TITLE: Phase 1/2 Study of Gemcitabine/Taxotere/Xeloda (GTX) in combination with Cisplatin and Irinotecan in Subjects with Metastatic Pancreatic Cancer

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1. OBJECTIVES

1.1. Primary Objectives

Part 1: The primary objective of the phase I portion is to assess safety of the combination of gemcitabine, docetaxel, capecitabine, cisplatin, and irinotecan in patients with untreated metastatic pancreatic adenocarcinoma (PDA) and to determine the maximally tolerated dose (MTD) of the combination;

Part 2: The primary objective of the phase II portion is to assess the efficacy of the combination of gemcitabine, docetaxel, capecitabine, cisplatin, and irinotecan in patients with untreated metastatic PDA based on the overall survival (OS) rate at 9 months.

1.2. Secondary Objectives

To estimate the response rate (RR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) of the combination of gemcitabine, docetaxel, capecitabine, cisplatin, and irinotecan in patients with untreated metastatic PDA.

1.3 Exploratory Objectives

1.3.1 To assess changes in quality of life measures as assessed by the EORTC QLQ-C30 questionnaire.

1.3.2 To assess tumor burden dynamics using both standard protein biomarkers such as CA19-9 and CEA and exploratory biomarkers such as circulating tumor DNA.

1.3.3 To assess baseline characteristics of the patients enrolled and correlate these molecular and clinicopathologic criteria with treatment response and toxicity.

1.4 Study design

This is a two part, single-institution, open-label, dose-escalation, phase 1/2 study to evaluate the clinical activity of gemcitabine, taxotere, and xeloda (GTX) in combination with cisplatin and irinotecan in patients with metastatic pancreatic cancer.

Part 1 of the study is a traditional 3 + 3 dose escalation study designed to evaluate the maximally tolerated dose (MTD), dose limiting toxicities (DLTs), and safety of increasing doses of irinotecan in combination with GTX-C.

Part 2 is an expansion cohort study for the evaluation of efficacy once the MTD has been determined. The primary endpoint of Part 2 will be the OS rate at 9 months, which is defined as the proportion of subjects alive at 9 months. The treatment regimen would be considered of insufficient activity for further study in this population if OS rate at 9 months

is 57% or less, and the minimum required level of efficacy that would warrant further study with the proposed regimen is a 80% OS rate at 9 months. The study includes one interim analysis for futility using a two-stage design (**Section 12**).

2. BACKGROUND

2.1 Study Disease

In 2013, there was an estimated 45,220 new cases of pancreatic cancer diagnosed in the United States[1]. Generally, most new cases of pancreatic cancer are advanced with extensive tumor growth usually due to the lack of symptoms during the early stages of the disease. As a result, few patients are considered candidates for surgical resection. Patients with advanced pancreatic cancer are usually treated with chemotherapy in an effort to improve survival and alleviate symptoms. Median survival time ranges from 4 to 6 months in patients with metastatic disease. With treatment, survival has improved to 6 to 11 months[2,3]. Overall, the 5-year survival rate is about 6% for all stages combined and decreases to 2% for patients with metastatic pancreatic cancer[4]. Currently, there are a few standard therapy options for patients. Single agent gemcitabine was FDA approved based on a comparative study between gemcitabine and 5-FU. Gemcitabine produced significant improvement in disease-related symptoms and prolonged survival (1-year survival: 18% versus 2%, respectively)[5]. Subsequently, the oral tyrosine kinase inhibitor, erlotinib, was approved in combination with gemcitabine based on a slight increase in median survival over gemcitabine alone (6.24 months compared to 5.91 months)[6]. Other phase III studies testing combination regimens have been disappointing. More recently, a randomized phase III study performed in France comparing FOLFIRINOX (5-FU/irinotecan/oxaliplatin) to gemcitabine resulted in an improvement in survival of 6.8 months versus 11.1 months[2]. While this regimen is being used, there are still concerns about its potential toxicity in a North American population and is being reserved for the most fit patients. Nab-paclitaxel has now been approved in combination for gemcitabine with a median survival of 8.5 months compared to 6.7 months with gemcitabine alone[7]. Therapies for patients with metastatic pancreatic cancer are urgently needed.

2.2 Rationale

Combination chemotherapy is now extending the lives of those with metastatic PDA, however, overall survival (OS) remains less than 1 year[2,7]. In most cases, responses and prolonged survival are limited by the emergence of resistance mutations that render even triplet chemotherapy ineffective[2,8,9]. Increasing the number of agents in a therapeutic cocktail could, in theory, improve outcomes and create a scenario where the emergence of solitary resistance mutations would no longer result in loss of efficacy. This hypotheses is supported by mathematical modeling that evaluates the number of tumor cells at treatment onset and evolution of mutations to predict the response to single versus dual versus multi-agent therapy[9,10]. These models predict that patients with high tumor burden and monotherapy are unlikely to have a prolonged response. The converse is true as well. Patients with lower burden disease and multi-agent therapy are more likely to have durable responses.

The rationale for using multi-agent chemotherapy in the first line setting is to deliver combinations of drugs when the patients are most likely to tolerate therapy and to decrease the likelihood of developing resistant clones which are more likely to occur when drugs are given individually and/or sequentially. The choice of GTX as a backbone is based on our collective experience with this regimen and its promise in phase II studies. Furthermore, we have observed that despite multiple dose reductions, usually due to bone marrow toxicity and not clinical symptoms, many patients still have a prolonged response to therapy, suggesting that with multi-agent chemotherapy, maximal doses are not necessary to show a continued effect. The doses reported in the phase II study are xeloda 1500mg/m^2/day, gemcitabine 750mg/m^2 at a rate of 10mg/m^2/min, and taxotere 30mg/m^2. We have recently completed a study using a low dose regimen of gemcitabine, taxotere, xeloda and added cisplatin (GTX-C) (clinical trial information: NCT01459614). Gemcitabine was administered in a prolonged infusion schedule at 10 mg/m^2/min based upon the study published by Brand et al[11] and Tempero et al[12] which demonstrated improved phosphorylation and activation of gemcitabine by deoxycytidine kinase with prolonged infusion times. Dr. Fine's research has shown that the order of administration of the drugs is important to the efficacy of the combination. The xeloda was started a few days before the rest of the drugs were administered. Xeloda was started on day 1 and administered every 12 hours for the following reasons: 1. xeloda, on an every 12 h schedule, mimics the continuous infusion of 5-FU; 2. preferential conversion of 5-dFUR to 5-FU in tumor cells by thymidine phosphorylase (TP) which activates xeloda to 5-FU which is more highly expressed in tumor than normal cells of the same histology; 3.taxotere upregulates TP levels in some cancer cells, enhancing conversion of xeloda to 5-FU, and 4. ease of administration (3). Preclinical studies suggest synergy between gemcitabine (G), taxotere (T) and xeloda based on the ability to inhibit MEK-ERK phosphorylation, increase BAX and BAK phosphorylation, and to decrease BCL-2 in pancreatic cancer cell lines[3]. Cisplatin was chosen based on the following observations: (1) cisplatin is a DNA intercalating agent which works through a different mechanism than gemcitabine, taxotere, or xeloda; (2) pancreatic cancers with defects in BRCA/Fanconi DNA repair pathway are sensitive to cisplatin; (3) meta-analyses suggest that gemcitabine/platinum combinations improve survival in good performance status patients; (4) patients with a personal or family history of cancers may benefit from cisplatin-based therapy; (5) early neurotoxicity is not a major concern given cisplatin and taxotere are often combined at 2-3X the doses proposed in this protocol. We postulated that a four drug regimens, even at low doses, would further improve OS by simultaneously targeting potentially non-redundant oncogenic pathways. The treatment doses included capecitabine 500 mg bid on days 1-14, and the combination of gemcitabine 500 mg/m2 (10 mg/m2/min), docetaxel 20 mg/m2 and cisplatin 20 mg/m2 on days 4 and 11. The primary endpoint was progression-free survival (PFS) rate at 6 months (mos); the regimen would be considered active if the 6-month PFS rate was >75% and inactive if < 50%.

To build on our results, we propose to test a multi-agent regimen of 5 drugs administered at low doses (below the effective dose) to patients with metastatic PDA. The regimen proposed consists of GTX-C plus irinotecan. Irinotecan is chosen as it a drug known to have activity in PDA with 5fluorouracil and oxaliplatin in the combination known as FOLFIRINOX. We believe that an effective cocktail for the treatment of PDA, using sub-therapeutic multi-agent dosing has the potential to significantly extend the survival of these patients while preserving quality of life.

3. PATIENT SELECTION

3.1 Eligibility Criteria

1. Subjects must have histologically or cytologically confirmed untreated metastatic pancreatic adenocarcinoma. Subjects with islet cell neoplasms are excluded. Subjects with mixed histology will be excluded.

2. Subject has one or more tumors measurable by CT scan using RECIST 1.1 criteria. MRI is acceptable if a CT scan is contraindicated.

3. Male or non-pregnant and non-lactating female of age ≥18 years.

4. ECOG performance status ≤1. ECOG 0 indicates that the patient is fully active and able to carry on all pre-disease activities without restriction; and, ECOG 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature.

5. Subjects must have adequate organ and marrow function as defined below:

   - WBC ≥3,500/mcL
   - Absolute Neutrophil Count ≥1,500/mcL
   - Platelets ≥100 x 10^9/L
   - Hemoglobin 8 g/dL

- Total Bilirubin — within normal institutional limits
- Alkaline phosphatase — ≤ 5 X ULN
- AST(SGOT)/ALT(SGPT) — ≤ 2.5 x ULN (≤ 5 X ULN for subjects with documented liver metastases)
- Creatinine — within normal limits (creatinine clearance ≥60 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.)

6. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

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

3.2 Exclusion Criteria

1. Subjects who have had any prior chemotherapy within 5 years of enrollment

2. Subjects who have had radiotherapy for pancreatic cancer.

3. Age ≥ 76 years

4. Subjects who are receiving or have received any other investigational agents within 28 days prior to Day 1 of treatment in this study.

5. Subject has undergone major surgery, other than diagnostic surgery (i.e.--surgery done to obtain a biopsy for diagnosis or an aborted Whipple), within 28 days prior to Day 1 of treatment in this study.

6. Subject has known brain metastases.

7. History of hypersensitivity or allergic reactions attributed to compounds of similar chemical or biologic composition to gemcitabine, taxotere, xeloda, cisplatin, or irinotecan.

8. Uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

9. Subject has serious medical risk factors involving any of the major organ systems such that the Investigator considers it unsafe for the subject to receive an experimental research drug.

10. Subject has a known history of infection with HIV, hepatitis B, or hepatitis C.

11. Subject is pregnant or breast feeding.

12. Subject is unwilling or unable to comply with study procedures.

13. Subject with clinically significant wound.

3.3 Inclusion of Women and Minorities

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

4. TREATMENT PLAN

4.1 Agent Administration

Treatment will be administered on an outpatient basis. The description of the regimen is further described in Table 3. Reported adverse events and potential risks are described in Section 6 and in Appendices B-E. Appropriate dose modifications are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Table 2: Dose Levels

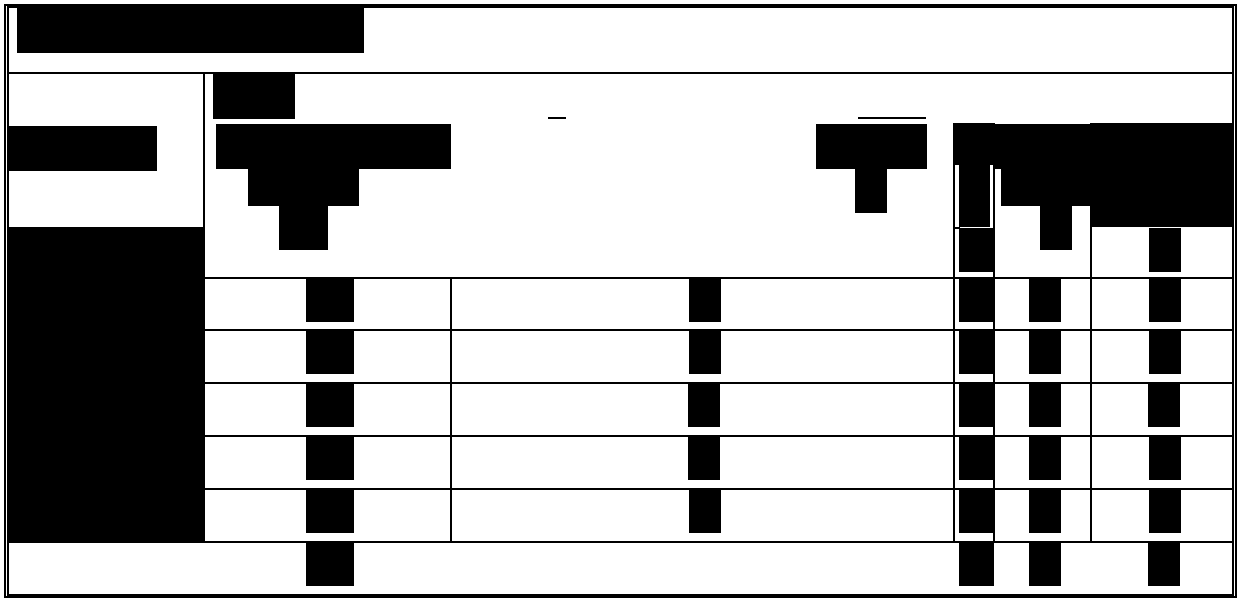

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Table 3: Regimen Description

Agent	Suggested pre and/or post medications	Route	Schedule	Cycle Length
Gemcitabine	5-HT3 antagonist IV + fosaprepitant IV, decadron 12mg IV, decadon 8mg orally bid on days 2-3, 5-HT3 antagonist on days 2-5.	IV at 10mg/m^2/min (40 minutes for 400mg/m^2 or 50 minutes for 500mg/m^2)*	Days 4 and 11	21 days
Taxotere	See gemcitabine	IV over 60 minutes*	Days 4 and 11	
Xeloda	5-HT3 antagonist oral or prochlorperazine oral prn	PO BID	Days 1 through 14	
Cisplatin	Normal saline 500cc IV pre and post	IV over 60 minutes*	Days 4 and 11	
Irinotecan	Atropine should be immediately available for anti-cholinergic reactions	IV over 60 minutes*	Days 4 and 11	

*Infusion times are approximate (+/- 15 minutes) and may need to be adjusted based on patient tolerability

The subject will be requested to maintain a medication diary of each dose of Xeloda. The medication diary will be returned to clinic staff at the end of each cycle.

4.1.1 Other Considerations

The order of administration of the IV chemotherapeutic agents is gemcitabine followed by taxotere followed by cisplatin followed by irinotecan. The hydration for cisplatin should occur pre and post infusion as standard of care for 30-60 minutes.

Xeloda tablets should be swallowed with water within 30 minutes after eating. Xeloda can have an effect on warfarin or coumadin and phenytoin metabolism.

4.2 Continuation of Therapy

Subjects will be evaluated during the treatment period to determine if continued treatment is appropriate. If, at any time during treatment the evaluation criteria are not met, GTX–CI

can be held or the dose adjusted. Suggested dose modification criteria are in **Section 5**. Patients with a hemoglobin of ≤ 8 can be treated and transfused.

To continue therapy, subjects must meet the following criteria (exceptions should be approved by the principal investigator):

• Absolute Neutrophil Count	Day 4 of cycle: ≥1000/mcL Day 11 of cycle: ≥900/mcL
• Platelets	Day 4 of cycle: ≥80 x 10^9/L Day 11 of cycle: ≥70 x 10^9/L
• Hemoglobin	> 8 g/dL
• Total Bilirubin	≤ 2 x ULN
• AST(SGOT)/ALT(SGPT)	□ 5 X ULN
• Creatinine	within normal institutional limits (creatinine clearance ≥60 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.)

4.3 Definition of a Dose Limiting Toxicity

The dose-limiting toxicity (DLT) for the combination in this study will be defined as one or more of the following possibly or probably related toxicities within the first cycle of treatment according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 4:

- Any Grade 3 or higher toxicity possibly or probably related to the study drug, with the exception of:
- Alopecia
- Grade 3 or 4 anemia, thrombocytopenia, or neutropenia that resolves to ≤grade 2 within 7 days. Subjects should have repeat labs within 7 days to document resolution.
- Grade 3 or 4 leucopenia/lymphopenia.
- Grade 3 or 4 nausea, vomiting, or diarrhea that resolves to ≤grade 2 within 72 hours.
- Grade 3 or 4 asymptomatic laboratory values that resolve to ≤ grade 2 within 7 days. Subjects should have repeat labs within 7 days to document resolution.

Management and dose modifications are outlined in **Section 5**.

Dose escalation will proceed within each dose level according to the following scheme. Dose-limiting toxicity (DLT) is defined above. However, the PI has the discretion to

expand at the current dose level or move to other dose levels to complete and expand that level if there are no safety concerns.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

4.4 General Concomitant Medication and Supportive Care Guidelines

The concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be documented. The Principal Investigator should be alerted if the subject is taking warfarin, coumadin, or phenytoin. These drugs are not contra-indicated but should be monitored closely while on Xeloda.

Subjects may not enroll in any other therapeutic clinical protocol or therapeutic investigational trial while enrolled in this study. Irradiation may be allowed during the study. Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed.

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Principal Investigator or Co-Investigators. Concurrent treatment with bisphosphonates is allowed. All concomitant treatments, including blood and blood products, must be reported on the case report form (CRF). Erythropoietin, G-CSF, or

Neulasta may be administered at the discretion of the Principal Investigator or CoInvestigators.

4.5 Duration of Therapy

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

- Disease progression: Subjects may be allowed to continue treatment if the Principal Investigator feels that the subject is receiving benefit (e.g. a mixed response). However, subjects who continue on study with progressive disease by RECIST should be taken off study after determination of disease progression on the next study scan.
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

Subjects will be followed for adverse events for a minimum of 28 days after the last dose of study drug or death, whichever occurs first. Survival status will be collected every 3 months (+/- 3 weeks). Subsequent therapies and responses may be collected. Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event or death. Subjects who are on treatment holidays will be followed only for progression and survival. Patients with disease stabilization for 2 years can receive treatment with their primary oncologist and only scans will be collected until progression or new therapy and all patients will be followed for survival. We will no longer collect labs, visits, Quality of life Questionnaires, or Adverse Events for these subjects.

4.7 Criteria for Removal from Study

Subjects will be removed from study when any of the criteria listed in **Section 4.5** applies. The reason for study removal and the date the subject was removed must be documented in the Case Report Form.

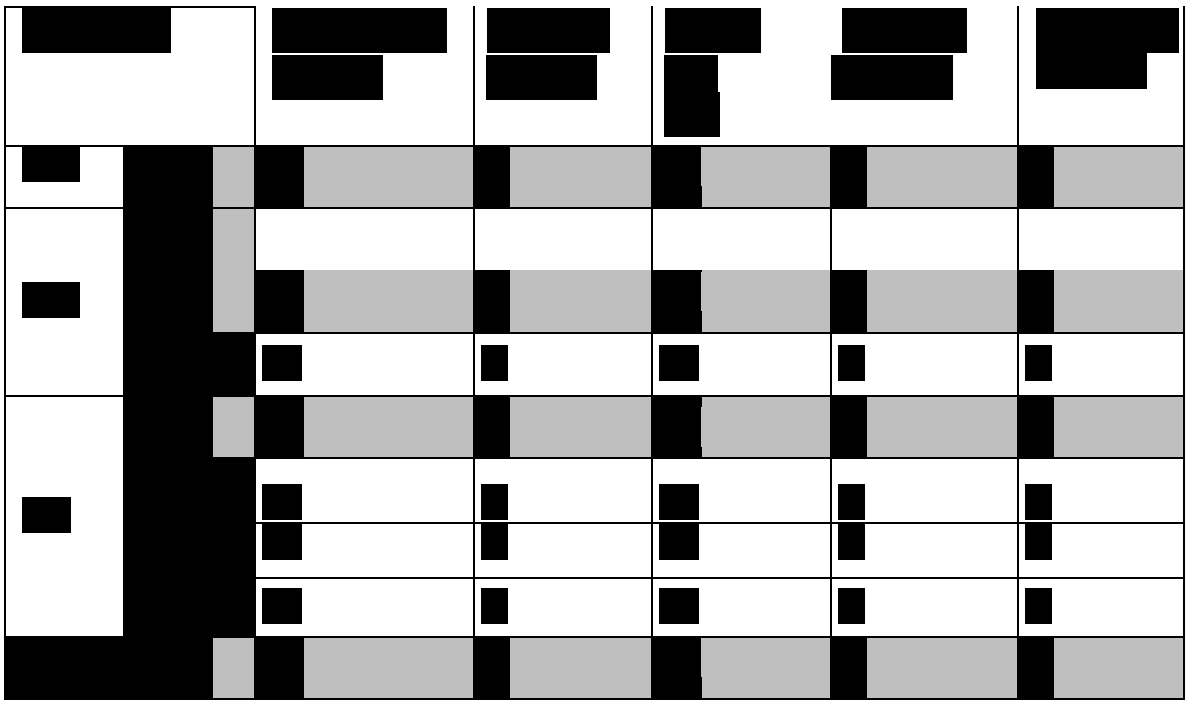
5. DOSING DELAYS/DOSE MODIFICATIONS

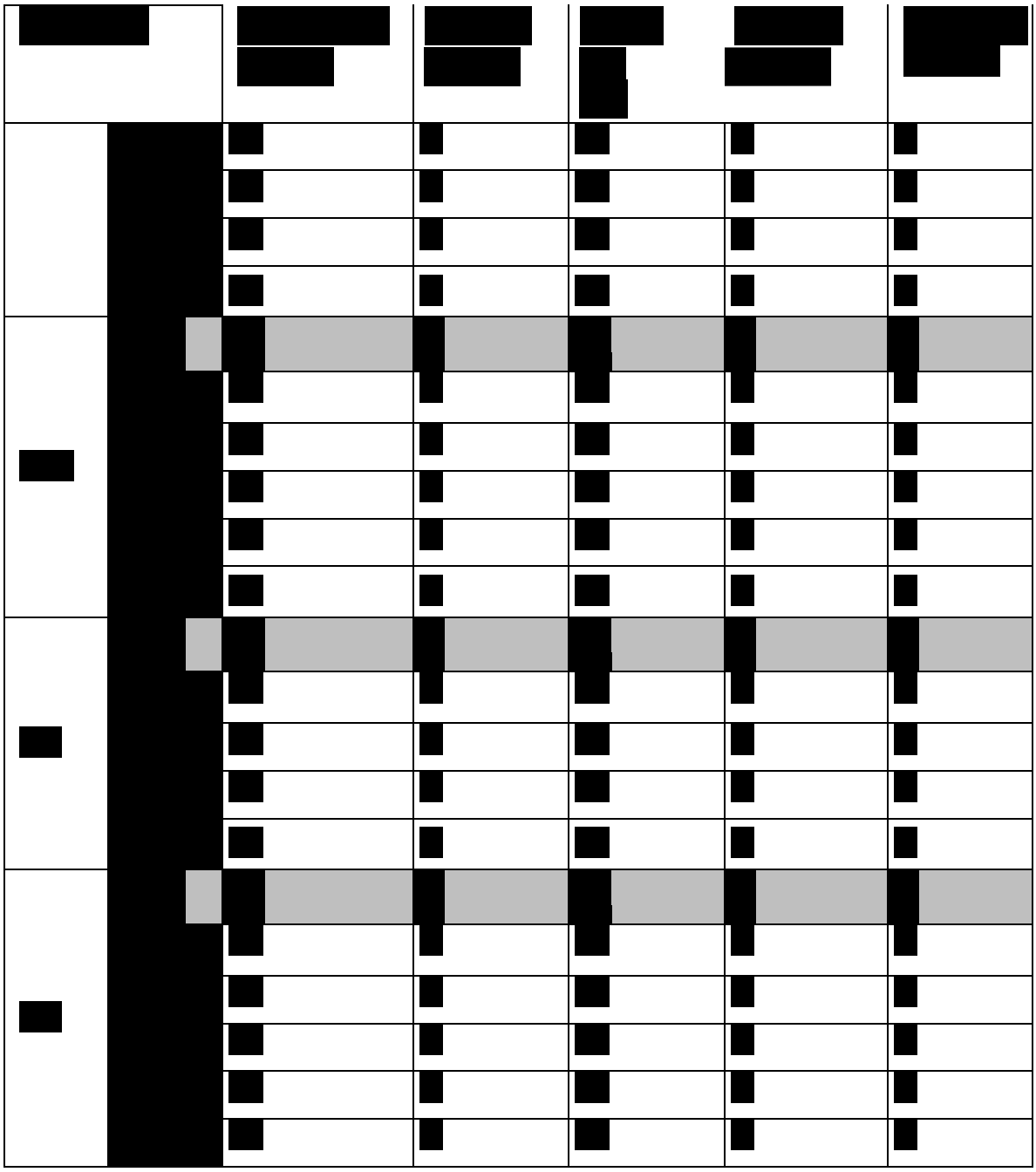
Allowance of chemotherapy breaks of greater than 2 weeks will be decided on a case-by-case basis by the principal investigator. When the delay is due to toxicity, then the next cycle may begin with a dose reduction.

If the delay is due to personal reasons, there will be no dose reductions. Any treatment delays beyond the protocol allowed window must be approved by the principal investigator.

Some discretion is left up to the investigators to account for patients who may be doing exceptionally well and request a longer break from therapy or may need a little extra time for clinical and laboratory status to recover. Dose reductions will be managed based on Table 3. Additional dose reductions (depending on starting dose) are up to the discretion of the principal investigator. Note that there are only 3 dose options for xeloda (500mg po bid, 300mg po bid and 150mg po bid) and given that palmar-plantar erythrodysesthesia syndrome is typically due to xeloda, investigators may choose to hold the xeloda and decrease within a cycle. In subsequent cycles, the xeloda will continue at the lower dose but the other agents do not need to be decreased to a lower dose level unless deemed necessary due to another adverse event. For example, if a subject on DL1 (Level 0) develops grade 2 palmar-plantar erythrodysesthesia syndrome during cycle 1, the xeloda can be held until ≤ grade 1 and restarted at a lower dose. The xeloda period, however, should not be more than the original 14 day period. The subject should receive the next cycle at DL1 (Level 0) except for the xeloda would remain at the lower dose unless deemed necessary to use DL-1 due to another adverse event. Xeloda dose reductions can be done independently of the dose reductions for the IV chemotherapy agents.

Table 4: Dose Reduction





Dose modifications are suggestions, but the final decision is left to the discretion of the Principal Investigator or Co-Investigator.

5.1 Suggested Dose Modifications for Other Non-Hematologic Toxicity

Dose modifications are suggestions, but the final decision is left to the discretion of the Principal Investigator or Co-Investigator.

Event Name	**Nausea**

Grade of Event	Management/Next Dose
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at one dose level lower, if indicated.
Recommended management: antiemetics.	

Event Name	Vomiting
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until < Grade 2. Resume at one dose level lower, if indicated.
Recommended management: antiemetics.	

Event Name	Diarrhea
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until < Grade 2. Resume at one dose level lower, if indicated.
Recommended management: Loperamide anti-diarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Event Name	Peripheral Neuropathy
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3-4	Hold until ≤ Grade 2. Resume at one dose level lower, if indicated.
Recommended management: consider medications for neuropathy.	

Event Name	Fatigue
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose

Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at one dose level lower, if indicated.

Event Name	**Palmar-plantar erythrodysesthesia syndrome**
Grade of Event	**Management/Next Dose**
≤ Grade 1	No change in dose
Grade 2	Hold xeloda until ≤ Grade 1. Resume at xeloda 300mg po bid. For 2nd occurrence, resume at 150mg po bid.
Grade 3	Hold xeloda until ≤ Grade 1. Resume at xeloda 300mg po bid. For 2nd occurrence, resume at 150mg po bid.
Recommended management: moisturizers to intact skin.	

5.2 Suggested Dose Modifications for Hematologic Toxicity

Event Name	**Neutropenia**
Laboratory Value	**Management/Next Dose**
Day 4 of cycle: <1000/mcL	Hold until ≥ 1000, no change in dose
Day 11 of cycle: <900/mcL	Hold until ≥900. Resume at one dose level lower, if indicated. Transient grade 3 neutropenia may occur during days 15-21 of a cycle.
The use of growth factors is permitted.	

Event Name	**Thrombocytopenia**
Laboratory Value	**Management/Next Dose**
Day 4 of cycle: <80 x 10^9/L	Hold until ≥ 80, no change in dose
Day 11 of cycle: <70 x 10^9/L	Hold until ≥70, no change in dose
Grade 3-4	Hold until ≥70. Resume at one dose level lower, if indicated.
A platelet goal of 50K should be considered for those on anticoagulation.	

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse

event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All adverse events experienced by subjects will be collected and reported from the first dose of the investigational combination (GTX-CI), throughout the study, and will only be followed for 30 days unless related to the investigational agent.

Subjects who have an ongoing adverse event related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

6.1 Definitions

6.1.1 Adverse Event (AE)

Adverse event is defined as any undesirable sign, symptom or medical condition occurring after starting the study drug (or therapy) even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). Medical conditions/diseases present before starting the study treatment are only considered adverse events if they worsen after starting the study treatment (any procedures specified in the protocol). Adverse events occurring before starting the study treatment but after signing the informed consent form will not be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

6.1.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Results in death
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions) $\geq$ 24 hours
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may

require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

Events **not** considered to be serious adverse events are hospitalizations for the:
- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

6.2 Relationship

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

6.3 Expectedness

Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

6.4 Reporting

6.4.1 Serious Adverse Event Reporting

Deaths, regardless of causality, within 30 days of study treatment and serious adverse events which are related and unexpected will be reported to following entity:

1. Johns Hopkins IRB

Adverse events that are serious, unexpected, and assessed by the investigator to be possibly, probably, or definitely related to the study drug will be reported to the postmarketing departments of the following manufacturers:

1. Eli Lilly and Company (Gemcitabine)
2. Sanofi-Aventis U.S. (Taxotere)
3. Genentech (Xeloda)
4. Bristol-Myers Squibb Company (Cisplatin)
5. Pfizer (Irinotecan)

Timelines for reporting SAE's:

1. Reporting of SAEs to the manufacturers should occur within 24 hours of becoming aware of the event occurrence.

2. SAEs must be reported to the Institution IRB per institutional guidelines.

Johns Hopkins Medicine IRB
Reed Hall B-130 1620
McElderry St.
Baltimore, MD 21205-1911
Phone: 410-955-3008

Follow up on SAE reports should also be sent to all the above agencies upon receipt of information per institutional guidelines.

6.4.2 **Routine Adverse Event Reporting**

If an ongoing AE changes in its intensity or in its perceived relationship to investigational product, a new AE entry for the event should be completed. Adverse events should be followed to resolution or stabilization, or reported as SAEs if they become serious. Followup is also required for AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with AEs at study completion should receive post-treatment follow-up as appropriate.

All identified non-serious AEs must be recorded and described on the appropriate nonserious AE page of the Case Report Form (CRF).

6.4.3 **Laboratory Test Abnormalities**

Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator.

In addition, the following laboratory abnormalities should also be captured on the nonserious AE CRF page or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have the investigational product discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

6.4.4 **Overdose**

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

6.4.5 **Pregnancy**

Sexually active women of child bearing potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

ALL WOCBP MUST HAVE A NEGATIVE SERUM PREGNANCY TEST 7 DAYS PRIOR TO RECEIVING INVESTIGATIONAL PRODUCT. All WOCBP should be instructed to contact the investigator immediately if they suspect they may be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of the investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner. Exceptions to the investigational product discontinuation may be considered for lifethreatening conditions only after consultation with the sponsor or as otherwise specified in this protocol. The investigator must immediately notify the sponsor of this event, record the pregnancy on the SAE form. Initial information on a pregnancy must be reported immediately to the sponsor and the outcome information provided once the outcome is known. Forward these forms to the sponsor according to SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-rays studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported. Infants should be followed for a minimum of 8 weeks.

6.4.6 **Other Safety Considerations**

Any significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by protocol, should also be recorded on the appropriate nonserious AE or SAE page of the CRF.

7. PHARMACEUTICAL INFORMATION

7.1 Gemcitabine (Gemzar)

Description, Formulation, and Storage

For complete details on preparation instructions, storage, clinical pharmacology, a comprehensive list of adverse events and the human pharmacokinetics of Gemcitabine, please see the Gemcitabine prescribing information (**Appendix C**).

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in *in-vivo* and *in vitro* tumors. Gemcitabine is approved for the treatment of patients with pancreatic cancer and will be obtained commercially. Gemcitabine is commercially supplied as a powder for reconstitution in 200 mg and 1 gm vials.

Intact vials containing sterile powder are stored at room temperature (20° to 25°C) (68° to 77°F). Gemcitabine solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F). Do not refrigerate as crystallization can occur. The diluted solution should be clear and colorless to light straw-colored solution

Preparation and Administration

Reconstitute the 200 mg vial with 5 mL 0.9% NaCl and the 1 g vial with 25 mL 0.9%NaCl. The resulting solution is approximately 38 mg/mL, but the concentration varies. It is suggested that when the desired dose is less than the entire vial, the entire volume be drawn up into a syringe in order to determine the actual concentration. Then the desired amount should be measured and diluted in 0.9%NaCl for infusion. Reconstituted solution should be further diluted in 100 ml NS for intravenous infusion.

In this study, Gemcitabine may be administered on an outpatient basis. Gemcitabine should be administered by intravenous infusion weekly over approximately 10mg/m^2/min which for 400mg/m^2 is 40 minutes or 500mg/m^2 is 50 minutes. Infusion times are approximate and may need to be adjusted based on patient tolerability.

Toxicities of Gemcitabine

Please see the Gemcitabine prescribing information (**Appendix C**) for more details on the known precautions, warnings, and adverse reactions of Gemcitabine. Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia, and myelosuppression is usually the dose-limiting toxicity. Subjects should be monitored for myelosuppression during therapy. Hemolytic-Uremic Syndrome (HUS) has been reported rarely with the use of Gemcitabine. Gemcitabine is a Pregnancy Category D drug. Gemcitabine can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemcitabine in pregnant women. If Gemcitabine is used during pregnancy, or if the subject becomes pregnant while taking Gemcitabine, the subject should be apprised of the potential hazard to the fetus.

7.2 Taxotere (Docetaxel)

Description, Formulation, and Storage

For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Taxotere please see the Taxotere prescribing information (**Appendix D**).

Taxotere is an antineoplastic agent of the taxoid family that acts by disrupting the microtubular network in cells essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells.

Taxotere Injection Concentrate is a clear yellow to brownish-yellow viscous solution. Taxotere is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (1 mL) or 80 mg (4 mL) Taxotere (anhydrous). Each mL contains 20 mg Taxotere (anhydrous) in 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol solution.

Taxotere should be stored, reconstituted and administered according to the manufacturer's recommendation.

Taxotere should be stored between 2 and 25°C (36-77°F) in a secure and dry place. Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

Preparation and Administration

Preparation and administration of Taxotere should be per the Taxotere prescribing information (**Appendix D**).

Taxotere may be administered on an outpatient basis. Taxotere should be administered by intravenous infusion weekly following the gemcitabine infusion.

The Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, nonaqueous, viscous solution with an accompanying sterile, nonpyrogenic, diluent (13% ethanol in Water for Injection) vial.

Taxotere infusion solution, if stored between 2 and 25°C (35.6 and 77°F) is stable for 4 hours. Fully prepared Taxotere infusion solution (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the administration).

Directions for the preparation of Taxotere can be found in the Taxotere prescribing information (**Appendix D**).

Taxotere is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Taxotere solutions. The use of gloves is recommended.

If Taxotere concentrate, initial diluted solution or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.

Toxicities of Taxotere

Please see the Taxotere prescription information (**Appendix C**) for more details on the known precautions, warnings, and adverse reactions of Taxotere. The most common adverse reactions across all Taxotere indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving Taxotere.

7.3 Xeloda (Capecitabine)

Description, Formulation, and Storage

For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Xeloda, please see the Xeloda prescribing information (**Appendix E**). Xeloda is a fluoropyrimidinecarbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. Normal cells, as well as tumor cells metabolize 5- Fluorouracil into 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). Both are metabolites that cause cell injury by two different mechanisms. FdUMP and the folate factor, N5-10methylenetetrahydrofolate, bind to thymidylate synthase (TS) to inhibit the formation of thymidylate. This deficiency of thymidylate causes cell cycle division to halt. This is because thymidalate is necessary for thymidine triphosphate production, which is essential for DNA synthesis. FUTP works by incorporating itself into transcription in place of uridine triphosphate therefore interfering with RNA transcription and protein synthesis.

Xeloda is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg xeloda and each peach-colored tablet contains 500 mg xeloda.

Xeloda will be provided as an outpatient prescription. Xeloda should be stored at 25□C (77□F); excursions permitted to 15° to 30°C (59° to 86°F). Keep tightly closed.

Dosing and Administration of Xeloda

Xeloda will be administered on an outpatient basis. Xeloda will be given by oral administration twice daily. Xeloda tablets should be taken within 30 minutes after the end of a meal and swallowed with water.

Toxicities of Xeloda

Please see the Xeloda prescribing information (**Appendix E**) for more details on the known precautions, warnings, and adverse reactions of Xeloda. The most common side effects of Capecitabine are diarrhea, nausea, vomiting, stomatitis, abdominal pain, upset stomach, constipation, loss of appetite, dehydration, hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, hair loss, tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle pain), trouble sleeping, and taste problems. Xeloda is a Pregnancy Category D drug. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Xeloda. If Xeloda is used during pregnancy, or if the subject becomes pregnant while taking Xeloda, the subject should be apprised of the potential hazard to the fetus.

7.4 Cisplatin

Description, Formulation, and Storage

For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Cisplatin, please see the Cisplatin prescribing information (**Appendix F**).

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. Cisplatin inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanisms include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

Cisplatin Injection is a sterile aqueous solution, available commercially in 50, 100 and 200 mL multiple dose vials, each mL containing 1 mg of cisplatin and 9 mg sodium chloride in water for injection. HCl and/or sodium hydroxide added to adjust pH to 3.5 to 4.5.

Intact vials should be stored at room temperature and be protected from light. Solutions diluted in 0.9% or 0.45% NaCl to a concentration of 0.05-2mg/mL are stable for up to 72 hours at room temperature and protected from light.

Preparation and Administration

Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature (25° C, 77° F). The reconstituted solution is stable for 20 hours at room temperature (25° C, 77° F). Solution removed from the amber vial should be protected from light if it is not to be used within six hours. Once reconstituted, the solution should be kept at room temperature (25° C, 77° F). If the reconstituted solution is refrigerated a precipitate will form.

Cisplatin may be administered on an outpatient basis. Cisplatin should be administered by intravenous infusion following the Taxotere infusion. Cisplatin should be administered in 250 mL NaCl, following intravenous hydration with at least 500 ml of normal saline. 500ml of normal saline may also be administered after cisplatin. Needles, syringes, catheters, or IV administration sets containing aluminum parts should not be used, as contact with cisplatin yields a black precipitate.

Toxicities of Cisplatin

Please see the Cisplatin prescribing information (**Appendix F**) for more details on the known precautions, warnings, and adverse reactions of Cisplatin. Common side effects include myelosuppression, nausea, vomiting, anorexia, elevation of BUN and creatinine, hyperuricemia, renal tubular damage, rare cardiac abnormalities, taste alteration, peripheral neuropathy, seizures, anaphylactoid and urticarial reactions (acute), rash, fatigue, otoxicity including hearing loss or tinnitus, and loss of muscle function. Cisplatin can cause fetal harm when administered to a pregnant woman. Cisplatin is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice, cisplatin is teratogenic and embryotoxic. If this drug is used during pregnancy or if the subject becomes pregnant while taking this drug, the subject should be apprised of the potential hazard to the fetus. Subjects should be advised to avoid becoming pregnant.

7.5 Irinotecan

Description, Formulation, and Storage

For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Irinotecan, please see the Cisplatin prescribing information (**Appendix G**).

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase IDNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan is a sterile, pale yellow, clear, aqueous solution. It is available in three single-dose sizes in brown glass vials: 2 mL-fill vials contain 40 mg irinotecan hydrochloride, 5 mL-fill vials contain 100 mg irinotecan hydrochloride, and 15 mL-fill vials contain 300 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial should remain in the carton until the time of use.

Preparation and Administration

Dilute irinotecan with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing irinotecan and admixtures of irinotecan may result in precipitation of the drug and should be avoided.

The irinotecan injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Irinotecan may be administered on an outpatient basis and should be administered by intravenous infusion following the Cisplatin infusion.

Toxicities of Irinotecan

Please see the Irinotecan prescribing information (**Appendix G**) for more details on the known precautions, warnings, and adverse reactions of Irinotecan. Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, alopecia. Common adverse reactions (≥30%) observed in single agent therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, alopecia.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Plasma Marker Studies

To assess tumor burden dynamics over the course of this study we will collect plasma at baseline, every 3 cycles thereafter, and at the off study evaluation. Whole blood will be collected in two 10 milliliter plasma preparation tubes with EDTA (PPT, BD Vacutainer, Franklin Lakes, NJ) at the designated time points and processed using standard laboratory procedures within one hour of collection. Using a pipette, plasma will be transferred to sterile 15 mL conical tube and stored at -80ºC.

Stored samples will be used to measure circulating tumor DNA[14].

8.2 Whole Blood Studies

To assess the baseline characteristic of the subjects enrolled and to correlate these molecular and clinicopathologic criteria with treatment response and toxicity, whole blood will be collected in a 10 milliliter plasma preparation tube with EDTA (PPT, BD Vacutainer, Franklin Lakes, NJ). Within two hours of collection, aliquots of 1 mL of whole blood will be transferred into 2 mL tubes and stored at -80ºC. This will be collected at baseline only.

DNA may be extracted from whole blood and used to evaluate for any germline mutations that may correlate with response or toxicity. These may include, but are not limited to FANC GENES, PALB2, BRCA1 and BRCA2. In addition, a SNP array may be performed on each case using the Affymetrix Genome-wide Human SNP Array 6.0 (Santa Clara, CA).

8.3 Tumor Tissue Studies

Tumor tissue specific somatic genetic changes and aberrations in protein expression may be explored in archived tumor tissue obtained prior to treatment on this protocol if blocks or slides are readily available.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans and x-rays must be done ≤ 14 days prior to the start of therapy. In the event that the subject's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. If a patient starts xeloda on days 1-3 and becomes ineligible for the intravenous chemotherapy, then this course would not be considered a cycle.

			Cycle (21 Days)						Off Study
	Pre-Study (baseline)	**Days 1-3**	**Day 4**	**Days 5-6**	**Days 7-10**	**Day 11**	**Days 12-14**	**Days 15-21**	
Visit Windows (days)[1]	-28 to 0	+/- 3	-3 to +14			+/- 3			+/- 28
Gemcitabine			A			A			
Taxotere			B			B			
Xeloda		C	→	→	→	→	→		
Cisplatin			D			D			
Irinotecan			E			E			
Informed consent	X								
Demographics (ethnicity and religion)[2]	X								
Medical history	X								
Family history of cancer	X								
Concurrent meds	X		X			X			X
Physical exam	X		X						X
Vital signs[3]	X		X			X			X
Height[4]	X								
Weight	X		X			X			X
Performance status	X		X						X
Quality of life survey	X		X						X
CBC w/diff, plts[5]	X		X[7]			X[7]			X
Serum chemistry[5,6]	X		X[7]			X[7]			X

CA19-9/CEA	X		X[7]						X
			Cycle (21 Days)						**Off Study**
	Pre-Study (baseline)	**Days 1-3**	**Day 4**	**Days 5-6**	**Days 7-10**	**Day 11**	**Days 12-14**	**Days 15-21**	
AE evaluation			X			X			X
Radiologic evaluation/ RECIST[8]	X		X						X
B-HCG[9]	X								
Plasma Sample[10]	X		X						X
Whole Blood Sample[11]	X								
Archived Tumor Sample[12]	X								

A: Gemcitabine: Dose as assigned; administration schedule B:
Taxotere: Dose as assigned; administration schedule
C: Xeloda: Dose as assigned; administration schedule
D: Cisplatin: Dose as assigned; administration schedule
E: Irinotecan: Dose as assigned; administration schedule

1: Longer delays to be approved by the Principal Investigator.
2: Specifically, Ashkenazi Jewish decent
3: Temperature, blood pressure, respiration rate, heart rate.
4: Height collected prior to study entry may be used.
5: Repeat labs within 7 days to follow and document the resolution of a limiting toxicity (**Section 4.3**)
6: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium.
7: Three day window
8: CT scan (chest/abdomen/pelvis) or MRI (if patient has contrast allergy); to be assessed at baseline (baseline scan must be within 14 days of the first dose) and every three cycles. CT scans may be done within 3 weeks prior to or after on study scheduled visit. If a scan is performed early for clinical reasons, the investigator can re-start the 3 cycle count as to not overuse imaging.
9: Urine pregnancy test (women of childbearing potential).
10: Plasma collection (approximately 20 cc) will occur at baseline, every 3 cycles thereafter, and at the off study evaluation.
11: Whole blood collection (approximately 10 cc) will occur at baseline only.

12: Attempts to obtain archival tumor samples will be made for every patient until the sample is obtained or documentation that the sample cannot be obtained.

10. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be reevaluated every 3 cycles.

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[15]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1.1 Definitions

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

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

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

10.1.2 Disease Parameters

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

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

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm 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.

[redacted]

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 nonmeasurable) since they are, by definition, simple cysts.

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are

not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.1.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and □10 mm 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.

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 breathhold scanning techniques, if possible.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate

cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

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

10.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

10.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks.

CR	Not evaluated	No	PR	Confirmation**
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

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

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

10.1.5 Duration of Response

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

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

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

10.1.6 Progression-Free Survival (PFS)

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

10.1.7 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death.

11. DATA REPORTING / REGULATORY REQUIREMENTS

11.1 Data Management

All information will be collected on study-specific case report forms (CRFs) by study staff. These data will be reviewed for completeness and accuracy by the Principal Investigator.

11.2 Safety Meetings

Scheduled meetings will take place weekly and will include the protocol principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3 Monitoring

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

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/6/2012). The Clinical Research Office QA Group will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee.

The PI is responsible for monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints, and confirm that the safety outcomes favor continuation of the study.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

The phase I portion will evaluate up to 3 dose levels of the regimen to determine the MTD. The dose escalation will commence in a standard 3+3 design. The MTD will be defined as the dose level in which < 2 of 6 patients experiences a dose limiting toxicity (DLT) with the next higher dose having at least 2 of 3 or 2 of up to 6 patients experiencing a DLT. A total of 6 – 30 patients will be enrolled, and the actual number will vary depending on the number of DLTs.

The phase II portion will evaluate the efficacy of the regimen. The PI has discretion on selection of the dose level for expansion based on considerations of general tolerability and efficacy if the dose level is deemed safe. The primary endpoint will be the OS rate at 9 months, which is defined as the proportion of subjects alive at 9 months. The treatment regimen would be considered of insufficient activity for further study in these population if OS rate at 9 months is 57% or less, and the minimum required level of efficacy that would warrant further study with the proposed regimen is a 80% OS rate at 9 months.

Six to 30 subjects will be enrolled in the dose escalation phase. Up to an additional 24 subjects will be enrolled at the recommended dose from phase I. The 6 subjects treated at that dose during the dose escalation phase will be counted toward the total sample size of 30 subjects. Subjects will be replaced if they do not receive any study treatment. Subjects will be considered efficacy evaluable if they received any study treatment. Subjects whose death is unequivocally accidental and unrelated to cancer or its treatment may also be replaced. A two-stage design based on Green and Dahlberg method will be used to enable early stopping for futility if sufficient clinical activity is not demonstrated. Enrollment will continue while we wait for the interim data to mature. The decision rule of the design is the following:

1. A total of 15 patients will be entered in the first stage.

- If 8 or fewer subjects are alive 9 months after the initiation of the treatment (i.e. 7 or more die in 9 months), the treatment regimen will be terminated and we will conclude the regimen is ineffective.
- If ≥9 subjects are alive, then

2. An additional 15 patients will be enrolled.
   - If a total of 21 or fewer subjects survive past 9 months in stage one and two combined (i.e. 9 or more deaths in 9 months), we consider this regimen ineffective.
   - If a total of 22 or more is alive, we conclude the regimen is promising and warrant further study. The maximum sample size of the phase II portion will be 30.

The study could be terminated also as soon as we observe 22 patients to be alive at 9 months to indicate sufficient efficacy.

This design provides 90% power to detect an absolute increase of 23% points in 9-months OS rate with a type I error of 0.1. The probability of early termination is 49% if the null hypothesis of 57% survival rate is true.

Safety monitoring

The study will be continuously monitored for adverse events after the dose escalation phase. If the limiting toxicity events appear to be higher than 33%, we will temporarily halt the study pending dose modification. Specifically, we will apply a Bayesian toxicity monitoring rule that suspends the enrollment if the posterior probability of risk being larger than 0.33 is 70% or higher. The monitoring rule uses beta (1.5, 5.5) as prior distribution. This means that our prior guess at the proportion of toxicity is 21%, and there is 90% probability that this proportion is between 3% and 49%. Starting from the 7th patient in the phase II portion, the decision rule for safety stopping is as follows:

Stop if:

# of patients with AE	3	4	5	6	7	8	9	10	11
Out of	3	4	7	10	13	15	18	21	24
		5	8	11	14	16	19	22	
		6	9	12		17	20	23	

For example, starting with the 7th patients, if three out of the next 3 patients have limiting toxicity events, we will stop the accrual. If four or more out of the first 4-6 patients have limiting toxicity events, we will stop.

The operating characteristics of the stopping rule are shown below and are based on 5000 simulations:

True AE rate	% simulated trials declaring unsafe	Average sample size (out of 24)
0.2	4.6	23.3
0.25	12.4	22.3
0.3	22.3	20.9
0.35	40.0	18.8
0.4	56.8	16.6
0.45	75.1	13.9

Data analysis

The primary objective is to evaluate the efficacy of the combination drugs of GTX with cisplatin and irinotecan in metastatic pancreatic cancer patients. OS rate at 9 months is used as a primary outcome of efficacy. It is estimated as the proportion of patients alive at 9 months after the initiation of the treatment with corresponding 95% confidence interval (CI).

The secondary outcomes include toxicity, RR, PFS, and OS. We will characterize toxicity as percentage by grade. DCR is defined as percentage of patients who achieved complete response (CR), partial response (PR), or stable disease (SD) among all evaluable patients. 95% CIs will be computed. PFS is defined as the time from the date of initial dose to the date of disease progression or to death due to any cause, whichever occurs first. PFS will be censored on the date of the last evaluable tumor assessment documenting absence of progressive disease for patients who are alive and progression free. OS is defined as the time from the date of initial dose to death due to any cause. For patients who still alive at the time of analysis, the OS time will be censored on the last date the patients are known to be alive. PFS and OS will be summarized by the Kaplan-Meier method.

As exploratory analysis, the correlations between baseline characteristics of subjects and treatment response and toxicity will be examined using two-sample t-tests or fisher exact test depending on the variable type. To evaluate the correlations between tumor tissue specific somatic mutations and treatment response and toxicity, fisher exact test will be performed. In addition, regression analysis will be used to include other covariates. P-value less than 0.05 will be considered as statistically significant. We will not adjust for multiplicity in the hypothesis testing for these exploratory analyses.

Quality of Life will be assessed via EORTC QLQ-C30 (v3.0) questionnaires. For our study population of pancreatic cancer patients, the analysis will be focused on Global Health Status/QoL scale, symptom scale (fatigue, pain), and functional scale (physical functioning, role functioning, emotional functioning). For each module, summary statistics of the scores will be reported at baseline and each follow-up time. Changes in quality of life scores pre- and post- treatment will be computed, and their significance will be evaluated by paired-sample t-tests. In addition, mixture effect models will be fitted for accessing the quality of life changes over time. Frequency of patients who reach minimal

clinically important difference of 10-points change from baseline will be tabulated by time. Time to definitive deterioration in quality of life will be analyzed using Kaplan-Meier method. Other modules will be examined as an exploratory manner.

Although a comparison of quality of life data to completed combination chemotherapy research outcomes may not be statistically appropriate, the data will offer exploratory information to establish the tolerability of this new treatment regimen, and its effect on quality of life.

12.2 Reporting and Exclusions

12.2.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with GTX-CI.

12.2.2 Evaluation of response – All patients who start treatment must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause unless accidental, or 8) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-8 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible and treated patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all selfcare, 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 selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: SAE Reporting Form

Serious Adverse Event Reporting Form

[redacted]

Section A: Subject Information

Section B: Event Information

Relationship to:	**Gemcitabine**	**Taxotere**	**Xeloda**	**Cisplatin**	**Irinotecan**	**Underlying Disease**
Unrelated						
Probably Unrelated						
Possible Related						
Probably Related						
Definitely Related						

Section C: Brief Description of the Event:

Section D: Relevant Medical History

Section E: Concomitant Drug (Not related to SAE)

Name of the Drug	**Start Date**	**Stop Date**	**Route**	**Dose**	**Frequency**

Section F: Comments
Additional Documents: ☐ Please specify

APPENDIX C: Gemcitabine Prescribing Information

APPENDIX D: Taxotere Prescribing Information

APPENDIX E: Xeloda Prescribing Information

APPENDIX F: Cisplatin Prescribing Information

APPENDIX G: Irinotecan Prescribing Information

APPENDIX H: EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much

17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent