Part 2; research blood collected at laparoscopy #1 will be saved (i.e., will not be used for research) until after the participant has enrolled on the study and is at or past Baseline (see Section **3.4.1**).
[4] Refer to Section **5** for more details.
[5] Biopsy will only be taken if participant is deemed eligible per laparoscopy #1. Note: The biopsy will only be performed during laparoscopy.

NOTE: Other tests/assessments should be completed as clinically indicated.

15.9.2 Supplementary Calendar for Part B of Protocol Therapy (Participants With Stable Disease But Unresectable After Cycle 6)

1 cycle=4 weeks. For assessments before the end of Cycle 6 and after end of treatment, refer to Section **15.9.1**.

Assessments	**Cycle 7 and Beyond (Part B study therapy will not exceed one year)**				
	Day 1 (± 3 days at start of cycle)	Day 7	Day 15	D28	Every 3 Months
IV Paclitaxel	X	X	X		
PO Nilotinib	Twice daily through end of treatment, except hold AM dose of nilotinib on laparoscopy days				
CT Scan CAP					X
Vital Signs	X	X	X		
CBC with differential	X	X	X		
Serum Chemistries	X	X	X		
AE Assessment	X	X	X		
Laparoscopy	At time of radiographic response to confirm downstaging or at completion of therapy				
Blood Samples for ctDNA and CTCs				X[6]	
Ascites Samples for CTCs				At time of restaging	

				laparoscopy if performed	
Tumor Tissue				At time of restaging laparoscopy if performed	

[6] Samples may be collected within 3 days of time indicated.