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Protocol Level
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CAN-203

A Phase II Pilot Study of Disulfiram and Copper Gluconate in Patients with Metastatic Pancreatic Cancer and Rising CA-19-9 Levels While Receiving Abraxane-Gemcitabine or FOLFIRINOX or Single-Agent Gemcitabine

IND #: 139916
Version: 4.0
Version Date: 19 APR 2019

SPONSOR

Cantex Pharmaceuticals, Inc.
1792 Bell Tower Lane
Weston, FL 33326

SIGNATURES

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Stephen Marcus, M.D. Date
Chief Executive Officer
Cantex Pharmaceuticals, Inc.

Investigator's Agreement

I have read the CAN-203 protocol for which Cantex Pharmaceuticals, Inc. is the sponsor (the "Sponsor"). I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I confirm that I will conduct the study in accordance with FDA regulations, ICH GCP Guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, associated study documents, FDA regulations, ICH GCP Guidelines, and applicable local regulations to enable them to work in accordance with the provisions of these documents.

_____ _____

Investigator Signature Date

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Printed Name of Investigator

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Version	Date	Description of Change	Brief Rationale
2.0	6/26/2018	1. Include patients with Serum creatinine < 1.5 x ULN or estimated creatinine clearance of > 60 mL/min (as per Cockroft-Gault Formula). 2. Exclude patients with QTc of > 480 msec in the FOLFIRINOX arm of the study as oxaliplatin may cause QT prolongation leading to ventricular arrhythmias including fatal Torsade de Pointes. Drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics should be avoided during the FOLFIRINOX arm of the study 3. Include ECG monitoring at screening, pre-dose, around steady state C_{max} of oxaliplatin and as clinically indicated during the FOLFIRINOX arm of the study. 4. Monitor prothrombin time and adjust the dosage of oral anticoagulants (e.g., warfarin) if necessary as DSF may prolong prothrombin time during all arms of the study. 5. Monitor serum concentrations of phenytoin at baseline and after the initiation of DSF therapy since the concomitant administration of these two drugs can lead to phenytoin intoxication. Consider dosage adjustment with increased phenytoin levels. 6. Monitor patients taking isoniazid for the appearance of unsteady gait or marked changes in mental status, discontinue the DSF therapy if such signs appear. 7. Avoid the concomitant use of alcohol-containing products (e.g., cough and cold syrups,) and metronidazole as it has been recommended in Cantex's Investigator's Brochure. 8. Avoid the concomitant use of strong CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 inhibitors (e.g., atazanavir, gemfibrozil, indinavir) during the study and at study entry of the FOLFIRINOX arm as irinotecan and its	Changes requested by FDA

		active metabolite, SN-38, are metabolized by CYP3A4 and UGT1A1, respectively. 9. Avoid the concomitant use of strong CYP3A4 inducers (e.g., phenytoin, phenobarbital, carbamazepine, or St. John's wort) during the study and at study entry of the FOLFIRINOX arm as irinotecan is metabolized by this enzyme. 10. Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. When administered during the FOLFIRINOX arm of the study, consider a reduction in the starting dose by at least one level of CAMPTOSAR for patients known to be homozygous for the UGT1A1*28 allele. A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes. 11. Avoid the concomitant use potentially nephrotoxic drugs as oxaliplatin is primarily eliminated through the kidney during the study and at study entry of the FOLFIRINOX arm.	
3.0	8/6/2018	Primary Objective – clarify % change in CA 19-9 level Inclusion Criteria – clarify % change in CA 19-9 level Primary Endpoint – clarify % change in CA 19-9 level Schedule of Events: Physical Exam, BSA only Day 1 of each cycle; For cycle 2 and beyond, weight to be collected on Day 1 only Laboratories: change AST/ALT to AST or ALT; Uric acid and Chloride have been removed Deleted Exploratory Objectives and EndPoints.	Clarifications to also accommodate for clinical practice in foreign country sites.
4.0	3/28/19	1. Remove activities related to DSMC 2. Remove activities related to optional pharmacokinetics testing 3. Removed activities related to stem cell study 4. Excluded phenytoin as a concomitant medication 5. Deleted exploratory objective endpoints and analyses 6. Patient safety will be monitored throughout the study starting at the time of consent and safety	1. DSMC was deemed not necessary for this study. 2. PK testing will not be performed in this study.

		concerns documented in source documents. Adverse events will captured in case report forms starting with the first dose of DSF. Serious AEs will be captured in case report forms starting with the time of consent. 7. Various administrative corrections and clarifications	3. Stem cell studies will not be performed. 4. Disulfiram can alter phenytoin levels. 5. Exploratory objectives were optional and will not be performed. 6. Non-serious AE collection can start with first dose of IP as the screening procedures are minimal and part of standard of care.

Glossary of Abbreviations

ALDH	Aldehyde dehydrogenase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CR	Complete Response
Cu	Copper
DDTC	Diethyldithiocarbamate
DSF	Disulfiram
FDA	Food and Drug Administration
Me-DDTC	Methyl ester of diethyldithiocarbamate
MGMT	O^6-methylguanine-DNA-methyltransferase
MRI	Magnetic resonance imaging
OBG	O^6-benzylguanine
ORR	Objective response rate
OS	Overall survival
PCSCs	Pancreatic cancer stem cells
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PFS6	Progression-free survival at six months
PR	Partial response
ULN	Upper limit of normal
UGT1A1	Uridine 5'-diphospho-glucuronosyltransferase 1A1
WHO	World Health Organization

1.0 BACKGROUND AND RATIONALE

1.1 Pancreatic Cancer

Pancreatic ductal adenocarcinoma is a major cause of cancer-related deaths and is projected to become the second leading cause of cancer-related deaths in the US by 2030. Its prognosis remains extremely poor, with a 5-year survival rate of just 8%. Although surgery is potentially curative for some patients with localized pancreatic cancer, only 10–15% of patients with pancreatic cancer are eligible for potentially curative surgery at the time of diagnosis. Over half of patients have metastatic disease at the time of diagnosis, approximately 30% have locally advanced resectable or borderline unresectable disease, and most patients who receive potentially curative surgery ultimately relapse with metastatic disease. The treatment available for patients with metastatic pancreatic cancer patients consists of systemic chemotherapy which seeks to prolong survival, relieve symptoms such as abdominal pain and gastrointestinal discomfort, and maintain or improve quality of life.

1.2 Initial Chemotherapy with FOLFIRINOX

For over 30 years, 5-Fluorouracil (5-FU) was the most common chemotherapy agent used to treat metastatic pancreatic cancer, although its efficacy was only marginal. In 1997 single-agent Gemcitabine was approved by the FDA as a palliative treatment based upon a study indicating a "clinical benefit response" compared, in a randomized study, with 5-FU and also indicating an increased median survival from 4.4 to 5.7 months. Gemcitabine, in this study, was well generally tolerated, with few severe side effects. In the fifteen years, from 1997 until 2012, after Gemcitabine approval, a large number of doublet or triplet chemotherapy regimens including Gemcitabine were evaluated in randomized clinical trials, with none showing a significant benefit as regards overall survival or quality of life.

In 2011, Conroy and colleagues reported in the New England Journal of Medicine the results of a clinical trial comparing the efficacy of "FOLFIRINOX" (a combination of 5-FU, leucovorin, irinotecan and oxaliplatin) versus Gemcitabine for metastatic pancreatic cancer. The median overall survival in patient receiving FOLFIRINOX was 11.1 months as compared with 6.8 months in patients receiving Gemcitabine. Median progression-free survival was 6.4 months in the FOLFIRINOX patients and 3.3 months in the Gemcitabine patients. The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the Gemcitabine group. The safety profile of FOLFIRINOX was inferior to that of Gemcitabine. FOLFIRINOX was associated with a higher incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, as well as grade 2 alopecia. Despite this, at 6 months, 31% of the patients in the FOLFIRINOX group had significantly diminished quality of life as compared to 66% in the Gemcitabine group.

The FOLFIRINOX regimen has since emerged as a front-line treatment option for some patients with metastatic pancreatic cancer with a good performance status who are able to tolerate an intensive approach. Although FOLFIRINOX can result in cancer remissions or stability, recurrence of disease is almost universal, underlining the need for effective regimens to maintain remission.

1.3 Abraxane + Gemcitabine

In 2013, Von Hoff and colleagues reported the results of an 861 patient randomized phase 3 study comparing the efficacy and safety of the combination of Gemcitabine plus Abraxane versus Gemcitabine monotherapy in patients with metastatic pancreatic cancer. The median overall survival was 8.5 months in the Abraxane-Gemcitabine group as compared with 6.7 months in the Gemcitabine group. The median progression-free survival was 5.5 months in the Abraxane-Gemcitabine group, as compared with 3.7 months in the Gemcitabine group. The survival rate was 35% in the Abraxane-Gemcitabine group versus 22% in the Gemcitabine group at 1 year, and 9% versus 4% at 2 years. The response rate was 23% versus 7% in the two groups. The most common adverse events of grade 3 or higher were neutropenia (38% in the Abraxane-Gemcitabine group vs. 27% in the Gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). Febrile neutropenia occurred in 3% versus 1% of the patients in the two groups.

Although Abraxane-Gemcitabine can result in cancer remissions or stability, recurrence of disease is almost universal, underlining the need for effective regimens to maintain remission.

1.4 FOLFIRINOX vs. Abraxane-Gemcitabine as Initial Therapy

A direct comparison of the efficacy of FOLFIRINOX relative to the efficacy of Abraxane-Gemcitabine, is challenging as a consequence of difference in the entry criteria and enrollment patterns of the studies demonstrating the efficacy of these regimens. The pivotal FOLFIRINOX and Abraxane-Gemcitabine metastatic pancreatic cancer trials were both randomized controlled trials that included 342 and 861 patients respectively. Although the median age of the patients in both trials was comparable, the FOLFIRINOX trial included only patients less than 76 years old with an ECOG performance status of 0 or 1, while the Abraxane-Gemcitabine did not have an upper age limit and included patients with lesser performance status, based on the Karnofsky Performance scale of less than 90, in over 40% of patients. Whereas the FOLFIRINOX study only included patients in France, the Abraxane-Gemcitabine study was a multinational study including centers from the USA, Canada, Italy, Russia, Ukraine, Australia, France, Spain, and Belgium. Although the median survival of the patients enrolled in the Abraxane-Gemcitabine study was 8.7 months, an analysis of the 63 patients enrolled in Canada indicated a median survival of patients treated with Abraxane-Gemcitabine of 11.9 months, comparable to the reported survival in the FOLFIRINOX trial. A forest plot of the hazard ratio for death clearly showed an effect of age and country on the hazard ratio. Based upon the existing data, both FOLFIRINOX and Abraxane-Gemcitabine are considered to be appropriate front-line choices for chemotherapy of metastatic pancreatic

cancer, with selection of treatment often based on patients' performance status, physician preference, institutional and national standards, and relative costs of the treatment regimens.

Although both FOLFIRINOX and Abraxane-Gemcitabine can result in cancer remissions or stability, recurrence of disease is almost universal, underlining the need for effective regimens to maintain remission.

1.5 The Significance of a Rising CA19-9

CA 19-9 is an antigen that is commonly expressed in pancreatic cancer and is the most common and important tumor marker used to assess treatment effect in patients with pancreatic cancer. In patients receiving chemotherapy for metastatic disease, CA 19-9 levels are of prognostic significance with regard to overall survival. Rising CA 19-9 levels in absence of radiographic progression is often considered a harbinger of progressive metastatic disease, however, the current guidelines do not recommend alteration of treatment based only on rising CA 19-9 levels. Available second-line treatments have only modest benefit and may be best reserved for development of new, radiographically documented and/or symptomatic metastatic disease.

1.6 Disulfiram + Copper for Cancer

Cantex Pharmaceuticals, Inc. (Cantex) is developing an oral sequential administration of disulfiram (DSF) and elemental copper in the form of copper gluconate (Cu) for the treatment of cancer. Disulfiram is an FDA-approved oral drug that was first approved by the FDA in 1951 for alcohol aversion therapy and, since then, has been administered to many millions of alcoholic patients in the United States and around the world. Copper gluconate is a dietary food supplement generally recognized as safe (GRAS) under §21CFR184.1260. Disulfiram avidly chelates copper, and when immediately combined in an aqueous solution, forms a tar-like black insoluble precipitate. As a consequence, when co-administered, the disulfiram and copper must be administered at separate time points, or in a formulation which permits immediate release of disulfiram and delayed release of copper.

Disulfiram inhibits aldehyde dehydrogenase (ALDH), which leads to accumulation of acetaldehyde in the blood after ingestion of alcohol consumption, has an excellent safety record with an estimated cumulative risk of any adverse event of 1 case per 2000 patients per year. The most serious side effect from DSF is hepatitis. Transaminases have been reported to be elevated in as many as 9% of alcoholic patients receiving DSF, with a peak frequency at 60 days after starting the drug. However, clinical hepatitis from DSF is rare and has an estimated fatality rate of 1 case in 30,000 patients treated per year.

Cytotoxic effects of the combination of disulfiram + copper have been extensively reported in pre-clinical studies, *in vitro* and *in vivo* in a range of cancers including triple-negative and inflammatory breast cancer, glioblastoma, prostate cancer, and pancreatic cancer. The exact mechanism by which the combination of DSF and Cu exerts cytotoxic effects on tumor cells has not been elucidated. DSF is a potent inhibitor of the enzyme acetaldehyde dehydrogenase (ALDH) which has been implicated in the survival of cancer

stem cells, however, it is unclear whether ALDH inhibition is also critical to anti-cancer activity. Another proposed mechanism for the anti-cancer effect of DSF is related to its ability to complex metal ions such as copper and zinc. When DSF and copper gluconate are administered independently in conventionally approved human doses and absorbed into the body, it is believed that DSF is converted to diethyldithiocarbamate (DDC), which chelates Cu (II), forming the DDC–Cu complex the entity which is thought to be the active drug substance absorbed into cells. Once taken up by the cell, the DDC-Cu complex exerts numerous downstream cellular effects by inhibiting enzymatic machinery via chelating metals in enzyme active sites. As a result of this inhibition, there is a potent induction of reactive oxygen species which increases oxidative stress in the intracellular compartment. Overall, this has the effect of oxidation of numerous cellular proteins required for tumor cell growth and survival, depleting the high anti-oxidant reserves in tumor cells, and inhibiting anti-apoptotic processes.

Other proposed mechanisms of action that promote tumor cell death include proteasome inhibition and inhibition of NF-kappa B. Disulfiram potently inhibits the activity of purified human 20S proteasome at low micromolar pharmacological concentrations.

1.7 Disulfiram + Copper for Pancreatic Cancer

An *in vitro* study was conducted by Cantex in collaboration with TGen, to determine the half-maximal inhibitory concentration(s) (IC_{50}) and combination interaction of disulfiram as a single agent and in combination with copper as copper glycinate in pancreatic tumor cell lines. Whereas disulfiram had virtually no anticancer activity, the combination of disulfiram and copper had striking activity had very low IC_{50} levels.

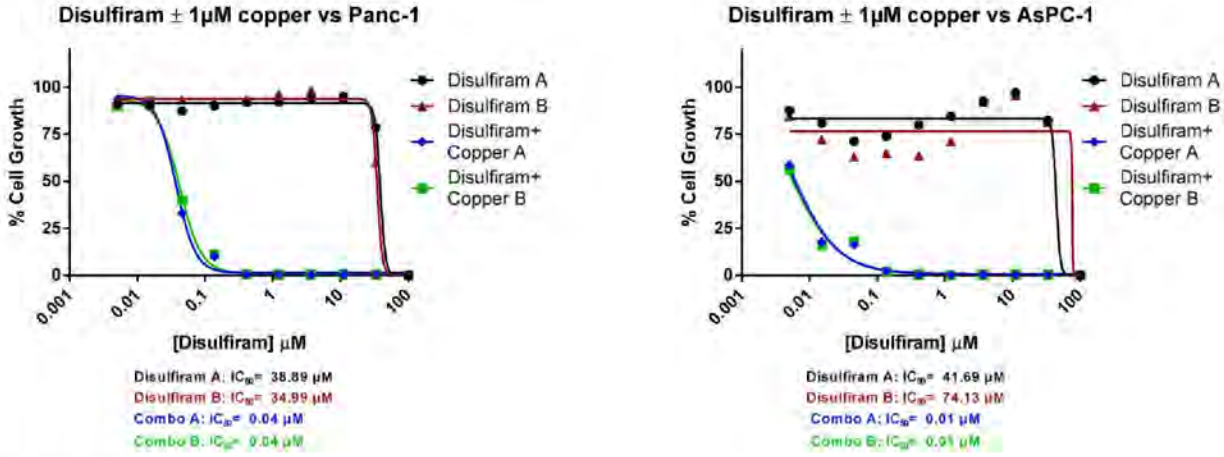

Figure 1

Inhibition of proteasome activity is an important target for cancer therapy. Disulfiram binding to copper forms a DSF/Cu complex that is capable of inducing apoptosis in cancer cells by inhibiting proteasome activity. Orally administered DSF is rapidly converted to diethyldithiocarbamate (DDTC). Orally administered Copper (II) is reduced to copper (I) when it enters cells. DDTC and copper (I) forms a complex which might be

entitled DDTC-Cu (I). Han and colleagues investigated the anticancer potential of this complex on pancreatic cancer and the possible mechanism of its anticancer activity. Pancreatic cancer cell lines, SW1990, PANC-1 and BXPC-3 were used for in vitro assays. Female athymic nude mice with SW1990 xenografts were used as animal models. DDTC-Cu (I) inhibited pancreatic cancer cell proliferation and proteasome activity *in vitro* and *in vivo*. Accumulation of ubiquitinated proteins, and decreased NF-κB expression were detected in tumor tissues of DDTC-Cu (I)-treated group. This data suggested that DDTC-Cu (I) is an effective proteasome activity inhibitor with the potential to be explored as a drug for pancreatic cancer.

1.8 Gemcitabine + DSF/Cu or DSF/Zn in Cancer

Gemcitabine resistant cell lines manifest high NF kappa B activity. The chemo-sensitizing effect of disulfiram an anti-alcoholism drug and NF kappa B inhibitor, and copper on chemo-resistant breast and colon cancer cell lines was examined by Guo and colleagues. The DSF/Cu complex significantly enhanced the cytotoxicity of Gemcitabine and completely reversed the Gemcitabine resistance in the resistant cell lines. Gemcitabine induced NF kappa B activity was markedly inhibited by DSF/Cu complex. This data suggested that DSF/Cu may improve the therapeutic effect of Gemcitabine in breast and colon cancer patients.

Dalla Pozza and colleagues investigated the effect of the combination of Gemcitabine and disulfiram on pancreatic adenocarcinoma cell growth. DSF synergistically inhibited cell proliferation when used in combination with Gemcitabine by inducing apoptotic cell death. This effect was further enhanced by zinc ions. In vivo experiments performed on nude mice who had received a xenotransplant with the Gemcitabine-resistant PaCa44 cell line showed that only the combined treatment with GEM and DSF-Zinc completely inhibited the growth of the tumor masses. The authors concluded that these results and the consideration that DSF is already widely used strongly supported the Gemcitabine and DSF/Zinc combination as a new approach to overcoming pancreatic cancer resistance to standard chemotherapy.

Bobustuc and colleagues evaluated, *in vitro*, the effect of the administration of disulfiram (without copper) at low doses in combination with Gemcitabine and Abraxane on pancreatic cancer cells. DSF has been extensively reported to be an inhibitor of O^6 methylguanine DNA methyltransferase (MGMT) which is overexpressed in a majority of cancers, including pancreatic cancer. MGMT has been the focus of significant research for its role in the repair of DNA damage caused by chemotherapeutic agents. DSF is also a potent of inhibitor of aldehyde dehydrogenase (ALDH), which is implicated in cancer stem cell viability. In this study, Bobustuc confirmed the dual inhibition of MGMT and ALDH by DSF, and reported that DSF sensitized pancreatic cancer cells to the combination of Gemcitabine and Abraxane, significantly inhibiting pancreatic cancer growth.

1.9 DSF/Cu Targeting Pancreatic Cancer Stem Cells: MGH Research

Drs. Wang, Ferrone and colleagues at the Massachusetts General Hospital reported that radiation-induced breast cancer stemness is blocked by targeting the NF-κB-stemness gene pathway with disulfiram (DSF) and Copper (Cu2+). DSF binds to Cu2+ to form DSF/Cu complexes (DSF/Cu), a potent proteasome inhibitor which, in turn, inhibits NF-κB activation. This groundwork prompted testing as to whether DSF/Cu depletes pancreatic ductal adenocarcinoma cells (PDAC) and pancreatic cancer stem cells (PCSCs) in combination with chemotherapy and/or radiation (chemoradiation). As reported by the authors, "recent convincing evidence shows that cancer stem cells and relatively differentiated non-stem cancer cells coexist in dynamic equilibrium and are subject to bidirectional conversion. Thus, any successful therapeutic strategy needs to target preexisting PCSCs and block formation of therapy–induced PCSCs from non-stem PDAC cells."

The authors evaluated the effect of DSF/Cu as a novel chemoradiation sensitizer for PDAC cells by comparing DSF/Cu + radiation + 5-FU to radiation + 5-FU in their ability to target PCSCs, defined either as $ALDH^{bright}$ or CD24+/CD44+/ESA+ or sphere-forming cells, and non-stem bulk cancer cells and to reduce growth of human PDAC cell lines *in vitro* and mouse PDAC cells *in vivo*.

Chemoradiation or FOLFIRINOX, currently standard care for PDAC, can increase stemness in some established or primary PDAC cell lines. However, DSF in the presence of exogenously or endogenously supplied copper (Cu), when combined with chemotherapy or chemoradiation, targets both PCSCs and non-stem PDAC cells. Previously, it was demonstrated that DSF/Cu effectively targets breast cancer stem cells in the context of fractionated radiation by inhibiting the NF-κB–stemness gene pathway. Therefore, the hypothesis that PCSCs can be effectively targeted by incorporating DSF/Cu into the standard chemoradiation regimen consisting of 5-FU and fractionated radiation was investigated and found to be effective *in vitro* in targeting PCSCs, identified as either $ALDH^{bright}$ or CD24+/CD44+/ESA+ or sphere-forming cells, as well as non-stem PDAC cells. *In vivo*, the combination of radiation +5-FU+DSF/Cu was more effective (72.46%) than either radiation +5-FU (30.32%) or radiation +FOLFIRINOX therapy (43.04%) in inhibiting growth of the mouse Panc02 tumor. These encouraging results provide a rationale for a clinical trial of DSF/Cu, seeking to improve the outcomes of chemotherapy treatment for pancreatic cancer.

1.10 NCI-Funded Clinical Study of Disulfiram in Muscle Loss in Pancreatic Cancer

The NCI Division of Cancer Prevention is currently funding a clinical study at the Mayo Clinic in Rochester, Minnesota, to determine if disulfiram can ameliorate the muscle loss that occurs in pancreatic cancer patients. The authors of the proposal from the Mayo Clinic hypothesized that disulfiram, an inhibitor of the ubiquitin-proteasome pathway and an inhibitor of autophagy, the two main muscle degradative pathways in cancer, can augment muscle or stabilize its loss and can improve muscle function. This hypothesis is bolstered by data from the Mayo Clinic and from others indicating that disulfiram

ameliorates muscle loss in an animal model and that proteasome inhibition appears to lead to weight gain or weight stability in advanced cancer patients. The combination of disulfiram and Gemcitabine will be evaluated at this NCI-sponsored clinical trial at the Mayo Clinic in 50 pancreas cancer patients in a randomized, double-blind, placebo-controlled trial and will serially examine 1) muscle biopsies to show disulfiram is hitting its intended muscle targets and to identify new pathways to better understand muscle pathobiology; 2) muscle area at the L3 level with computerized tomography scans (primary endpoint); and 3) fist-grip strength.

1.11 Administration of Disulfiram + Copper in Cancer Patients

A previous phase I study for patients with advanced liver metastasis showed that 6 mg of elemental Cu in the form of copper gluconate is well tolerated when given with 250 mg of DSF daily. In this study, Cu was given in the morning half hour before breakfast, and DSF was given with the evening meals to avoid gastro-intestinal irritation from complexation of DSF and Cu in the stomach. Currently, Dr. Jiayi Huang at Washington University, is conducting a phase I study in which patients are taking 500 mg of DSF every morning along with 2mg of Cu three times a day (TID). The combination of DSF and Cu has been well tolerated to date.

A phase II, multicenter, randomized, double-blinded, 40 patient study reported by Nechushtan et al, assessed the safety and efficacy of adding disulfiram to cisplatin and vinorelbine for six cycles in patients with stage IIIB or IV, newly diagnosed NSCLC. No patient in this study received surgery or radiation. Disulfiram was administered at a dose of 40 mg three times daily. Patients who received concurrent DSF had significantly better PFS (5.9 vs. 4.9 months, p = 0.043), and OS (10.0 vs. 7.1 months p = 0.041), than those who received chemotherapy alone. (See Figure 2 below). Two long-term survivors were reported: both received disulfiram.

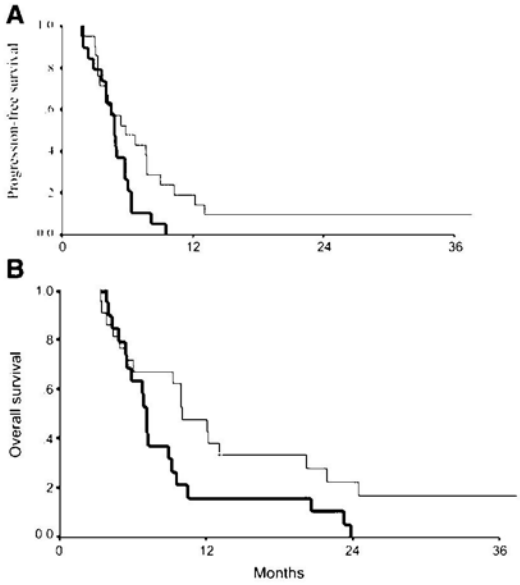

Figure 2. From Nechushtan, et al.

Given the half-life of DSF is approximately 7-14 hours, depending on the assays used to measure half-life, BID or TID administration may be superior to improve its bioavailability. In addition, disulfiram is poorly soluble in aqueous solutions, therefore a lower dose twice or thrice daily may improve absorption. Further, by dividing DSF into two or three doses, it may also be more tolerable to take Cu at the same time as DSF to optimize metabolism of DSF leading to formation of the DDC-Cu complex and its anti-cancer effect. In addition, administration of disulfiram and copper 2-3 times daily may permit a more even exposure of the cancer to the cytotoxic effects of this combination. Finally, by keeping the total daily dose of disulfiram at 240 mg (120 mg BID), which is well below the total 500 mg dose that has been safely used for decades by patients treated for alcoholism, and recognizing the context of patients undergoing treatment for cancer, a large margin of safety is present which should mitigate theoretical risks such as drug accumulation upon repeated administration. The phase II studies of DSF/Cu that are ongoing administer DSF at 80 mg TID together with 1.5 mg of Cu TID. In practice, however, patients have found it cumbersome and challenging to take pills six times daily (disulfiram three times daily followed by copper one hour later three times daily).

Two clinical trials are in progress.

The first clinical trial, in patients with recurrent glioblastoma, is in progress at 6 academic medical centers in the U.S., with the lead center as Washington University in St. Louis. At the time of this writing, 19 patients have been enrolled and no safety issues have been identified. Insufficient time has elapsed at this time since the beginning of enrollment of patients to draw any conclusions about efficacy.

The second trial is being conducted as an investigator-initiated trial and Duke University Medical Center in metastatic castration-resistant prostate cancer. In addition to administration of DSF at 80 mg TID together with 1.5 mg of Cu TID, patients will also receive three intravenous doses of copper, seeking to load the cancer cells with copper and make them more susceptible to the cytotoxic effect of disulfiram. Two patients have thus far been enrolled without safety issues. It is too early to comment about efficacy.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To determine safety as well as preliminary evidence of an anticancer effect of DSF/Cu, as determined by $\geq$ 30% reduction in plasma CA19-9 levels, when administered in combination with Abraxane + Gemcitabine or FOLFIRINOX or single-agent Gemcitabine in patients with metastatic pancreatic cancer who have a rising CA 19-9 level while receiving one of these regimens.

2.2 Secondary Objectives

To determine preliminary evidence of an anticancer effect of DSF/Cu in combination with Abraxane + Gemcitabine or FOLFIRINOX or single-agent Gemcitabine in patients with metastatic pancreatic cancer and rising CA 19-9 levels while receiving one of these regimens as indicated by:

1- incidence of complete response (CR)
2- disease control rate (DCR) as indicated by CR + PR + SD at 6 months
3- overall response rate (ORR)
4- overall survival (OS)
5- progression free survival (PFS)
6- duration of response
7- changes from baseline for serum albumin and body weight
8- safety and tolerability of DSF/Cu administered BID in combination with Abraxane + Gemcitabine or FOLFIRINOX or single-agent Gemcitabine

3.0 STUDY POPULATION

Subjects with metastatic adenocarcinoma of the pancreas who have received a minimum of 8 weeks of treatment with Abraxane-Gemcitabine, single-agent Gemcitabine or FOLFIRINOX and with rising CA 19-9 levels in the absence of radiographic evidence of progression:

- 5 subjects will continue to receive Abraxane-Gemcitabine with DSF/Cu
- 5 subjects will continue to receive FOLFIRINOX with DSF/Cu.
- 5 subjects will continue to receive single-agent Gemcitabine with DSF/Cu

If any patient on any of the 3 regimens has a reduction in CA 19-9 level with DSF/Cu, an additional 9 patients (for a total of 14 patients) will be enrolled (consented) to be treated with that regimen.

Duration of study treatment: Patients will receive study treatment until disease progression is documented per protocol by the investigator based on CT scan and RECIST assessments or continued rise of CA 19-9 level.

4.0 STUDY DESIGN

4.1 Overall Study Design

This is an open label study with three study arms. 15 patients will be enrolled (consented) into the study with 5 patients assigned into each of the three treatment arms based upon whether the patient has previously received Abraxane-Gemcitabine or FOLFIRINOX or

single-agent Gemcitabine without radiographic evidence of disease progression for a minimum of 8 weeks, based on the investigator's opinion, but with a rising CA 19-9 levels.

Arm A: **Abraxane + Gemcitabine + DSF/Cu:** 5 subjects

- If any of the 5 subjects has a CA 19-9 response, an additional 9 patients (to a total of 14 subjects) will be consented and assigned to Arm A.
- The Abraxane-Gemcitabine regimen will be administered consistent with the institutional standard of care.
- Patients will receive Abraxane-Gemcitabine with DSF at a dose of 120 mg BID and copper 3 mg, as copper gluconate, BID daily.

Arm B: **FOLFIRINOX + DSF/Cu:** 5 subjects

- If any of the 5 subjects has a CA 19-9 response, an additional 9 patients (to a total of 14 subjects) will be consented and assigned to Arm A.
- Patients will receive FOLFIRINOX with DSF at a dose of 120 mg BID and copper 3 mg, as copper gluconate, BID daily.
- The FOLFIRINOX regimen will be administered consistent with the institutional standard of care.

Arm C: **Gemcitabine + DSF/Cu:** 5 subjects

- If any of the 5 subjects has a CA 19-9 response, an additional 9 patients (to a total of 14 subjects) will be consented and assigned to Arm C.
- Patients will receive Gemcitabine with DSF at a dose of 120 mg BID and copper 3 mg, as copper gluconate, BID daily.
- Gemcitabine will be administered consistent with the institutional standard of care.

4.2 Primary Endpoints

The primary endpoint is $\geq$30 % reduction in plasma CA19-9 level from baseline, when administered in combination with Abraxane + Gemcitabine or FOLFIRINOX or single-agent Gemcitabine in patients with metastatic pancreatic cancer who previously had rising CA 19-9 levels while receiving these regimens in the absence of radiographic evidence of progression.

4.3 Secondary Endpoints

Secondary endpoints will include:

1- incidence of CR
2- DCR as indicated by CR + PR + SD at 16 weeks
3- ORR
4- OS
5- PFS
6- duration of response
7- changes from baseline for serum albumin and body weight
8- safety and tolerability of DSF/Cu administered BID in combination with Abraxane + Gemcitabine

Objective Tumor Response (See Appendix B):

- DCR is also based on RECIST criteria and is defined as the percentage of patients who have a CR, PR or stable disease (SD) ≥ 16 weeks.

- ORR is based on RECIST criteria and is the percentage of patients with complete response (CR) or partial response (PR). Response to be evaluated approximately every 8 weeks until disease progression.

- Duration of response. The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence, i.e. progressive disease (PD) is determined by RECIST criteria or cancer-related death.

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

4.4 Patient Enrollment

Patients will be considered enrolled upon signing consent. Fifteen (15) patients will be assigned to study treatment, with 5 patients assigned to each of the three treatment arms based upon whether the patient has previously received Abraxane-Gemcitabine or FOLFIRINOX or single-agent Gemcitabine without radiographic evidence of disease progression for a minimum of 8 weeks, but with rising plasma CA 19-9 levels. If any one patient on either Abraxane-Gemcitabine or FOLFIRINOX or single-agent Gemcitabine have a fall in their CA 19-9 level, an additional 9 patients will be enrolled and assigned to Abraxane-Gemcitabine or FOLFIRINOX or single-agent Gemcitabine respectively.

If a patient discontinues from the study prior to receiving study treatments (chemotherapy or study drug) a replacement patient can be enrolled in order to have 5 patients receiving treatment in each study arm.

Study sites will provide all chemotherapy for patients participating in the study as a "standard of care".

DSF/Cu will be provided by the Sponsor and shipped from the Sponsor's central depot to the study sites. Sufficient amounts of DSF/Cu will be available at the study site prior to enrolling patients in the study.

5.0 PATIENT SELECTION

5.1 Inclusion Criteria

1. Patients must have histologically confirmed metastatic adenocarcinoma of the pancreas for which potential curative measures, such as resection of an isolated metastasis, are not available. Patients with islet cell neoplasms are excluded.
2. Patient should currently be receiving a chemotherapy regimen comprising FOLFIRINOX or Abraxane-Gemcitabine or single-agent Gemcitabine as front-line treatment for metastatic disease. Patients who have had chemotherapy in the adjuvant or neoadjuvant setting are eligible.
3. Patients must have previously received a minimum of 8 weeks of therapy with Abraxane-Gemcitabine or FOLFIRINOX or single-agent Gemcitabine without radiographic evidence of disease progression based on the investigator's opinion, but a rising CA 19-9 level, and still be undergoing treatment with Abraxane-Gemcitabine or FOLFIRINOX or single-agent Gemcitabine. Increased CA 19-9 is defined as an increased over baseline of $\geq$ 20% in two consecutive time points within 8 days of each other.
4. Patient has one or more metastatic tumors measurable by CT scan. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan.
5. Male or non-pregnant and non-lactating female and $\geq$ 18 to $\leq$ 80 years of age.
6. Patient has adequate biological parameters as demonstrated by the following blood counts at Screening (obtained $\leq$ 14 days prior to enrollment) and at Baseline-Day 0: Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L; Platelet count $\geq$ 100,000/mm^3 (100×10^9/L); Hemoglobin (Hgb) $\geq$ 9 g/dL.
7. Patient has the following blood chemistry levels at Screening (obtained $\leq$ 14 days prior to enrollment) and at Baseline-Day 0:
    - AST (SGOT), ALT (SGPT) $\leq 2.5 \times$ upper limit of normal range (ULN), unless liver metastases are present, then $\leq 5 \times$ ULN is allowed. Total bilirubin $\leq 1.5 \times$ ULN.
    - Serum creatinine < 1.5X ULN or estimated creatinine clearance of > 60 mL/min (per Cockroft-Gault formula)
8. Patient has ECOG performance status from 0 to $\leq$ 1.
9. Patient has been informed about the nature of the study, and has agreed to participate in the study, and signed the Informed Consent Form (ICF) prior to participation in

any study-related activities.

5.2 Exclusion Criteria

Patients will not be eligible to participate in this study if any of the following criteria apply:

1. Patient has brain metastases.
2. Patient has experienced an increase of ECOG to > 1 between Screening and the time of first dose with study drug.
3. QTc > 480 msec, per institutional standards, if patient receiving oxaliplatin-containing regimen.
4. Patient has active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.
5. Patient has a history of allergy or hypersensitivity to any of the study drugs, their pharmaceutical class or any of their excipients. The patient exhibits any of the events outlined in the Contraindications or Special Warnings and Precautions sections of the most current Gemcitabine or Abraxane® Prescribing Information package inserts or on the Investigator's Brochure for DSF/Cu.
6. Patient has a concomitant serious medical or psychiatric illness that, in the opinion of the investigator, could compromise the patient's safety or the study data integrity.
7. Patient is enrolled in any other clinical protocol or investigational trial involving administration of antineoplastic compounds for the treatment of metastatic pancreatic cancer.
8. Patient is unwilling or unable to comply with study procedures.
9. The use of phenytoin is not allowed during the study.

5.3 Inclusion of Women and Minorities

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

6.0 TREATMENT PLAN

6.1 Pretreatment (Screening) Evaluation

Prior to dosing with any study treatments, patient must have a complete history, physical examination including neurological exam, evaluation of performance status using ECOG, baseline laboratory studies (CBC, CMP, and LFTs), and imaging scan (CT/MRI) as noted in the schedule of events.

A screening baseline CT/MRI is not required if the patient's last scan was performed within 28 days prior to dosing.

6.2 Abraxane + Gemcitabine Dosing or FOLFIRINOX or single-agent Gemcitabine (Standard of Care)

Abraxane + Gemcitabine Dosing or FOLFIRINOX or single-agent Gemcitabine will be administered in a manner consistent with the institutional standard of care.

6.3 Disulfiram and Copper Dosing (Investigational Product)

Two study drugs will be provided: DSF in 40 mg capsules and Copper (Cu) 1.5 mg capsules, as Copper Gluconate. DSF and Cu dosing will begin on the first day of chemotherapy administration.

DSF will be given at 120 mg (three capsules) twice daily, approximately 6-8 hours apart, at least one hour before or after meals with approximately 8 ounces of water. Copper gluconate will be taken 1-2 hours after each dose of DSF at a dose of 3 mg (two capsules). DSF/Cu will be administered BID. The DSF dose will be a total of 240 mg per day, which is approximately the daily dose of disulfiram (250 mg) given safely and chronically to patients treated for alcoholism. If a patient misses a dose, s/he should be instructed not to make up that dose but should instead resume dosing with the next scheduled dose.

6.4 Study Evaluations

Consistent with standard of care, patients will be seen approximately every 4 weeks and typically within 7 days before the start of the next cycle. At each visit, an ECOG evaluation will be recorded. A CA 19-9 level, CT or MRI scan, to evaluate tumor response, will be obtained as consistent with the standard of care, approximately every 8 weeks (+ 4 weeks), to assess radiological response.

Patients are evaluated and monitored for safety throughout the course of the study. Serious adverse events will be recorded in case report forms from the time of consent to 30 days after the last treatment of DSF/Cu, or until death. Non-serious adverse events will be recorded in case report forms from the time of first dose of DSF to 30 days after the last treatment of DSF/Cu, or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Table 1 lists adverse events associated with DSF.

Table 1 Potential Adverse Events Related to DSF

MedDRA Term	**Frequency:** *Likely: greater than 10%* *Less Likely: 1-10%* *Rare: 1% or less*
Neoplasms	*Rare:* Tumor necrosis
Blood and lymphatic system disorders	*Rare*: Neutropenia, anemia, leukopenia, thrombocytopenia, lymphopenia (likely due to Abraxane and/or Gemcitabine)
Immune system disorders	*Rare:* Hypersensitivity
Metabolism and nutrition disorders	*Likely:* Alcohol intolerance, metallic or garlic-like aftertaste
Psychiatric disorders	*Less Likely*: psychosis, delirium (need to rule out tumor progression)
Nervous system disorders	*Likely*: Drowsiness, headache, confusion *Less Likely:* ataxia, gait disturbance, peripheral neuropathy *Rare*: Extrapyramidal symptoms
Eye disorders	*Rare*: Optic neuritis
Cardiac disorders	*Less Likely*: Tachycardia, hypotension (need to rule out DSF-alcohol reaction)
Respiratory, thoracic, and mediastinal disorders	*Less Likely*: Dyspnea (need to rule out DSF-alcohol reaction)
Gastrointestinal disorders	*Likely*: Nausea, vomiting, diarrhea *Less Likely:* constipation (likely due to Abraxane and/or Gemcitabine)
Hepatobiliary disorders	*Rare*: Hepatitis
Skin and subcutaneous tissue disorders	*Less Likely*: Allergic dermatitis
Musculoskeletal	*Rare*: Arthralgia, myalgia
Renal and urinary disorders	*Rare*: Dysuria, hematuria
Reproductive system	*Less likely*: impotence
General disorders	*Likely*: Fatigue

6.5 General Concomitant Medication and Supportive Care Guidelines

Patients are to be instructed to abstain from alcohol while enrolled in this study.

The investigator should use their discretion and the institution's standards of medical care to treat medical conditions or manifestations of the patient's malignancy, taking into consideration the following information.

The following medications and procedures are **prohibited** during the study:

- Any antineoplastic therapy other than Gemcitabine, Abraxane, 5 FU, Leucovorin, Irinotecan, Oxaliplatin, or DSF/Cu
- Any investigational therapy of pancreatic cancer other than DSF or Cu
- Phenytoin: Concomitant administration of phenytoin and DSF can lead to phenytoin intoxication.

The use of alcohol-containing medications and products should be avoided during the study, such as cough and cold syrups.

The use of the following medications/supplements should be avoided at study entry and during the study as they may affect Cu levels in the body:

- Estrogen
- Penicillamine
- Allopurinol
- Cimetidine
- Nifedipine
- Zinc

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Anticoagulants

Monitor prothrombin time and adjust the dosage of oral anticoagulants (e.g., warfarin) if necessary as DSF may prolong prothrombin time during all arms of the study.

Concomitant Use of Isoniazid

Monitor patients taking isoniazid for the appearance of unsteady gait or marked changes in mental status, discontinue the DSF therapy if such signs appear.

Nephrotoxic Drugs

Avoid concomitant use of potentially nephrotoxic drugs with oxaliplatin-containing regimens, as oxaliplatin is primarily eliminated through the kidney.

Enzyme Inducers and Inhibitors

Avoid the concomitant use of strong CYP3A4 inducers (e.g., phenobarbital, carbamazepine, or St. John's wort) during the study and at study entry of the FOLFIRINOX arm, as irinotecan is metabolized by this enzyme.

Avoid the concomitant use of strong CYP3A4 (e.g., clarithromycin, indinavir, itraconozole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconozole) or UGT1A1 inhibitors (e.g., atazanavir, gemfibrozil, indinavir) during the study and at study entry of the FOLFIRINOX arm, as irinotecan and its active metabolite, SN-38, are metabolized by CYP3A4 and UGT1A1, respectively,

UGT1A1*28 allele homozygous

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan treatment. When administered during the FOLFIRINOX arm of the study, consider a reduction in the starting dose by at least one level of irinotecan for patients known to be homozygous for the UGT1A1*28 allele. A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes. Sites are to follow standard of care and institutional guidelines.

6.5.1 Nausea and Vomiting

Prophylactic antiemetic therapy may be used in this study at the discretion of treating physician and as per the institution's standard of care (see Table 2 as a guide). Because of the potential of benzodiazepines to interact with DSF, the use of benzodiazepines for antiemetic prophylaxis should be reserved for patients who cannot be satisfactorily managed otherwise.

Table 2 Prophylactic Antiemetic Therapy

Drug	Dose	Route of Administration	Regimen/Treatment Period	Use
Palonosetron	0.25 mg	IV Infusion	30 minutes prior to start of selected regimen	Pre-medication antiemetic prophylaxis
Fosaprepitant	150 mg	IV Infusion	30 minutes prior to start of selected regimen	Pre-medication antiemetic prophylaxis

Drug	Dose	Route of Administration	Regimen/Treatment Period	Use
Dexamethasone	12 mg	IV infusion	30 minutes prior to start of selected regimen	Pre-medication antiemetic prophylaxis

6.5.2 Diarrhea

Antidiarrheal medications will not be used prophylactically; however, patients will be instructed to take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, patients may take 4 mg of loperamide every 4 hours. Fluid intake should be maintained to avoid dehydration.

6.5.3 Central Nervous System Effects

In patients with glioblastoma, doses of 500-1000 mg of DSF per day with adjuvant temozolomide produced neurological toxicities in some patients, including delirium/psychosis, ataxia, and peripheral neuropathy, especially at the 1000 mg dose. Patients should be carefully monitored for early signs of these symptoms. Once other causes such as tumor progression are ruled out, dose reduction of DSF to 40 mg (one capsule) three times daily should be considered if the toxicity is grade 2 or greater (refer to Section 6.2). If symptoms are not improving with dose reduction, DSF should be discontinued. Patients whose symptoms are not considered immediately life-threatening should be carefully monitored. Each patient may be approached individually with a systematic assessment to rule out other causes. Appropriate tests may include vital signs measurement, computerized tomography, MRI scans, or other appropriate medical assessment.

If the patient's level of consciousness is considered to be life-threatening, the patient should be hospitalized and necessary measures should be instituted to secure the airway, ventilation, and intravenous access.

6.5.4 Management of Disulfiram-Alcohol Reaction

In severe reactions caused by the patient's excessive ingestion of alcohol, supportive measures to restore blood pressure and treat shock should be instituted. Potassium levels should be monitored, particularly in patients on digitalis, since hypokalemia has been reported.

6.6 Duration of Therapy

Patients assigned to continue to receive Abraxane + Gemcitabine + DSF/Cu can receive Abraxane + Gemcitabine + DSF/Cu during approximately 6 (or more) four-week cycles over the course of six months or longer, depending on their response and the investigators' clinical judgment. Upon discontinuation of Abraxane + Gemcitabine,

patients may continue to receive DSF/Cu at the same dose and schedule as previously administered, until clear evidence of progressive disease is identified.

Patients assigned to continue to receive FOLFIRINOX + DSF/Cu can receive FOLFIRINOX + DSF/Cu up to approximately 12 (or more) two-week cycles over the course of 6 months or longer, depending on their response and the investigators' clinical judgment. Upon discontinuation of FOLFIRINOX, patients may continue to receive DSF/Cu at the same dose and schedule as previously administered, until clear evidence of progressive disease is identified.

Patients assigned to continue to receive single-agent Gemcitabine + DSF/Cu can receive single-agent Gemcitabine + DSF/Cu during up to approximately 12 (or more) two-week cycles over the course of 6 months or longer, depending on their response and the investigators' clinical judgment. Upon discontinuation of single-agent Gemcitabine, patients may continue to receive DSF/Cu at the same dose and schedule as previously administered, until clear evidence of progressive disease is identified.

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report form.

In the absence of treatment delays due to adverse events, DSF/Cu treatment may continue until:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- Patient develops unacceptable toxicity deemed possibly, probably, or definitely related to drug that does not resolved to grade 1 or to the patient's baseline status
- Patient requires more than 2 dose reductions
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent at any time for any reason
- Investigator removes the patient from study
- The Sponsor (Cantex), the investigator, or the investigator's institution decides to close the study

In the case of tumor progression, both Abraxane + Gemcitabine and DSF/Cu should be discontinued, and patient should be considered for alternative therapy. If Abraxane + Gemcitabine is temporarily withheld due to toxicity, DSF/Cu should be continued until Abraxane + Gemcitabine may be resumed again. If Abraxane + Gemcitabine is discontinued, DSF/Cu may be continued as per the discretion of the treating physician. If

DSF/Cu is discontinued due to toxicity, Abraxane + Gemcitabine may be continued as per the discretion of the treating physician.

6.7 Duration of Follow-up

Patients are evaluated for adverse events for 30 days after the last dose of DSF/Cu or until death, whichever occurs first. Patients removed from study for adverse events will be followed until resolution or stabilization of the adverse event. Follow-up after the conclusion of the study treatment will be per routine clinical care with data from the patients' chart reviewed to collect data on progression and survival.

7.0 RESPONSE ASSESSMENT

7.1 Efficacy Parameters Measurement of Effect

- The assessment of efficacy for the primary endpoint of progression free survival (PFS) will be based on measurement of effects by RECIST Version 1.1 as included in **Appendix B**.
- Changes of CA19-9 from baseline will be assessed.
- Overall survival (OS) will be censored for all the subjects enrolled at the End of the Study.
- Assessment of tumor response will be based on RECIST Criteria Version 1.1 per **Appendix B**.
- Body weight and serum albumin will be measured on Day 1 of each chemotherapy cycle and compared to Baseline-Day 0.

8.0 DOSE MODIFICATIONS

In general, for any treatment arm, if one drug is discontinued, it will be a matter of patient situation and clinical judgment as to whether some or all of the other agents are also discontinued.

8.1 Abraxane-Gemcitabine Dose Modifications

The following modifications of Abraxane or Gemcitabine dosing are recommended, based upon the current prescribing information for each product.

Table 3 Dose Levels

Dose Level	Abraxane (mg/m^2)	Gemcitabine (mg/m^2)
Level - 0 (baseline)	$125mg/m^2$	$1000mg/m^2$
Level -1	$100mg/m^2$	$800mg/m^2$
Level -2	$75mg/m^2$	$600mg/m^2$

8.1.1 Hematology Toxicity

In the event dose modification are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of abraxane and gemcitabine may be adjusted as follows. Please note that all study drugs will be held at the start of a new cycle if criteria are not met.

Dose Modifications at Day 1:

Table 4 Dose Modifications at Day 1

ANC		Platelets	Timing
$\geq 1.5 \times 10^9$/L	And	$\geq 100 \times 10^9$/L	Treat on time
$<1.5 \times 10^9$/L	Or	$< 100 \times 10^9$/L	No treatment

Dose Adjustments within a Treatment Cycle:

In the event that patients have missed doses within a treatment cycle due to hematologic toxicities, those doses not given during a cycle will not be made up. Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined below.

Dose Modification for Days 8, 15 of Each Cycle:

Table 5 Dose Modifications for Days 8-15 of Each Cycle

Day 8, 15 Laboratory Results	Day 8, 15 Abraxane	Day 8, 15 Gemcitabine
ANC > 1000 and Platelets ≥ 75,000	100%	100%
ANC 500-1000[a] or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)
ANC < 500 or Platelets <50,000	Hold	Hold
Febrile Neutropenia (Grade 3 or 4) [b]	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment
Recurrent Febrile Neutropenia (Grade 3 or 4)	Decrease 2 dose levels (to 75mg/m^2) and do not re-escalate throughout the rest of treatment	Decrease 2 dose levels (to 600mg/m^2) and do not re-escalate throughout the rest of treatment

[a]If patients do not experience resolution of neutropenia within 28 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.

[b]Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 4 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

8.1.2 Non-Hematological Toxicity

Dose reductions for non-hematologic toxicity that occur despite adequate background medical therapy should be undertaken as outlined below.

Table 6 Abraxane and Gemcitabine Dose Modifications for Day 1 of Each Cycle Non-hematologic Toxicity and/or Dose Hold with Previous Cycle

Toxicity/Dose Held	Abraxane + Gemcitabine this cycle	DSF-Cu
Grade 0, 1 or 2 toxicity	Same as Day 1 previous cycle	Consider further work-up and dose reduction*
Grade 3 toxicity[a, c]	Decease abraxane, gemcitabine	Decrease 1 dose level
Grade 4 toxicity[b]	Off protocol treatment[b]	Discontinue
Dose held in 2 previous consecutive cycles	Decrease abraxane, gemcitabine to next lower dose level and continue throughout the rest of treatment	Not applicable

* Special attention should be paid to neurological symptoms such as delirium/psychosis, gait disturbance/ataxia, and peripheral neuropathy. A grade 2 toxicity of these neurological symptoms should prompt a consideration for further work-up and dose reduction of DSF-Cu.
[a] If the toxicity only affects neuropathy, then only abraxane should be reduced (please see Section 8.1.2.1).
[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 8.1.2.2).
[c] Excluding electrolyte abnormalities per judgement of the investigator.

8.1.2.1 Peripheral Neuropathy

Abraxane treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Abraxane treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. Patients experiencing peripheral neuropathy that requires a delay in scheduled Abraxane dosing for ≥ 21 days will discontinue study treatment. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting.

8.1.2.2 Pulmonary Embolism

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

Table 7 Abraxane and Gemcitabine Dose Modifications Day 8, 15 of Each Cycle (Non-hematological Toxicity)

CTC Grade	Percent of Day 1 Abraxane + gemcitabine dose
0-2	100%
3+	Hold treatment until resolution to ≤ Grade 1

8.2 FOLFIRINOX Dose Modifications:

The following modifications of FOLFIRINOX dosing are recommended, based upon a common standard of care:

Table 8 FOLFIRINOX SOC Dose Modifications

Dose Level	Irinotecan	Oxaliplatin	5FU Bolus	5FU Infusion
0 – Baseline	180 mg/m^2	85 mg/m^2	400 mg/m^2	2400 mg/m^2
-1	150 mg/m^2	60 mg/m^2	300 mg/m^2	1800 mg/m^2
-2	---	---	200 mg/m^2	1200 mg/m^2

8.2.1 Hematological Toxicity

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of irinotecan, oxaliplatin and fluorouracil may be adjusted as follows.

Table 9 Dose Modifications Day 1, 15

Toxicity	Occurrence	Irinotecan	Oxaliplatin	5-FU
Febrile Neutropenia OR Grade 4 ANC > 7 days OR Delay 1-2 weeks for ≥ Grade 1 ANC	1st	Decrease 1 dose level	No change	Discontinue Bolus
	2nd	As above	Decrease 1 dose level	
Thrombocytopenic bleeding OR ≥ Grade 3 thrombocytopenia OR Delay 1-2 weeks for Grade thrombocytopenia	1st	No change	Decrease 1 dose level	Decrease 1 dose level
	2nd	Decrease 1 dose level	As above	Decrease 1 further dose level is ≥ Grade 3 thrombocytopenia

Do not treat until ANC $\geq$ 1.5 x 10^9/L, platelets $\geq$ 75 x 10^9/L. Do not escalate dose if reduced for toxicity. Discontinue the regimen if toxicity recurs after 2 dose reductions or if cycle is delayed for > 2 weeks.

8.2.2 Non-Hematological Toxicity

Table 10 Non-Hematological Toxicity

Toxicity	Occurrence	Irinotecan	Oxaliplatin	5FU	DSF-Cu
Diarrhea $\geq$ Grade 3 OR diarrhea with fever or $\geq$ Grade 3 ANC	1st	Decrease 1 dose level	No change	Discontinue bolus	No change
	2nd	As above	Decrease 1 dose level	As above and decrease 1 dose level	No change
Grade 3 or 4 mucositis or hand-foot syndrome	---	No change	No change	Decrease 1 dose level	No change
Grade 2 persistent neurotoxicity	---	No change	Decrease 1 dose level	No change	Consider further work-up and dose reduction*
Grade 2 other non-hematological toxicity	---	Consider decreasing dose	Consider decreasing dose	Consider decreasing dose	
Grade 3 neurotoxicity (recovers prior to next cycle)	---	No change	Decrease 1 dose level	No change	Decrease 1 dose level
Grade 3 other non-hematological toxicity	---	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level
Pneumonitis	Any	Discontinue	Discontinue	Discontinue	Discontinue
Grade 3 persistent neurotoxicity OR Grade 4 neurotoxicity	Any	Discontinue	Discontinue	Discontinue	Discontinue
Grade 4 other non-hematological OR reversible posterior leukoencephalopathy syndrome (RPLS) or hemolytic uremic syndrome or any signs of	Any	Discontinue	Discontinue	Discontinue	Discontinue

Toxicity	Occurrence	Irinotecan	Oxaliplatin	5FU	DSF-Cu
microangiopathic hemolytic anemia					
Pharyngolaryngeal dysesthesia	---	---	Increase infusion to 6 hours	----	---
Total Bilirubin 1-1.5x ULN or Gilbert's	---	Consider decreasing 1 dose level	No change	No change	No change
> 2.5x ULN (or 5x ULN with liver mets) AST/ALT and T. Bilirubin > 1.5-4x ULN	---	Omit	No change	No change	Omit
> 4x ULN	---	Omit	Consider decreasing 1 dose level	Omit	Omit
*Special attention should be paid to neurological symptoms such as delirium/psychosis, gait disturbance/ataxia, and peripheral neuropathy. A grade 2 toxicity of the above neurological symptoms should prompt a consideration for further work-up and dose reduction of DSF-Cu.					
Do not treat until diarrhea resolved to baseline and other toxicity is < Grade 2. Do not escalate dose if reduced for toxicity. Discontinue the regimen if toxicity recurs after 2 dose reductions or if cycle is delayed for > 2 weeks.					

Table 11 Renal Impairment

Creatinine Clearance (mL/min)	Irinotecan	Oxaliplatin	5FU	DSF-Cu
>60	No change	No change	No change	No change
>30 – 60	No change	Consider further work-up and dose reduction	No change	No change
10 – 30	Consider further work-up and dose reduction	Discontinue	Consider further work-up and dose reduction	Decrease 1 dose level
<10	Consider further work-up and dose reduction	Consider further work-up and dose reduction	Consider further work-up and dose reduction	Decrease further dose level

8.3 Disulfiram Dose Modifications

Table 12 Disulfiram and Copper Gluconate Dose Modifications

Dose Level	Disulfiram Dose	Copper Dose (as copper gluconate)
0 – baseline	120 mg PO BID	3 mg PO BID
-1	80 mg PO BID	3 mg PO BID
-2	40 mg PO BID	3 mg PO BID

Hematologic toxicity is uncommon for DSF and is likely related to Abraxane and/or Gemcitabine or to FOLFIRINOX.

8.3.1 Administration of DSF to Patients with Abnormal Hepatic Function

DSF/Cu should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from DSF/Cu is uncommon but may occur. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of hepatotoxicity from concurrent medications.

8.3.2 Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require no intervention; however, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reaction to DSF should discontinue DSF immediately and not be re-challenged.

9.0 INVESTIGATIONAL PRODUCT INFORMATION

9.1 Disulfiram and Copper Gluconate

9.1.1 Disulfiram Description

DSF is an alcohol antagonist drug approved by the FDA for the treatment of alcoholism. Its powder is white, odorless, and almost tasteless. It is soluble in water to the extent of about 20mg in 100mL, and in alcohol to the extent of about 3.8 g in 100 mL.

Molecular formula: $C_{10}H_{20}N_2S_4$
Chemical name: bis(diethylthiocarbamoyl) disulfide.
Molecular weight: 296.54.

9.1.2 Clinical Pharmacology

DSF is mostly known as an irreversible inhibitor of aldehyde dehydrogenase, which affects alcohol metabolism and causes accumulation of acetaldehyde. However, increasing preclinical studies have shown that DSF is also a proteasome inhibitor, specifically the chymotrypsin-like activity. DSF is very lipophilic and readily crosses the blood-brain barrier.

9.1.3 Supplier

DSF has been manufactured by IriSys, LLC in San Diego, California in accordance with current Good Manufacturing Practices (cGMP) and will be provided by Cantex for the study participants. Label text will be compliant with FDA requirements.

9.1.4 Dosage Form

DSF is supplied as 40 mg capsules in bottles containing 60 capsules.

9.1.5 Storage and Stability

DSF is dispensed in a tight, light-resistant container. It should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its original container to protect from bright light. A broader range is acceptable for subject home storage (15° to 30°C or 59° to 86°F).

9.1.6 Disulfiram Administration

DSF is taken by mouth two times daily. It should be taken on an empty stomach. Patients should not have consumed any alcohol at least 12 hours prior to the first dose. In the rare event of a severe hypersensitivity reaction, discontinue DSF immediately.

9.1.7 Copper Gluconate Description

Cu gluconate is a dietary food supplement generally recognized as safe (GRAS) under §21CFR184.1260. Cu is an important nutrient in the human body and plays an essential role by participating in numerous metabolic reactions in the body (Lecyk 1980; Stern et al. 2007). Exposure to Cu usually occurs from consumption of food and drinking water. Several studies have concluded that chronic dietary intakes of Cu less than 10 mg/day pose no significant health risk.

9.1.8 Supplier

Cu gluconate capsules have been manufactured by IriSys, LLC in San Diego, California in accordance with current Good Manufacturing Practices (cGMP) and

will be provided by Cantex for the study participants. Label text will be compliant with FDA requirements.

9.1.9 Dosage Form

Copper, as copper gluconate, is supplied as 1.5 mg capsules in bottles containing 60 capsules.

9.1.10 Storage and Stability

Copper gluconate is dispensed in a tight, light-resistant container. It should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its original container to protect from bright light. A broader range is acceptable for subject home storage (15° to 30°C or 59° to 86°F).

9.1.11 Copper Gluconate Administration

Copper gluconate is taken by mouth two times daily. It should be taken with food or meals.

9.2 Treatment Compliance, Accountability and Return

Study medications will be dispensed to patients at the investigational site by authorized site personnel. The investigator or designee must maintain accurate records of all study treatments, including dates, lot numbers and quantities of study drug received at the site as well as dates, lot numbers and quantities dispensed to each patient as well as the amount returned at each visit.

The investigator will instruct patients to return empty bottles and unused product back to the site for each visit. New bottles will be dispensed at each visit.

The Sponsor will assure the quantity of the study drug is adequate for the duration of the study.

Upon completion of the study, all unused and/or partially used study drug must be returned to the Sponsor or authorized designee, or destroyed per site standard operating procedures. If product is returned to the Sponsor, the clinical supplies return documentation must be included. Study drug may only be returned to the Sponsor or designee, or destroyed, after accountability has been completed and documented, and verified by the study monitor. Any discrepancies must be identified and explained. Drug accountability records, study drug supply receipt and retunes must be maintained by the investigator. If study drug is to be destroyed at the site, the Sponsor must be notified in advance.

Patients will be asked to complete a dosing diary to record when they dose with DSF and Cu.

10.0 STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done no more than 28 days prior to the start of the protocol therapy. Each treatment cycle is 28 days. The number of cycles will vary per patient but are estimated to be 6-12 cycles.

Table 13 Evaluations Overview

	Screening / Baseline		**End of Treatment**	**Follow-Up[1]**
Informed consent	X			
H&P and ECOG status	X	As per institutional standard of care		
CBC	X	As per institutional standard of care		
PT	X	As per institutional standard of care		
CA 19-9 level	X	As per institutional standard of care		
CT Scans	X	As per institutional standard of care		
Abraxane + Gemcitabine or FOLFIRINOX or single-agent Gemcitabine		As per institutional standard of care		
Disulfiram[1]		Daily[1]		
Copper gluconate[2]		Daily[2]		
AE assessment	X ---------- X			

1. To be taken twice daily at least one hour before or after meals.
2. To be taken twice daily, approximately 1 hour after DSF, with food

Table 14 Schedule of Events: Abraxane + Gemcitabine Group or Single-Agent Gemcitabine Group

Screen thru Treatment Period	Screening[a]	Cycle 1				Cycle 2 and beyond				End of Treatment	Follow-Up
Study Week		1	2	3	4	1	2	3	4		
Cycle Day	-14 to -1	1	8	15	22	1	8	15	22		30 days post last treatment
Scheduling Window (Days)	-14 to -1	±1	±1	±1	±1	±1	±1	±1	±1		±7
Informed Consent	X										
Inclusion/Exclusion	X										
Medical History	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X			
Complete Physical Exam	X										
Directed Physical Exam		X	X[b]	X[b]	X[b]	X				X	
Weight	X	X	X	X	X	X				X	
Height	X										
BSA	X	X				X					
ECOG PS	X	X	X	X	X	X				X	
Vital Signs per SOC	X	X	X	X	X	X				X	
Hematology	X	X[c]	X	X	X	X	X	X		X	
Serum Chemistry	X	X[c]	X	X	X	X	X	X		X	
Urinalysis	X					X				X	
PT/INR, aPTT	X	Per investigator discretion[d]									
CA19-9	X					X				X	
Serum Pregnancy[e]	X									X	
12-Lead ECG[f]	X										
Abraxane		X	X	X		X	X	X			
Gemcitabine		X	X	X		X	X	X			
DSF/Cu Dispensing		X[g]				X					
Dosing diary review and DSF/Cu return						X				X	
Adverse Event Assessment		Continuously								X	X
Tumor Imaging[h]	X					X[i]				X	
Phone Contact: AEs and Medication Review									X		

[a]Written IRB-approved informed consent must be obtained prior to any screening assessments being performed

[b]Directed PE done per SOC as needed to complete ECOG or other assessments during these visits.

[c]Day 1 labs only need to be re-done if not completed within the prior 72 hours.

[d]Monitor prothrombin time and adjust the dosage of oral anticoagulants (e.g., warfarin) if necessary as DSF may prolong prothrombin time during all arms of the study.

[e]Negative serum pregnancy test is required for women of child-bearing potential within 72 hours of start of study medication; adequate contraception (both males and females) as defined by the protocol should be used throughout the study. For end of treatment urine pregnancy test is allowed.

[f]ECG monitoring at screening and as clinically indicated during treatment

[g]Patients will be provided dosing diaries to record when they take DSF/Cu. Diaries will be reviewed along with DSF/Cu returns at the start of each cycle, starting with Cycle 2.

[h]CT/MRI and FDG-PET (as per investigator discretion) scan to document disease status at baseline to include chest abdomen and pelvis and other regions as clinically indicated. Brain scan is required to rule out brain metastases if clinically indicated. A screening CT/MRI is not necessary if the patient's last scan was obtained within 28 days before the screening visit.

[i]The same radiographic procedures used to document disease status at baseline must be used throughout the study. Tumor assessments will be conducted using CT or MRI, approximately every 8 weeks (e.g., prior to Cycle 3, 6, 9, etc.) or per SOC until study discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response.

Table 15 Schedule of Events: FOLFIRINOX Group

Screen thru Treatment Period	Screening[a]	Cycle 1				Cycle 2 and beyond				End of Treatment	Follow-Up
Study Week		1	2	3	4	1	2	3	4		
Cycle Day	-14 to -1	1	8	15	22	1	8	15	22		30 days post last treatment
Scheduling Window (Days)	-14 to -1	±10	±1	±1	±1	±10	±1	±1	±1		±7
Informed Consent	X										
Inclusion/Exclusion	X										
Medical History	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X		X	X		
Complete Physical Exam	X										
Directed Physical Exam		X	X[b]	X[b]	X[b]	X				X	
Weight	X	X	X	X	X	X				X	
Height	X										
BSA	X	X				X					
ECOG PS	X	X	X	X	X	X				X	
Vital Signs per SOC	X	X	X	X	X	X				X	
CBC with Differential, Platelets	X	X[c]	X	X	X	X		X		X	
Comprehensive Metabolic Panel	X	X[c]	X	X	X	X		X		X	
Urinalysis	X					X				X	
PT/INR, aPTT[d]	X	Per Investigator Discretion									
CA19-9	X					X				X	
Serum Pregnancy[e]	X									X	
12-Lead ECG[f]	X										
Oxaliplatin		X		X		X		X			
Leucovorin		X		X		X		X			
Irinotecan		X		X		X		X			
5-FU Bolus		X		X		X		X			
5 FU 46 hr infusion		X		X		X		X			
DSF/Cu Dispensing		X[g]				X					
Dosing diary review/DSF/Cu return						X				X[e]	
Adverse Event Assessment		Continuously								X	X
Tumor Imaging[h]	X					X[h]				X	
Phone Contact: AEs and Medication Review							X		X		

[a]Written IRB-approved informed consent must be obtained prior to any screening assessments being performed

[b]Directed PE done per SOC as needed to complete ECOG or other assessments during these visits.

[c]Day 1 labs only need to be re-done if not completed within the prior 72 hours.

[d]Monitor prothrombin time and adjust the dosage of oral anticoagulants (e.g., warfarin) if necessary as DSF may prolong prothrombin time during all arms of the study.\

[e]Negative serum pregnancy test is required for women of child-bearing potential within 72 hours of start of study medication; adequate contraception (both males and females) as defined by the protocol should be used throughout the study. For end of treatment urine pregnancy test is allowed.

[f]ECG monitoring at screening, pre-dose, around steady-state Cmax of oxaliplatin and clinically indicated during FOLFIRINOX arm of the study

[g]Patients will be provided dosing diaries to record when they take DSF/Cu. Diaries will be reviewed along with DSF/Cu returns at the start of each cycle, starting with Cycle 2.

[h]CT/MRI and FDG-PET (as per investigator discretion) scan to document disease status at baseline to include chest abdomen and pelvis and other regions as clinically indicated. Brain scan is required to rule out brain metastases if clinically indicated. A screening CT/MRI is not necessary if the patient's last scan was obtained within 28 days before the screening visit.

[h]The same radiographic procedures used to document disease status at baseline must be used throughout the study. Tumor assessments will be conducted using CT or MRI, approximately every 8 weeks (e.g., prior to Cycle 3, 6, 9, etc.) or per SOC until study discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response.

Table 16 Laboratory Tests – performed locally

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	β-hCG†
Platelet count	Alanine aminotransferase (ALT) OR Aspartate aminotransferase (AST)	Protein	PT/INR
WBC (total and differential)		Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	
Absolute Neutrophil Count	Carbon Dioxide ‡		
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*		
	Calcium		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		

† Perform on women of childbearing potential only.
‡ If considered standard of care in your region.

11.0 DATA SAFETY MONITORING

The treatment regimens in this study combine several chemotherapeutic agents with known toxicity profiles and a new drug disulfiram-copper gluconate with unknown toxicity profiles. Although disulfiram is an FDA drug with extensive data for the treatment alcoholism, the combination with copper and chemotherapeutic agents has not been tested. Because cancer is a life-threatening disease, treatments that result in Grade 3 and 4 toxicities are considered to have an acceptable risk profile. Data will be reported to the Medical Monitor and Sponsor on a regular basis and not less than once a month. In addition, SAEs will be reported to the Sponsor immediately and reviewed by the Medical Monitor as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the

Sponsor, the site Principal Investigators and the Medical Monitor who will decide jointly whether the study should be modified, interrupted, or stopped. A monthly conference call will be held with investigators participating in the study. The statistical group will provide listings of toxicities to the Sponsor and Medical Monitor on a regular basis.

12.0 STATISTICAL CONSIDERATIONS

12.1 Definition of Primary Endpoints and Analytical Plan

The primary endpoint of this study is to assess the effect of administration of DSF/Cu in combination with Abraxane-Gemcitabine or FOLFIRINOX or single-agent Gemcitabine in patients with metastatic pancreatic cancer with rising CA 19-9 levels while receiving either regimen.

12.2 Sample Size & Power Calculations

As this is a small pilot study to determine evidence of an effect of DSF/Cu on CA 19-9 levels, no formal sample size power calculation has been made.

12.3 Statistical Methods

12.3.1 Analysis of Primary & Secondary Endpoints

Progression free survival (PFS), overall survival (OS) as well as duration of response will be analyzed using the method of Kaplan Meier and compared between arms using the log-rank test.

CA19-9 plasma levels will be measured each month. The decline of CA19-9 was shown to correlate to overall survival and progression free survival in two previous studies in patients with advanced pancreatic cancer treated with Gemcitabine and Abraxane. Generalized estimating equations will be used to determine whether there is a significant difference in the magnitude and duration of CA19-9 plasma levels decline from baseline between arms. We will also adjust for other standard prognostic factors.

Tumor response rates, such as ORR and DCR, in each treatment arm will be determined by the number of patients achieving the respective response by RECIST criteria, divided by the number of patients on the treatment arm. Comparisons between arms will be made using Fisher's exact test.

The incidence of Adverse Events and Toxicity will be presented as a summary statistics only.

Changes in serum albumin from Baseline. AUC of albumin across time from Baseline-Day 0 until death or disease progression will be determined for each treatment arm.

Changes in body weight from Baseline. Percent weight loss across time from Baseline-Day 0 until death or disease progression will be determined for each patient; summary

statistics for each arm will be determined. Comparisons of percent weight loss will be done using the t-test.

12.3.2 Analysis of Toxicity & Safety

Toxicity and accrual monitoring are done routinely by the PI, the Medical Monitor and the study statistician. The maximum grade for each toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.
All toxicity and safety analyses will be performed on the safety population.

13.0 REGULATORY AND REPORTING REQUIREMENTS

13.1 Adverse Events (AEs)

The investigator or designee (such as the Medical Monitor) will monitor patient safety on a routine basis throughout the study, starting after a patient signs consent. Any safety concerns noted from the time of consent to the time of the first dose of DSF will be documented in source documents which will also be routinely reviewed by the clinical research associate/clinical trial monitor. The investigator will immediately notify the Sponsor (in the same manner as for serious adverse event reporting) of any safety concerns that arise prior to the start of DSF that could impact the conduct of the study or safety and welfare of participants.

The investigator or designee will assess and record all AEs in the source documents, including seriousness, the date of onset, description, severity, duration and relationship to study drug, action taken and outcome, from the time of consent until 30 days after the last dose of study drug (DSF or Cu, whichever is the last dose taken) or until death, whichever occurs first..

Non-serious AEs will be captured in case report forms (CRF) starting from the time of the first dose of DSF and will continue to be captured until 30 days after the last dose of study drug (DSF or Cu, whichever is the last dose taken) or until death, whichever occurs first.

Serious AEs will be captured in case report forms from the time of consent to 30 days after the last treatment of DSF/Cu, or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Definition (as per 21 CFR 312.32): An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

Conditions that started before signing of consent and for which no symptoms or treatment are present at the time of consent are considered medical history.

Conditions that started before signing consent and for which symptoms are present after signing consent are considered part of medical history if the condition did not worsen (change in frequency or severity).

Conditions that start or worsen after signing consent will be captured as AEs.

Surgical or diagnostic procedures in and of themselves are not AEs. The condition leading to the procedure or the resulting diagnoses would be considered an AE.

Abnormal laboratory test results will be considered AEs if they are considered clinically significant. If the abnormality is part of a diagnosis, only the diagnosis would be considered an AE.

Pre-planned procedures that were scheduled prior to signing consent will not be considered AEs. However, if the pre-planned procedure is performed earlier due to a worsening of a pre-existing condition, the worsening condition would be considered an AE.

Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the source documents.

All AEs will be followed until resolution or stabilization of the event, completion of the patient's participation or study termination, or upon agreement between the investigator and Sponsor that no further follow-up in necessary whichever occurs first.

All AEs will be treated appropriately. Such treatment may include changes in study drug treatment.as outlined in section 6.0 of this protocol.

Serious adverse events (as defined in 21 CFR 312.32)
A serious adverse event (SAE) is defined as any AE occurring during an investigational study that, in the opinion of the investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE
- Hospitalization of prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs must be reported to the Sponsor (or designee) within 24 hours from the time when the site personnel first learn about the event via any of the following methods using a

report form provided by the Sponsor (paper or electronic data capture (EDC) forms will be acceptable), Form FDA 3500A, or as otherwise described in a Safety Monitoring Plan:

Safety Contact Methods:
Fax: 954-315-3662
Email: safety@cantex.com

If the subject is hospitalized because of or during the course of an SAE, the investigator should attempt to obtain a copy of the hospital discharge summary and any pertinent laboratory or diagnostic reports and provide them to the Sponsor (or designee) as soon as possible.

New information about the event as it becomes available to the investigator must be reported to the Sponsor within 1 working day of receipt by the investigator and site personnel via the same methods as described above.

All SAEs will be followed until resolution or stabilization of the event, or upon agreement between the investigator and Sponsor that no further follow-up in necessary.

Severity Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (20017), or more current version if available, will be utilized for all toxicity reporting. A copy of the CTCAE can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Expectedness: AEs will be assessed by the Sponsor as to whether they were expected to occur or unexpected. An unexpected AE is one that is not listed in the investigator brochure or that is not listed at the specificity or severity that has been previously observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Causality assessments: A causal relationship between all AES and SAEs to study drug (investigational product) will be assessed by the investigator and the Sponsor.

13.2 Unanticipated Problems (UAP)

Definition (as per Department of Health and Human Services' Office for Human Research Protections [ORHP] Guidance):

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); **and**

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

UAPs will reported by the investigator to regulatory authorities and the IRB as required per 45 CFR part 46 and as per the local IRB requirements.

13.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects' research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

13.4 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

13.5 Protocol Deviations

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Protocol exceptions are not expected or encouraged, and should be discussed first with the study Sponsor.

Deviations are any intentional or unintentional changes from an IRB-approved protocol that is not approved by the IRB prior to initiation of the change. Major protocol deviations are deviations that result in increased risk to subjects, affect the rights, safety, or welfare of the subjects or affect the integrity of the study (impacts the quality of the data or the outcome of the study). Examples include (but are not limited to) deviations from inclusion/exclusion criteria, informed consent deviations, and concomitant medication restriction deviations. Major protocol violations are to be reported to the IRB.

13.6 Reporting to the Institutional IRB

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others that impacts

participants or the conduct of the study.

- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event. Occurrences will be reported as per the requirements of the local IRB.

13.7 Reporting to the FDA and other investigational sites

The conduct of the study will comply with all FDA safety reporting requirements. It is the responsibility of the investigator to report any SAEs to the Sponsor (or the Sponsor's designee) (within 24 hours) and the Sponsor (or designee) will report events to FDA and all investigational sites as per applicable regulations.

13.8 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days after the last dose of DSF/Cu.

14.0 ADMINISTRATIVE PROCEDURES AND CONSIDERATIONS

14.1 IRB Approval

The protocol and informed consent form (ICF) will be reviewed and approved by the Institutional Review Board (IRB). The investigator must submit and obtain (when applicable) approval from the IRB for all subsequent protocol amendments. If requested, the investigator will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The investigator will provide the IRB with progress reports at required intervals (not to exceed one year) and a Study Progress Report following completion, termination, or discontinuation of the investigator's participation in the study.

14.2 Ethical Conduct

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICD consolidated Guideline E6 for GCP, and the applicable regulatory requirements and laws.

14.3 Informed Consent

Written informed consent will be obtained from the patient prior to any study related procedures are conducted. Information about the study will be provided to the subject both verbally and in writing and will include an explanation of the objectives of the study, the risks, and the benefits. The patient will be permitted time and opportunity to inquire about details of the study and to decide whether or not to participate and will be informed that participation is voluntary and that he/she can withdraw consent at any time without penalty or loss of benefits to which the patient is otherwise entitled. The investigator/designee will answer any questions regarding the study, prior to obtaining consent.

The investigator must be satisfied that the patient has read and understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written and verbal information, the patient should not participate in the study.

If the patient agrees to participate in the study, the patient will be asked to sign and date the study ICF which will be retained by the investigator. The investigator/designee must sign and date the ICF before the patient can participate in the study. A copy of the signed and dated ICF will be given to the patient. The informed consent process will be in accordance with all applicable regulatory requirements and must be documented in the patient's source documents. The original ICF must be retained by the investigator and made available for inspection by the study monitor.

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use of an amended form (including for ongoing patients). The patients will be required to sign an updated ICF if there is any information that affects the conduct of the study or the subject's willingness to participate in the study.

14.4 Subject Confidentiality

Subject confidentiality will be strictly held in trust by the participating investigators, their staff, the Sponsor and their authorized representatives. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating patients.

No information that would permit the identification of a specific individual will be provided for entry into the study database or study report. Study documentation submitted to the Sponsor will identify patients by study code numbers and initials. The investigator will keep a separate confidential enrollment log that matches identifying study codes with the patients' names and residences.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party, without prior written approval of the Sponsor.

Authorized representatives of the Sponsor, the designated contract research organization (if applicable), the study monitor, employees of the government authorities such as the US FDA or other government authorities, and members of the IRB 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 patients in the study. The clinical study site will permit access to such records.

14.5 Study Monitoring

The Sponsor or its designee are responsible for monitoring the study in accordance with the requirements of ICH/GCP, and in accordance with written SOPs and monitoring plans. The study will be monitored by the Sponsor or designee at all stages of study conduct from inception to completion in accordance with ICH/GCP. The investigator will allocate adequate time for such monitoring activities. This monitoring will be in the form of site visits and other communication and will include review of original source documents, case report forms (CRFs), facilities and equipment, recruiting, record-keeping, protocol adherence, data collection, AE reporting, and other factors. The frequency of these visits will depend upon the progress of the study.

The investigator will ensure that the monitor or other compliance or quality assurance reviewers are given access to all the above noted study-related documents and study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.) and has adequate space to conduct the monitoring visit.

14.6 Case Report Forms and Study Records/Data

Source documents are defined as original documents, data, and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The management and recording of data will be consistent with applicable ICH/GCP guidelines.

Case report forms (CRFs) can be paper or electronic and will be used to collect data during the study. CRFs will be patient-specific. CRFs will be completed as soon as data are available in the source documents as some monitoring procedures may be done in real-time. Sites will be trained on the appropriate completion of the CRFs and training records will be maintained. A CRF will be completed for each patient who signs an ICF. Data collected in the CRF may be queried by the Sponsor. All queries must be resolved in a timely manner.

The investigator will sign and date where indicated in the CRF which will indicate that the investigator has reviewed all data collected, queries, or other clarifications and agrees that the content is accurate.

The investigator is responsible for the accuracy, completeness, and timeliness of the data reported in the CRF. Study data management, monitoring, statistical analysis, and reporting will be performed by the Sponsor or designee according to SOPs.

Completed datasets and associated files are the property of the Sponsor and should not be made available in any form to third parties, except for authorized business representatives or appropriate government health or regulatory authorities, without the written permission of the Sponsor.

The investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, and all study documents as specified in ICH/GCP and as specified by applicable regulatory requirements. The investigator/institution will take measures to prevent accidental or premature destruction of documents. Essential documents should be retained for at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug (investigational product). These documents should be retained longer if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

The Sponsor must be notified if the investigator retires, relocates or otherwise will no longer work on the study and record custody and retention must be transferred to a person who will accept the responsibility. The investigator must not relocate study documents or dispose of any study documents before obtaining written approval from the Sponsor.

14.7 Criteria for Termination of the Study

If the Sponsor or designee, the investigator or regulatory authority discovers any condition arising during the study that indicates that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor or its designee and the investigator. The Sponsor or its designee has the right to terminate the participation of wither an individual site or the study at any time, for any reason, which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator(s) do(es) not adhere to the protocol or applicable regulatory guidelines in conducting this study
- Submission of knowingly false information from the study site to the Sponsor or its designee or regulatory authorities.

14.8 Investigator Final Report(s)

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the Sponsor with all required reports, the IRB with a summary of the trial's outcome, and the regulatory authority (ies) with any report(s) they require of the investigator/institution.

14.9 Financial Disclosure

The principal and sub-investigators are required to provide certification of the following:

- no financial arrangements with the Sponsor exist where study outcome could affect compensation
- the investigator does not have significant equity interest in the Sponsor
- the investigator has not received payments of other sorts.

The principal and sub-investigator must inform the Sponsor if the above circumstances change during the course of the study or within 1 year of the end of his/her participation in the study.

14.10 Publication and Disclosure

All unpublished information that the Sponsor gives to the investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentation to regulatory agencies, one or more of the investigators who has/have contributed significantly to the study may be asked to endorse the final report.

The investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in a clinical study agreement.

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Appendix A

ECOG Performance Status Criteria

ECOG Performance Status Scale*		Karnofsky Performance Scale**	
Grade	**Descriptions**	**Percent**	**Description**
0	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	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	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	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	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.

* As published in Am. J. Clin. Oncol.:*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

** Karnofsky Performance Scale provided for reference purposes only to correlate with ECOG PS.

Appendix B

RECIST Guidelines Version 1.1

MEASUREMENT OF EFFECT

Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans must also be obtained 4 to 5 weeks (no less than 4 weeks) following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009] included in this appendix. 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.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with the study medications.

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.

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.

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, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

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 2 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.

Conventional CT: 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. The tumor response in this study is based on conventional CT. Other radiology or imaging studies can be done, however only conventional CT scans will be documented on the CRF for tumor response.

Tumor markers: Tumor markers alone will not be used to assess disease progression. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. As a primary endpoint in this study CA19-9, as a tumor marker of pancreatic cancer activity, will be measured at baseline and every 4 weeks.

Response Criteria

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.

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 clinical opinion of the investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the investigator.

Evaluation of Best Overall Response

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

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

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

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

** 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.

≥ 4 weeks confirmation with a range of 28 to 32 days.

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		

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.

Progression-Free Survival

As a secondary endpoint, Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Tumor Response Review

As a secondary endpoint, the tumor responses will be reviewed by the Investigators participating in the study.
No central review of tumor responses is planned for this study.