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SWOG

A RANDOMIZED PHASE II STUDY OF PERIOPERATIVE mFOLFIRINOX VERSUS GEMCITABINE/NAB-PACLITAXEL AS THERAPY FOR RESECTABLE PANCREATIC ADENOCARCINOMA

NCT #02562716

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AGENTS:

IND-Exempt Agents:
Fluorouracil (5-FU, Adrucil®) (NSC-19893)
Gemcitabine hydrochloride (Gemzar®) (NSC-613327)
Irinotecan (Camptosar®) (NSC-616348)
nab-Paclitaxel (NSC-736631)
Oxaliplatin (Eloxatin) (NSC-266046)

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NRG/NRG Oncology

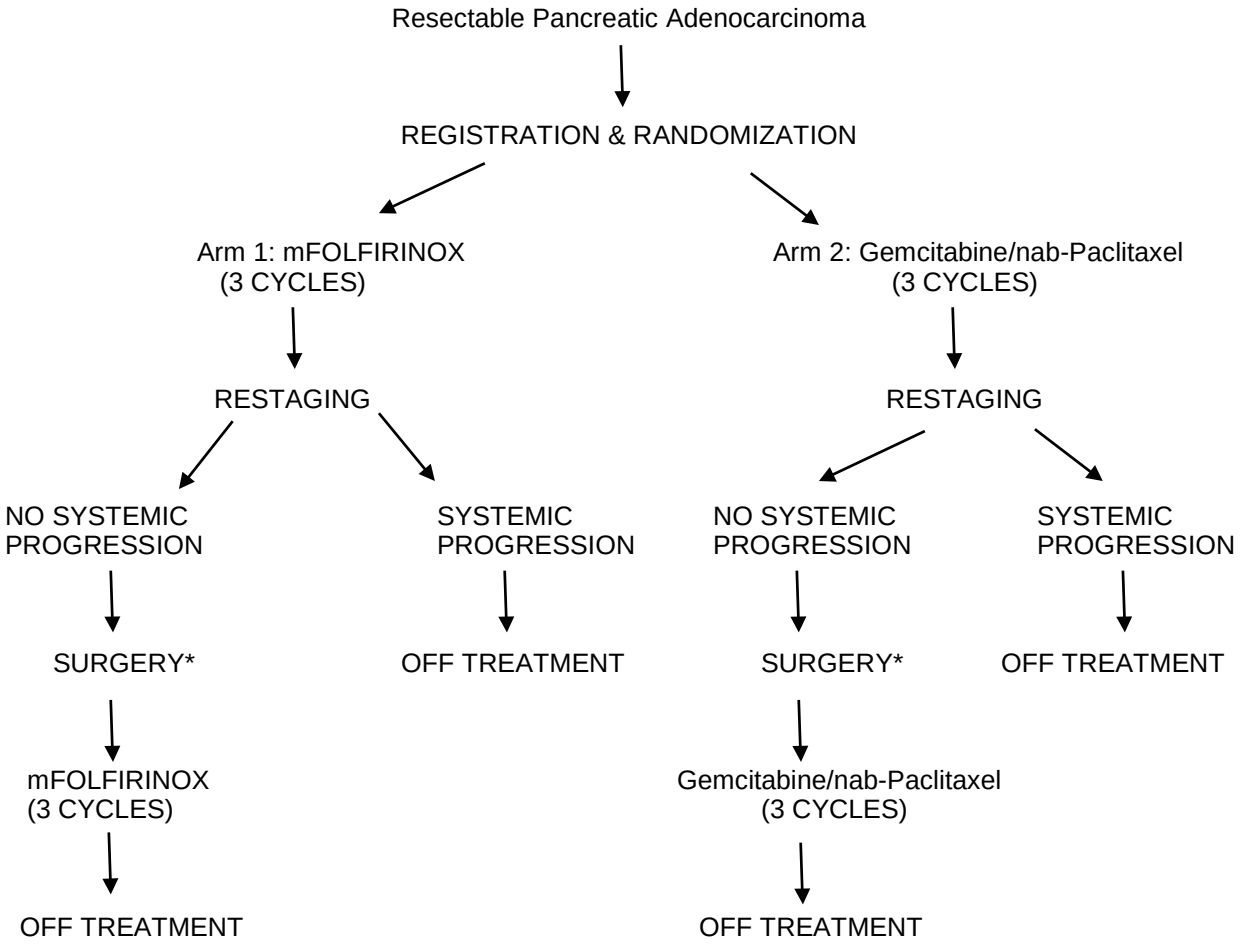
SWOG/SWOG

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: 206-652-2267 giquestion@crab.org **For treatment or toxicity related questions** contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website: https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA



*NOTE: If patient is unable to undergo R0 or R1 surgical resection, he or she must be taken off protocol treatment (see Sections 7.4g and 7.6d).

1.0 OBJECTIVES

1.1 Primary Objectives

a. To assess 2-year overall survival in each treatment arm (mFOLFIRINOX and gemcitabine/nab-paclitaxel) in patients with resectable pancreatic cancer.

b. If the stated threshold is met in one or both arms: to choose the better regimen with respect to 2-year overall survival.

1.2 Secondary Objectives

To estimate, for all patients and within treatment arms:

a. Frequency and severity of adverse events associated with chemotherapy in the perioperative setting.

b. Proportion of patients going to surgery for resection after preoperative chemotherapy.

c. Proportion of patients achieving R0 resection after preoperative chemotherapy.

d. Overall response rate following preoperative chemotherapy, including confirmed and unconfirmed, complete and partial response, per RECIST 1.1.

e. Pathologic response rates after R0 or R1 resection.

f. Patterns of recurrence (loco-regional, distant) after R0 or R1 resection.

g. Disease-free survival from the time of R0 or R1 resection.

2.0 BACKGROUND

Pancreatic adenocarcinoma, even when presenting as resectable disease, remains a lethal malignancy. An estimated 10,000 persons (~20% of ~50,000 annual cases of pancreatic adenocarcinoma) each year in the United States will present with resectable disease. *(1,2)* While perioperative mortality for pancreatic cancer resection has declined considerably over the last few decades, to less than 2% in high-volume centers, overall survival remains largely unchanged. *(3,4)* This indicates that poor outcomes are largely attributable to recurrent/metastatic disease, and not surgical complications. To improve outcomes, adjuvant therapy has been evaluated and the current standard of care is surgical resection followed by adjuvant therapy, which usually consists of 5-fluorouracil or gemcitabine, with or without the addition of radiation. *(5,6)* However, median overall survival with best care standards remains less than 2 years. *(7)* A meta-analysis of all randomized controlled trials for the adjuvant treatment of resected pancreatic adenocarcinoma showed that chemotherapy with 5-fluorouracil or gemcitabine improves survival only modestly. *(8)* Therefore, there is an urgent need to improve systemic therapies.

Furthermore, now there is accumulating preclinical and clinical evidence that pancreatic cancer is a systemic disease from the outset. *(9,10)* Even in margin-positive resections, three-fourths of all patients with recurrence have systemic relapse. *(11)* Autopsy series have also shown that after surgical resection, most patients die of systemic disease. *(12,13)* All these data suggest that the administration of more effective systemic therapy may lead to improvement in clinical outcomes.

Until recently, systemic therapy options in pancreatic cancer were limited. Now, we have two multi-agent chemotherapy regimens that have demonstrated improved overall survival in metastatic pancreatic cancer. *(14,15)* Modified FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin) improves overall survival to 11.1 months, compared with 6.8 months with gemcitabine

alone (HR=0.57, p<0.001). *(16)* Toxicities were considerable; since then, more clinical experience with this regimen has accumulated, and the omission of 5-fluorouracil bolus and use of hematopoietic growth factor support has allowed mitigation of some of these toxicities without appreciable compromise of efficacy. *(17,18,19)* The other regimen is gemcitabine with nab-paclitaxel, which achieved a median overall survival of 8.5 months in patients with metastatic pancreatic cancer, compared with 6.7 months with gemcitabine alone (hazard ratio [HR]=0.72, p<0.001). *(20)* Toxicities were manageable, and considerable clinical experience with this regimen has accumulated. *(21)* In addition, the objective response rates with these regimens are impressive – up to 31.6% with mFOLFIRINOX. *(22)* It should be noted that mFOLFIRINOX was restricted to persons 75 years or younger. These regimens now provide us the opportunity to improve outcomes by testing them in the curative setting. Both these regimens remain attractive options; however there are no head-to-head comparisons of these two regimens in either advanced or localized pancreatic cancer, either ongoing or planned.

The appropriate setting in which to incorporate these regimens is the next question. While the timing of chemotherapy does not appear to influence survival outcomes – as evidenced by studies of preoperative and postoperative chemotherapy in resectable breast cancer, early stage lung cancer, and even oligo-metastatic colorectal cancer – the ability to administer aggressive adjuvant systemic therapy in pancreatic cancer is limited. Even standard single-agent gemcitabine and 5-fluorouracil carry toxicities. *(23,24)* Similar evidence exists in other cancers where major abdominal surgery is required for curative resection – in the MAGIC study of perioperative chemotherapy for esophagogastric cancers, While 91% of patients completed preoperative therapy, only 50% of patients undergoing resection were able to complete postoperative therapy. *(25)* Therefore, the preoperative setting should allow improved delivery of aggressive systemic therapy with the ultimate goal of improving survival outcomes. Prior studies (including the ongoing ACOSOG Z5041 study) of preoperative chemotherapy or chemoradiation have included less active regimens, but demonstrate feasibility of this approach. *(26,27)* Meta-analyses of smaller studies of preoperative therapy in resectable pancreatic cancer show approximately 75-90% of patients undergoing surgical resection. *(28,29)* In these studies, most patients dropped out due to progressive disease – as opposed to toxicities – which is likely attributable to less effective systemic therapies. Therefore, this test of effective multi-agent systemic chemotherapy in the preoperative setting is planned.

The preoperative setting will also allow drop-out of patients with occult micro-metastatic disease and poor performance status – these patients are unlikely to benefit from surgical resection and can be therefore spared unnecessary surgery. Furthermore, if the preoperative approach is shown to be feasible and to provide improvement in clinical outcomes, a head-to-head comparison of these two regimens will allow selection of the more promising regimen, which can then be tested against the current standard of care – surgery followed by adjuvant therapy – in a definitive study. A perioperative regimen can also be a platform for the addition of new agents such as targeted therapies. Finally, the preoperative platform allows testing of predictors of response to therapy, which are planned in a parallel translational study.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTICPLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1	1	0	3
Asian	2	3	1	0	6
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	7	7	0	0	14
White	56	60	4	5	125
More Than One Race	0	0	0	0	0
Total	67	72	6	5	150

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, all drugs are commercially available; therefore, Investigator Brochures are not applicable to this/these drug/s. Information about commercial drugs is publicly available in the prescribing information and other resources.

3.1 Fluorouracil (5-FU, Adrucil ®) (NSC-19893)

a. PHARMACOLOGY

Mechanism of Action: Fluorouracil is a pyrimidine analog antimetabolite that interferes with DNA and RNA synthesis in the S phase of cell division. After activation, the active metabolite F-UMP is incorporated into RNA to replace uracil and inhibit cell growth. The active metabolite, F-dUMP, inhibits thymidylate synthetase and depletes thymidine triphosphate.

b. PHARMACOKINETICS

Absorption: Rapid intravenous injection of fluorouracil results in high early levels of drug achieved both in plasma and bone marrow with a rapid fall afterwards. Prolonged infusions of fluorouracil show constant levels of the drug in plasma and significantly less in bone marrow.

1. Distribution: Fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver, third space fluids and other tissues. Fluorouracil diffuses

readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

2. Metabolism: Fluorouracil is primarily metabolized in the liver via dihydropyrimidine dehydrogenase (DPD) to the active metabolites 5-fluoroxyuridine monophosphate (F-UMP) and 5-5-fluoro-2'-deoxyuridine-5'-O-monophosphate (F-dUMP).

3. Elimination: The mean elimination half-life of fluorouracil from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. Seven to 20% of fluorouracil is excreted unchanged in the urine.

c. ADVERSE EFFECTS

1. Possible Side Effects of Fluorouracil:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Common (> 20%): alopecia, hand-foot syndrome, maculopapular rash, photosensitivity, pruritis, diarrhea, nausea, vomiting, anorexia, esophagopharyngitis, stomatitis, indigestion, headache

Less common (4 to ≤ 20%): angina, coronary arteriosclerosis, thrombophlebitis, gastrointestinal ulcer, bleeding, anemia, leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, cough, hoarseness, epistaxis, anaphylaxis, hypersensitivity reaction, confusion, nystagmus, visual changes, lacrimation, lacrimal duct stenosis, photophobia, dermatitis, acute cerebellar syndrome

Rare (≤ 3%): cardiotoxicity, secondary malignancy

2. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

3. Pregnancy and Lactation: Pregnancy Category D. Excretion in human breast milk is unknown and the manufacturer recommends against breastfeeding while receiving fluorouracil.

4. Drug Interactions: Fluorouracil is a strong inhibitor of CYP2C9. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including fluorouracil, should be screened prior to initiation of and during treatment with fluorouracil. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Fluorouracil is commercially available and drug will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.2 Gemcitabine hydrochloride (Gemzar®) (NSC-613327)

a. PHARMACOLOGY

Mechanism of Action: Gemcitabine (2'-Deoxy-2', 2'-difluorocytidine monohydrochloride), like cytarabine, is a nucleoside analog of deoxycytidine. This antimetabolite, a pyrimidine analog inhibiting both DNA and RNA viruses, is cell-cycle-specific in blocking the cells at the G1/S and is retained in human tumor cells for long periods. Studies suggest that gemcitabine is activated by deoxycytidine kinase. Deoxycytidine has been shown to reverse the growth inhibitory activity of gemcitabine.

b. PHARMACOKINETICS

1. Distribution: Gemcitabine plasma protein binding is negligible. The volume of distribution is increased with the infusion length. In a pharmacokinetics study of patients with various solid tumors, the volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions (70 to 285 minutes), the volume of distribution rose to 370 L/ m^2.

2. Metabolism: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. The gemcitabine di- and tri-phosphates do not appear to circulate in plasma in measurable amounts. Gemcitabine is metabolized by the liver to form the inactive uracil derivative, 2'-deoxy-2',2'-difluorouridine (dFdU). The inactive metabolite does not appear to accumulate with weekly dosing; however, it is excreted by the kidneys and may accumulate in patients with decreased renal function.

3. Elimination: Following a single 1,000 mg/m^2/30 min [^{14}C]-gemcitabine infusion, 92% to 98% of the dose was recovered within 1 week after gemcitabine administration. Urinary excretion of the parent drug and the dFdU metabolite accounted for 99% of the excreted dose, and less than 1% of the dose was excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

Clearance of gemcitabine is affected by age and gender and is lower in women and the elderly. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Studies showed that gemcitabine half-life for short infusions ranged from 42 to 94 minutes, for long infusions it varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The terminal phase half-life for the active metabolite, gemcitabine triphosphate, in mononuclear cells ranges from 1.7-19.4 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of gemcitabine:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in >20% to 100% of subjects treated with gemcitabine include: flu-like symptoms, nausea, vomiting, rash, alopecia,

infection, myelosuppressionincluding anemia, leukopenia, neutropenia, and thrombocytopenia, muscle weakness, hematuria, paresthesia, sensory neuropathy, fatigue, somnolence, hearing loss, peripheral edema.

Adverse effects reported in 4% to 20% of subjects include: diarrhea, constipation, stomatitis, dyspnea, capillary leak syndrome, posterior reversible encephalopathy syndrome (PRES).

Adverse effects reported in 3% or less of subjects include: arrhythmias, supraventricular arrhythmias, congestive heart failure, myocardial infarction, desquamation and bullous skin eruptions, gangrene, cerebrovascular accident, hepatic failure, adult respiratory distress syndrome (ARDS), anaphylaxis, renal failure, pulmonary fibrosis, pulmonary edema, and, Interstitial, pneumonitis.

2. Pregnancy and Lactation: Category D. Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of < 2 mg/m^2. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.

3. Drug Interactions: Per gemcitabine package insert, no formal drug interaction studies have been performed to date. When gemcitabine was administered with carboplatin or paclitaxel there was minimal or no effect on the pharmacokinetics of the studied drugs. .

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Gemcitabine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.3 Irinotecan (Camptosar®) (NSC-616348)

a. PHARMACOLOGY

Mechanism of Action: Irinotecan and its metabolite SN-38 inhibit topoisomerase I. Topoisomerase I relieves torsional strain in the DNA helix during replication and RNA transcription by inducing single-strand breaks. By binding with the topoisomerase I—DNA complex, irinotecan or SN-38 prevents the relegation of the single-strand breaks. Irreversible DNA damage occurs when a DNA replication fork encounters the irinotecan or SN-38/topoisomerase I complexes resulting in double-strand DNA breaks. Camptothecins are highly S-phase specific in their activity due the requirement of DNA synthesis.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Protein binding of irinotecan is 30-70%, whereas SN-38 shows a higher protein binding of 95%. Both irinotecan and SN-38 are primarily bound to albumin. Volume of distribution of irinotecan is approximately 110-234 L/m^2.

3. Metabolism: Irinotecan is metabolized primarily in the liver by carboxylesterase to SN-38, and via hepatic cytochrome P450 (CYP) 3A4 to aminopentane carboxylic acid (APC). SN-38 is conjugated to form a glucuronide metabolite by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1). Genetic polymorphisms exist in the enzyme UGT1A1, leading to different levels of exposure and toxicity among patients. In addition, both irinotecan and SN-38 undergo plasma hydrolysis between their active (lactone) and inactive forms (carboxylate). Finally, a small amount of irinotecan is metabolized by the intestinal wall.

4. Elimination: Approximately 10-25% of irinotecan is recovered unchanged in urine whereas only small amounts of SN-38 have been found. Clearance is approximately 13.5 L/hr/m^2. In addition, irinotecan has approximately 25% biliary excretion.

c. ADVERSE EFFECTS

1. Possible side effects of irinotecan:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in >20% to 100% of subjects treated with irinotecan include: diarrhea and cholinergic reaction (may be severe), constipation, nausea, vomiting, asthenia, infection, leukopenia, neutropenia, alopecia, anorexia, weight loss, anemia, fatigue, fever, pain, dizziness, cough, dyspnea, mucositis, rash, thrombocytopenia.

Adverse effects reported in 4% to 20% of subjects include: gastrointestinal perforation, hypersensitivity reaction, cardiovascular events, thromboembolic events, interstitial lung disease.

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether irinotecan or its derivatives are excreted in human milk.

3. Drug Interactions: Irinotecan and its active metabolite SN-38 may be substrates for CYP3A4, CYP2B6, OATP1B1/SCLO1B1, P-glycoprotein/ABCB1 and UGT1A1. Inducers or inhibitors may affect serum concentrations of irinotecan. Due to potential drug interactions, a complete patient medication list, including irinotecan, should be screened prior to initiation of and during treatment with irinotecan. Refer to the current FDA-approved package insert. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

Dosing – See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Irinotecan is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.4 Nab-paclitaxel (Abraxane®) (NSC-736631)

a. PHARMACOLOGY

Mechanism of action: Nab-paclitaxel for injectable suspension (paclitaxel protein-bound particles for injectable suspension) is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

NAB paclitaxel utilizes a receptor-mediated (gp60) pathway on microvessel endothelial cells to transport the albumin-paclitaxel complex out of the blood stream and into the tumor interstitium. In addition, studies have shown an albumin-binding protein, SPARC, is over-expressed in breast tumors and may play a role in the accumulation of NAB paclitaxel in breast cancer cells. It is suggested that once the albumin-paclitaxel complex is in the tumor interstitium, this complex would bind to the SPARC protein and would be rapidly internalized by the tumor cell.

b. PHARMACOKINETICS

1. Absorption: NA

2. Distribution: nab-paclitaxel is 94% bound to plasma proteins. The agent exhibits a very large volume of distribution at 1741L suggesting extensive extravascular distribution.

3. Metabolism: nab-paclitaxel is extensively metabolized by the CYP2C8 enzyme of the liver. Both major and minor metabolites are produced through this process.

4. Elimination: Only 4% of nab-paclitaxel is recovered in the urine unchanged, and 20% is found in feces. Mean total clearance of the agent is 13-30 L/hr/m^2 and mean terminal half-life is 13-27 hours.

c. ADVERSE EFFECTS

1. Possible side effects of Abraxane®: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Hematologic: Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2. In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m^2 given as a 30-minute infusion. Oral candidiasis,

respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE® arm and 1% of patients in the paclitaxel injection arm. Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm. Anemia (Hb < 11 g/dL) was observed in 33% of patients treated with ABRAXANE in the randomized trial and was severe (Hb < 8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs): In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of ABRAXANE® administration and consisted dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all < 1%). The use of ABRAXANE® in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied. During post marketing surveillance, rare occurrences of severe hypersensitivity reactions have been reported with ABRAXANE®. Patients who experience a severe hypersensitivity reaction to ABRAXANE® should not be rechallenged with the drug.

Cardiovascular: Hypotension, during the 30-minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia, during the 30-minute infusion, occurred in < 1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. Severe cardiovascular events possibly related to single-agent ABRAXANE® occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely. Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory: Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE® in the randomized trial. Rare reports (< 1%) of pneumothorax were reported after treatment with ABRAXANE®. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE® treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE® with concurrent radiotherapy.

Neurologic: The frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents. In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent ABRAXANE®. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE® arm and

in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with ABRAXANE® developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE® and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 2) was observed in either arm of the controlled trial. Cranial nerve palsies have been reported during post marketing surveillance of ABRAXANE®. Because these events have been reported during clinical practice, true estimates of frequency cannot be made and a causal relationship to the events has not been established. Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety. Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE® in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia: Forty-four percent of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE® administration, and resolved within a few days.
exhibits a very large volume of distribution at 1741L suggesting extensive extravascular distribution.

Metabolism: nab-paclitaxel is extensively metabolized by the CYP2C8 enzyme of the liver. Both major and minor metabolites are produced through this process.

Hepatic: Among patients with normal baseline liver function treated with ABRAXANE® in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE® and 10% of patients treated with paclitaxel injection in the randomized trial. Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE® treatment.

Renal: Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI): Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE® treated patients in the randomized trial. Rare reports of intestinal obstruction, intestinal

perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE® treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions have occurred infrequently with ABRAXANE® and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported rarely. Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia: Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE® in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

2. Pregnancy and Lactation:

Pregnancy Category D. ABRAXANE® can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats on gestation Days 7 to 17 at doses of 6 mg/m^2 (approximately 2% of the daily maximum recommended human dose on a mg/m2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m^2 (approximately 1% of the daily maximum recommended human dose on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE®. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with ABRAXANE®.

Nursing Mothers: It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving ABRAXANE® therapy.

3. Drug Interactions:

Paclitaxel is metabolized by hepatic cytochrome P450 (CYP) isoenzymes 2C8 and 3A4 and its metabolism could be affected by agents inhibiting these enzymes.

Due to potential drug interactions, a complete patient medication list, including Abraxane®, should be screened prior to initiation of and during treatment with Abraxane® See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Nab-paclitaxel is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.5 Oxaliplatin (Eloxatin®) (NSC-266046)

a. PHARMACOLOGY

Mechanism of Action: Oxaliplatin is a non-cell cycle specific, alkylating antineoplastic agent that inhibits DNA synthesis through the formation of crosslinks between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription.

b. PHARMACOKINETICS

1. Absorption: N/A

Distribution: At the end of a 2-hour infusion, approximately 15% of the administered oxaliplatin is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of oxaliplatin is irreversible and greater than 90%. The main binding proteins are albumin and gamma-globulins.

2. Metabolism: Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism *in vitro*. Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples from patients, including several cytotoxic species and a number of noncytotoxic, conjugated species.

3. Elimination: The major route of oxaliplatin elimination is renal excretion. At five days after a single 2-hour infusion, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Oxaliplatin was cleared from plasma at a rate (10 – 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultrafilterable oxaliplatin. The renal clearance of ultrafilterable oxaliplatin is significantly correlated with GFR.

c. ADVERSE EFFECTS

1. Possible Side Effects of Oxaliplatin:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Common (> 20%): anemia, diarrhea, nausea, vomiting, constipation, loss of appetite, fatigue, thrombocytopenia, leukopenia, neutropenia, neuropathy, paresthesia, pain, fever, cough

Less common (4 to ≤ 20%): thromboembolic event, cardiac arrhythmias, hearing loss, dry eye/mouth/skin, conjunctivitis, visual changes (including loss), ascites, gastroesophageal reflux disease, flatulence, nervous system disorders, edema, dyspnea, bleeding, gastrointestinal ulcers, pulmonary toxicity, stomatitis, chills, injection site reaction, abnormal liver function tests, hemolytic uremic syndrome, anaphylaxis, hypersensitivity, dehydration, dizziness, headache, dysgeusia, rigors, stroke, pharyngolaryngeal dysesthesia, myasthenia, seizure, anxiety, confusion, depression, urinary frequency, rhinitis, hiccups, sinus disorders, pulmonary fibrosis, alopecia, pruritis, rash, hives, diaphoresis, hypertension, hypotension.

Rare (≤ 3%): acute interstitial nephritis, hand-foot syndrome, reversible posterior encephalopathy syndrome

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether oxaliplatin or its derivatives are excreted in human milk.

3. Drug Interactions: No specific cytochrome P-450-based drug interaction studies have been conducted. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied. Refer to the current FDA-approved package insert.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Oxaliplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

4.0 STAGING CRITERIA

Pancreas Cancer Clinical Staging Criteria, AJCC 7th Edition, 2009

DEFINITION OF TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ*

T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery

* This also includes the “PanInIII” classification.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

M0 No distant metastasis

STAGE GROUPING

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14, 21 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have histologically or cytologically proven pancreatic adenocarcinoma. Histologies other than adenocarcinoma, or any mixed histologies, will NOT be eligible.

b. Patients must have measurable disease in the pancreas as defined in Section 10.1. CT scans or MRIs used to assess measurable disease must have been completed within 28 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

c. Patients must have resectable primary tumor based on contrast-enhanced CT or MRI (CT or MRI without contrast as part of PET/CT or PET/MRI is NOT acceptable; CT or MRI with contrast as part of PET/CT or PET/MRI is acceptable) of the chest, abdomen, and pelvis. The local interpreting radiologist must review the scans and sign the **S1505** Local Radiology Checklist prior to registration. Resectable is defined as:

1. No involvement of the celiac artery, common hepatic artery, and superior mesenteric artery (and, if present, replaced right hepatic artery).

2. No involvement, or < 180° interface between tumor and vessel wall, of the portal vein and/or superior mesenteric vein; and patent portal vein/splenic vein confluence.

3. No evidence of metastatic disease. Lymphadenopathy (defined as nodes measuring > 1cm in short axis) outside the surgical basin (i.e., para-aortic, peri-caval, celiac axis, or distant nodes) is considered M1 disease and makes the patient ineligible. If, however, such nodes are biopsied and are negative, then enrollment can be considered after review with the study chairs.

NOTE: For tumors of the body and tail of the pancreas, involvement of the splenic artery and vein of any degree is considered resectable disease.

d. CT scans or MRIs used to assess disease at baseline must be submitted for central review (see Section 15.1).

e. Patients must have surgical consult to verify patient is a surgical candidate within 21 days prior to registration.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must not have received prior surgery, radiation therapy, chemotherapy, targeted therapy, or any investigational therapy for pancreatic cancer.

5.3 Clinical/Laboratory Criteria

a. Patients must have a Zubrod Performance Status of 0-1 (see Section 10.5).

b. Patients must be ≥ 18 and ≤ 75 years old.

c. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to registration: ANC ≥ 1,500/mcL; platelets ≥ 100,000/mcL; and hemoglobin ≥ 9 g/dL.

d. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to registration: total bilirubin ≤ 1.5 x Institutional Upper Limit of Normal (IULN); AST and ALT both ≤ 2.5 x IULN; and serum albumin ≥ 3 g/dL.

e. Patients must have adequate kidney function as evidenced by serum creatinine ≤ IULN within 14 days prior to registration.

f. Patients with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements will NOT be eligible.

g. No prior malignancy is allowed except for adequately treated basal (or squamous cell) skin cancer, *in situ* cervical cancer, *in situ* breast (ductal or lobular) cancer, or other cancer for which the patient has been disease and treatment-free for two years.

h. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Women/men of reproductive potential must have agreed to use an effective contraceptive method for up to 3 months after the final administered dose of chemotherapy. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

i. CA19-9 must be performed within 14 days prior to registration.

j. Prestudy history and physical must be obtained within 28 days prior to registration.

5.4 Specimen Submission Criteria

a. Sites must seek additional patient consent for the future use of specimens as described in Section 15.2.

5.5 Regulatory Criteria

a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.2 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be stratified according to Zubrod Performance Status: 0 vs. 1.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Sohal at 216/444-8258 or Dr. Ahmad at 513/558-7866. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication and Concomitant Medications and Care

a. Pre-Medication and Concomitant Medications

Pre-medications and concomitant medicines will be administered to counter the expected common side-effects of chemotherapy. These may include anti-emetic, anti-allergy, and anti-diarrheal medicine. These will be ordered by the treating physician per institutional standards and tailored to the patient's condition.

Appropriate anti-emetics include, but are not limited to, corticosteroids, 5-HT3 antagonists (ondansetron, palonosetron), and NK1 antagonists (aprepitant, fosaprepitant). Further intravenous medicines and fluids may also be used per the treating physician's recommendations. Oral medicines can be prescribed for use at home, as deemed appropriate by the treating physician. These may include anti-emetics, analgesics, anti-pyretics, anti-diarrheals, pancreatic enzyme supplements, appetite stimulants, antacids, H2-blockers, proton pump inhibitors, anxiolytics, anti-depressants, sleep aids, and other common medicines as needed. Referral to health care providers from other specialties, such as palliative medicine, nutrition, psychology, psychiatry, home care services, etc., may be made as needed per the patient's clinical situation.

b. Management of Biliary Obstruction

Patients with biliary obstruction, either at baseline or during the study period, may continue on the protocol treatment as long as all parameters for treatment are met. Biliary obstruction may be managed by biliary stents or drains per treating physician's discretion.

7.2 Arm 1: mFOLFIRINOX

Patients on Arm 1: mFOLFIRINOX will receive 3 cycles of the following treatment, surgery, and 3 additional cycles of the following treatment:

Agent	Dose	Route	Day	Schedule*
Oxaliplatin	85 mg/m^2	IV over 2 hours	1, 15	Prior to irinotecan
Irinotecan	180 mg/m^2	IV over 1.5 hours	1, 15	Following oxaliplatin
5-FU	2,400 mg/m^2	IV over 46 hours	1-3, 15-17	Following oxaliplatin and irinotecan

* Note: One cycle = 28 days
** 5-fluorouracil will be administered as a continuous intravenous infusion delivered by an infusion pump via a central venous infusion port placed subcutaneously. The specific chemotherapy port and infusion pump to be used are at the discretion of the treating physician.

Following the initial 3 cycles of mFOLFIRINOX treatment, patients will undergo restaging by contrast-enhanced CT or MRI. Patients with stable disease or better will undergo surgery for resection 4 to 8 weeks following completion of initial chemotherapy (see Section 7.4). Within 4 to 8 weeks following resection, patients will begin an additional 3 cycles of mFOLFIRINOX treatment.

7.3 Arm 2: Gemcitabine/nab-Paclitaxel

Patients on Arm 2: Gemcitabine/nab-Paclitaxel will receive 3 cycles of the following treatment, surgery, and an additional 3 cycles of the following treatments:

AGENT	DOSE	ROUTE	DAY	SCHEDULE*
nab-Paclitaxel	125 mg/m^2	IV over 30 min	1, 8, 15	Prior to gemcitabine
Gemcitabine	1,000 mg/m^2	IV over 30 min	1, 8, 15	Following nab-paclitaxel

* Note: One cycle = 28 days
** A central venous infusion port placed subcutaneously for the delivery of chemotherapy is allowed, but not required, in Arm 2.

Following the initial 3 cycles of gemcitabine/nab-paclitaxel treatment, patients will undergo restaging by CT or MRI. Patients with stable disease or better will undergo surgery for resection 4 to 8 weeks following completion of initial chemotherapy (see Section 7.4). Within 4 to 8 weeks following resection, patients will begin an additional 3 cycles of gemcitabine/nab-paclitaxel treatment.

7.4 Surgery

a. General Considerations

Pancreatectomy should occur within 4 to 8 weeks after the last dose of Cycle 3 preoperative chemotherapy. Staging laparoscopy may be performed at the time of planned laparotomy but is not required. Either standard or pylorus-preserving pancreaticoduodenectomy, distal subtotal pancreatectomy, or total pancreatectomy may be performed. Surgical drains and enteral tubes (e.g. gastrostomy and/or jejunostomy tubes) may be placed at the discretion of the operating surgeon.

Patients who are unable to complete 3 cycles of chemotherapy prior to surgery may continue to surgery, if patient is still resectable and a surgical candidate. Patient will then receive Cycles 4-6 with appropriate dose modification.

b. Specific Considerations

Exploration of the peritoneal cavity should include evaluation for radiologically occult macroscopic peritoneal or hepatic metastases. Biopsy proof of liver or peritoneal metastatic disease (by frozen section assessment) should be considered criteria for abandoning planned pancreatectomy.

Lymph node sampling or frozen section lymph node biopsy is not required or recommended as part of the intraoperative assessment for extra-pancreatic disease, and is at the discretion of the surgeon.

For patients undergoing pancreaticoduodenectomy, the retroperitoneal dissection along the medial edge of the uncinate process and the right lateral border of the superior mesenteric artery is believed to be an important oncologic part of the operation. All soft tissue to the right of the superior mesenteric artery (SMA) should be removed. This requires exposure and dissection along the right lateral border of the SMA.

Vascular resection and/or reconstruction of the superior mesenteric vein, portal vein, SMV/ Portal vein confluence, or hepatic artery will be done at the discretion of the operating surgeon. In general, vascular resection should be performed when necessary to achieve a R0 resection. This reconstruction can be performed by the operating surgeon or a vascular surgeon consult. The details of this operation should be delineated in the operative report.

c. Intraoperative Frozen Section Assessment of Surgical Margins

Frozen section evaluation of the pancreatic parenchymal should be performed. When a pancreaticoduodenectomy is performed, frozen section of the hepatic (or bile) duct margins should also be performed. In the event of a positive frozen section margin at either of these loci, further resection in an effort to achieve microscopically negative margins should be performed if possible. For patients undergoing pancreaticoduodenectomy, the superior mesenteric arterial (SMA) margin should be evaluated on permanent section only.

d. Specimen Orientation for Surgical Pathology

The surgeon should ensure that the specimen is oriented for the surgical pathologist. Any segment of resected vascular structure (e.g. superior mesenteric or portal vein) should be identified and marked. Relevant margins evaluated by intraoperative frozen section (i.e. the hepatic (bile) duct, and pancreatic parenchymal) should be identified. The SMA margin (the soft tissue immediately adjacent to the SMA) should be separately inked using the principles outlined in the 2009 AJCC staging system for exocrine pancreatic cancer.

Note: The SMA margin cannot be identified accurately after the specimen has been fixed in formalin or after the specimen has been dissected for histopathologic analysis.

e. Operative Note Dictation and Editing: Resection Classification

The attending surgeon should dictate the operative note. The operative report should contain:

1. A section detailing the operative findings with respect to the extent of disease and the primary tumor anatomy

2. A statement as to whether or not the surgeon believes there is residual macroscopic tumor.

The surgeon should integrate the operative findings with the microscopic surgical margins reported on the final pathology report in order to assign a resection classification prefix of R0, R1, or R2 (see Section 10.2). Whenever possible, this prefix should be added to the final operative note before finalizing the document. An example of the final procedure description for a patient who underwent macroscopically complete tumor removal with a positive SMA margin on permanent section final pathology is: "R1 pylorus-preserving pancreaticoduodenectomy."

f. Surgical Pathology

Pathological examination of the resected pancreatic tumor specimen should be carried out by a local pathologist experienced in the diagnosis of pancreatic adenocarcinoma.

For pancreaticoduodenectomies, three primary margins (bile duct, pancreatic neck, and SMA) should be identified and inked by the surgeon and/or pathologist. Any segment of resected vascular structure (e.g. superior mesenteric or portal vein) should be identified and marked. The SMA margin (that tissue immediately adjacent to the SMA) should be separately inked according to the procedures and recommendations of the American Joint Commission on Cancer 7th edition staging system and the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). The tumor should be thoroughly sampled (at least one section per 1 cm of greatest tumor dimension, taken perpendicular to the inked SMA margin). The distance between the closed tumor cell and the inked SMA margin should be reported.

1. Frozen Section Assessment of Margins

   Section assessment of bile duct and pancreatic neck margins should be performed by the local pathologist in all cases as requested by the surgeon

2. Permanent Section Assessments and Final Pathology Report

   The pathology report should contain all of the elements outlined in the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). In particular, there should be specific comment on:
   - Histologic diagnosis with comment on the cell of origin (pancreatic vs. bile duct vs. ampulla)
   - Degree of differentiation (well, moderate, poor)
   - Total number of lymph nodes examined
   - Number of positive nodes
   - Final margins status for the bile duct, pancreatic parenchymal, and SMA margin
   - Distance (in mm) from the tumor to the inked SMA margin
   - Extent of tumor infiltration (if present) of the blood vessel wall for any resected major blood vessels
   - Tumor Regression Grade (see Section 10.6)

g. Patients with Residual Gross Disease (R2 Resections)

In cases where the surgeon documents the presence of residual gross disease, the patient will be taken off protocol treatment.

h. Surgical Quality Assurance

See Section 12.2 for information.

i. Credentialing

This study will not require formal credentialing of the operating surgeon. This study is designed for centers skilled at the multidisciplinary management of pancreas cancer. Ideally, centers should perform more than 12 pancreaticoduodenectomies per year.

7.5 Radiation

Radiation is not allowed during protocol treatment.

7.6 Criteria for Removal from Protocol Treatment

a. Completion of 3 cycles of post-surgical resection chemotherapy.

b. Distant progression of disease prior to surgery, disease recurrence after surgery, or symptomatic deterioration (as defined in Section 10.3e).

c. Unacceptable toxicity.

d. Inability to undergo R0 or R1 surgical resection.

e. Treatment delay for any reason > 4 weeks except protocol-defined perioperative treatment delays (see Section 7.2 and 7.3).

f. Post-surgery chemotherapy delayed > 12 weeks from surgery.

g. The patient may withdraw from the study at any time for any reason.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow-Up Period

All patients will be followed until death or four years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

For chemotherapy doses that are held due to toxicities, they will not be "added at the end". The patient will continue subsequent doses per study calendar. For example, if Day 15 of Cycle 1 of gemcitabine/nab-paclitaxel is held, the next dose will be 14 days later, on Day 1 of Cycle 2, and will be counted as such.

The use of marrow growth factors (including, but not limited to, filgrastim, pegfilgrastim) is not allowed at the outset. They can be used in case of neutropenia, per dose modification guidelines in Section 8.3.

For post-operative chemotherapy, doses for Cycle 4 will resume at the levels for the final pre-operative dose, and NOT at initial dose levels. In addition, residual toxicities from pre-operative chemotherapy will be considered. For example, if a patient continues to have a Grade 2 toxicity, such as neuropathy or fatigue, Cycle 4 Day 1 drugs and doses will be modified/held accordingly.

8.3 Dose Modifications for Arm 1: mFOLFIRINOX

a. Dose Modifications

Drug	Initial dose	Dose Reduction Level 1	Dose Reduction Level 2
5-FU	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2
Irinotecan	180 mg/m^2	135 mg/m^2	90 mg/m^2
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2

NOTE: Patients who require dose reductions below values listed will be removed from protocol treatment.

b. Neutrophil Count Decreased

For Grade 2 or higher neutropenia, hold treatment for up to two weeks until recovery to at least Grade 1. If patient has not recovered to ≤ Grade 1 in two weeks, discontinue treatment. Follow drug specific modifications below for subsequent cycles. In addition, it is recommended that pegfilgrastim, 6 mg subcutaneously, be administered with each subsequent dose, on the day of 5-FU pump discontinuation.

Toxicity Grade	Modification: 5-FU	Irinotecan	Oxaliplatin
2	Maintain dose	Maintain dose	Maintain dose
3-4	Maintain dose	1st occurrence: Reduce by 1 dose level	1st occurrence: Maintain dose
		2nd occurrence: Reduce by 1 Dose level	2nd occurrence: Reduce by 1 dose level
		3rd occurrence: Discontinue treatment	3rd occurrence: Discontinue treatment

c. Platelet Count Decreased

For Grade 2 or higher thrombocytopenia, hold treatment for up to two weeks until recovery to at least Grade 1. If patient has not recovered to ≤ Grade 1 in two weeks, discontinue treatment. Follow drug specific modifications below for subsequent cycles.

Toxicity Grade	Modification: 5-FU	Irinotecan	Oxaliplatin
2	Maintain dose	Maintain dose	Maintain dose
3-4	1st occurrence: Reduce by 1 dose level	1st occurrence: Maintain dose	1st occurrence: Reduce by 1 dose level
	2nd occurrence: Reduce by 1 dose level	2nd occurrence: Reduce by 1 dose level	2nd occurrence: Reduce by 1 dose level
	3rd occurrence: Discontinue treatment	3rd occurrence: Discontinue treatment	3rd occurrence: Discontinue treatment

d. Diarrhea

Patients should be instructed in the use of loperamide as treatment for diarrhea. Patient should not be retreated with irinotecan until recovery from diarrhea has occurred.

Toxicity Grade	Modification
3-4	1st occurrence: Reduce irinotecan by 1 dose level and 5-FU dose by 1 dose level. 2nd occurrence: Reduce irinotecan by 1 dose level, oxaliplatin dose by 1 dose level, and 5-FU dose by 1 dose level. 3rd occurrence: Discontinue all protocol treatment

e. Mucositis

Toxicity Grade	Modification	
	Oxaliplatin	5-FU
2	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.
3-4	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.

f. Paresthesia or Peripheral Sensory Neuropathy – Dose modifications for oxaliplatin only

Toxicity Grade	Duration of Toxicity 1 – 7 days	> 7 days	Persistent between cycles
2	No dose modification	No dose modification	Next lowest dose level for oxaliplatin
3	Next lowest dose level for oxaliplatin	Next lowest dose level for oxaliplatin	Discontinue
Peripheral Sensory Neuropathy Grade 4	Discontinue	Discontinue	Discontinue

g. Hand-Foot Skin Reaction

Toxicity Grade	Modification:
3-4	Reduce 5-FU by 1 dose level

h. Other non-hematologic toxicities

All treatment related non-hematological toxicities (with the exception of hair loss) should resolve to Grade 1 prior to starting next cycle of therapy.

Toxicity Grade	Modification: 5-FU, Irinotecan, and Oxaliplatin
3	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level.
4	Discontinue all protocol treatment

8.4 Dose Modifications for Arm 2: Gemcitabine/nab-Paclitaxel

a. Dose Modifications

Drug	Initial dose	Dose Reduction Level 1	Dose Reduction Level 2
Gemcitabine	1000 mg/m^2	800 mg/m^2	650 mg/m^2
nab-Paclitaxel	125 mg/m^2	100 mg/m^2	80 mg/m^2

NOTE: Patients who require dose reductions below the values listed will be removed from protocol treatment.

b. Neutrophil Count Decreased

For Grade 2 or higher neutropenia, hold treatment for up to two weeks until recovery to at least Grade 1. If patient has not recovered to ≤ Grade 1 in two weeks, discontinue treatment. Follow drug specific modifications below for

subsequent cycles. In addition, it is recommended that pegfilgrastim, 6 mg subcutaneously, be administered with each subsequent Day 15 dose of gemcitabine/nab-paclitaxel.

Toxicity Grade	Modification	
	Gemcitabine	nab-Paclitaxel
2	Maintain Dose	Maintain dose
3-4	1st occurrence reduce dose by 1 level. 2nd occurrence reduce dose by 1 level. 3rd occurrence discontinue	1st occurrence reduce dose by1 level. 2nd occurrence reduce dose by 1 level. 3rd occurrence discontinue

c. Platelet Count Decreased

For Grade 2 or higher thrombocytopenia, hold treatment for up to two weeks until recovery to at least Grade 1. If patient has not recovered to ≤ Grade 1 in two weeks, discontinue treatment. Follow drug specific modifications below for subsequent cycles.

Toxicity Grade	Modification	
	Gemcitabine	nab-Paclitaxel
2	Maintain dose	Maintain dose
3-4	1st occurrence reduce dose by 1 level. 2nd occurrence reduce dose by 1 level. 3rd occurrence discontinue	1st occurrence reduce dose by 1 level. 2nd occurrence reduce dose by 1 level. 3rd occurrence discontinue

d. Peripheral Sensory Neuropathy – Dose modifications for nab-Paclitaxel only

Toxicity Grade	Duration of Toxicity 1 – 7 days	> 7 days	Persistent between cycles
2	No dose modification	No dose modification	Next lowest dose level for nab-paclitaxel
3	Next lowest dose level for nab-paclitaxel	Next lowest dose level for nab-paclitaxel	Discontinue
Peripheral Sensory Neuropathy Grade 4	Discontinue	Discontinue	Discontinue

e. Non-hematologic toxicities

All treatment related non-hematological toxicities (with the exception of hair loss) should resolve to ≤ Grade 1 prior to starting next cycle of therapy.

Toxicity Grade	Modification: Gemcitabine, nab-Paclitaxel.
3	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level.
4	Discontinue all protocol treatment

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Sohal at 216/444-8258 or Dr. Ahmad at 513/558-7866, or Dr. Philip at 313/576-8728.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm 1: mFOLFIRINOX

REQUIRED STUDIES	Pre-study	Cycle 1		Cycle 2		Cycle 3		F/U after Chemo-Re-staging	Surgery	Cycle 4		Cycle 5		Cycle 6		F/U prior to prog or recur-rence	F/U after prog or recur-rence
		D 1	D 15	D 1	D 15	D 1	D 15			D 1 £	D 15	D 1	D 15	D 1	D 15		
PHYSICAL																	
H&P Exam ⌂	X	X	X	X	X	X	X	X Ω		X	X	X	X	X	X	X	X
Weight and Performance Status ⌂	X	X	X	X	X	X	X	X Ω		X	X	X	X	X	X		
Toxicity Assessment ⌂			X	X	X	X	X	X Ω			X	X	X	X	X		
Surgical Complications Ə										X Ə							
LABORATORY																	
CBC † ⌂	X	X	X	X	X	X	X	X Ω		X	X	X	X	X	X		
Comprehensive Metabolic Panel δ	X							X Ω									
CA19-9	X							X Ω								X	
AST and ALT	X							X Ω									
Serum albumin	X							X Ω									
Serum creatinine	X							X Ω									
SCANS																	
CT or MRI for disease assessment ¿	X ʐ							X Ω								X ∑	
SPECIMEN SUBMISSION																	
Tissue from surgical resection √									X								
TREATMENT																	
Oxaliplatin		X	X	X	X	X	X			X	X	X	X	X	X		
Irinotecan		X	X	X	X	X	X			X	X	X	X	X	X		
5-FU §		X	X	X	X	X	X			X	X	X	X	X	X		
Surgery									X µ								

Note: 1 cycle = 28 days.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20upddate.pdf.

Click here for footnotes:

9.2 Arm 2: Gemcitabine/nab-Paclitaxel

REQUIRED STUDIES	PRESTUDY	Cycle 1			Cycle 2			Cycle 3			F/U after Chemo/ Restaging	Surgery	Cycle 4 4 £			Cycle 5			Cycle 6			F/U prior to prog or recur	F/U after prog or recur
		D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15			D 1	D 8	D 15	D 1	D 8	D 15	D 1	D 8	D 15		
PHYSICAL																							
History & Physical Exam ⌂	X	X		X	X		X	X		X	X Ω		X		X	X		X	X		X	X	X
Wt; Perform. Status ⌂	X	X		X	X		X	X		X	X Ω		X		X	X		X	X		X		
Toxicity Assessment ⌂				X	X		X	X		X	X Ω				X	X		X	X		X		
Surgical Complications Ə													X Ə										
LABORATORY																							
CBC † *	X	X	X	X	X	X	X	X	X	X	X Ω		X	X	X	X	X	X	X	X	X		
Comprehensive Metabolic Panel δ	X										X Ω												
CA19-9	X										X Ω											X	
AST & ALT	X										X Ω												
Serum albumin	X										X Ω												
Serum creatinine	X										X Ω												
SCANS																							
CT or MRI for disease assessment ¿	X ʒ										X Ω											X ∑	
SPECIMEN SUBMISSION																							
Tissue from surgical resection √												X											
TREATMENT																							
nab-Paclitaxel ◊		X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
Gemcitabine hydrochloride ◊		X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		
Surgery												X µ											

Note: 1 cycle = 28 days

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20upddate.pdf.

Click here for footnotes:

Footnotes for Arm 1 and Arm 2 Calendars:

α Follow-up performed every 3 months for Year 1, every 6 months for Years 2 and 3, then annually until four years from registration.
† Hemoglobin, WBC, platelet count, and ANC.
δ Sodium, potassium, bicarbonate, chloride, BUN, calcium, total protein, total bilirubin, and alkaline phosphatase.
Ω Within 2-4 weeks following last dose of chemotherapy in Cycle 3.
µ Within 4-8 weeks following last dose of chemotherapy in Cycle 3.
£ Cycle 4 chemotherapy should start within 4-8 weeks following surgery. If patient is unable to begin chemotherapy within 12 weeks after resection, patient must be taken off protocol treatment.
√ See Section 15.2 for information.
ʒ Submit scans as outlined in Section 14.0 and Section 15.0.
Θ Assess for surgical complications at this visit.
§ 5-FU treatment will occur on Days 1-3 and 15-17 of each cycle.
¿ CT or MRI must include chest, abdomen, and pelvis. Restaging scans must be done within 4 weeks following last dose of chemotherapy (whether chemotherapy was completed or not).
∑ The first scan following completion of Cycle 6 must be performed within 2 weeks.
⌂ Assessment must be performed on Days 1 and 15 of each cycle. For Cycle 1, assessment does not need to be performed on Day 1.
◊ Treatment on Days 1, 8, and 15 of each cycle. No treatment on Day 22 (see Section 7.3).
* CBC must be performed on Day 1, 8, and 15 of each cycle of treatment for patients on Arm 2.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

This study will use the RECIST 1.1 guidelines. *(30)*

10.1 Measurability of Lesions

a. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

b. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

c. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

d. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. 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.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 The definitions for the resection classification that should be utilized in operative notes include:

- R0 – macroscopically complete tumor removal with negative microscopic surgical margins (bile duct, pancreatic parenchyma, and SMA margins)
- R1 – macroscopically complete tumor removal with any positive microscopic surgical margin (bile duct, pancreatic parenchyma, or SMA margins)
- R2 – macroscopically *incomplete* tumor removal with known or suspected residual gross disease

10.3 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. 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. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site.

Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.3e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute

unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.4 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.5 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
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.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.6 Pathologic Response

Pathologic response will be evaluated after the patient has had surgery, and will be based on local pathology review of the resected surgical specimen, according to the following (Treatment effect per College of American Pathology Protocol for the Examination of Specimens From Patients With Carcinoma of the Exocrine Pancreas):

Tumor Regression Grade:

0: Complete response – no residual tumor
1: Moderate response – minimal residual cancer (single cells or small groups of cancer cells)
2: Minimal response – residual cancer outgrown by fibrosis
3: Poor or no response – no definite response identified (minimal or no tumor kill; extensive residual cancer)

10.7 Loco-regional recurrence

Any evidence of new disease within the pancreatic tumor bed based on surveillance scans. The pancreatic tumor bed includes:

a. Superior mesenteric artery and vein lymph nodes

b. Lymph nodes in porta hepatis (bile duct, portal vein, hepatic artery lymph nodes)

c. Lymph nodes around left renal vein, inferior vena cava or aorta

d. Celiac axis lymph nodes

10.8 Distant recurrence

Any evidence of new disease outside the primary tumor bed (liver, lungs, etc.) based on surveillance scans.

10.9 Disease-Free Survival (DFS)

DFS is calculated for patients who undergo surgical resection (R0/R1). DFS will be measured from the date of surgical resection to date of first documentation of recurrence (loco-regional or distant) or death due to any cause. Patients last known to be alive and free of disease will be censored at date of last contact.

10.10 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goals

Prior to temporary closure, the study was accruing approximately 6 patients per month. Allowing for an approximately 33% rate of ineligibility, we will accrue a total of 150 patients to have 100 eligible patients, and thus expect an additional 12 months of accrual.

11.2 Primary Analysis and Power Justification

SWOG will use a randomized Phase II "pick the winner" study design, with minimum activity requirements, to address the objective of choosing a chemotherapy regimen for further study in resectable pancreatic adenocarcinoma, since preoperative chemotherapy is not well-studied in this population. The goal of this design is to pick the best treatment regimen to carry forward into a Phase III trial in which the chosen regimen will be compared to the current standard approach of adjuvant chemotherapy only. Patients will be randomly assigned in equal proportions to the two treatment regimens. For each arm, the observed 2-year overall survival (OS) will first be compared to the null hypothesis of 40%, assuming a 58% alternative hypothesis, 88% power, and a 1-sided significance of 0.05. If rates in both arms meet this threshold, then a sample size of 100 patients (50 per arm) provides a 90% probability of selecting the better regimen with an OS hazard ratio of at least 1.4. OS will be assessed in all eligible patients according to the intent-to-treat principle. If only a single arm meets the 2-year OS threshold as described above, then that arm will be chosen to move forward; if neither arm meets this threshold then the overall approach will be reconsidered.

11.3 Interim Analysis

Given the lack of data on peri-operative chemotherapy, we do not have a dependable estimate of the rate of resection in this setting. There are several small, single-institution phase II studies using various chemotherapy agents (usually gemcitabine or 5-fluorouracil, with or without cisplatin) with or without radiation. These studies, and meta-analyses of these studies, indicate that 57-74% of patients with initially resectable cancer are able to undergo surgical resection. *(31,32,33,34)* With our aggressive chemotherapy regimens, patients experiencing toxicity that prevents them from undergoing resection is a safety concern. From the pivotal studies of these regimens, it is known that Grade 3 or higher toxicities are common – hematologic toxicities, fatigue, nausea, vomiting, and diarrhea being seen in 10-40% of cases. *(35,36)* Our best guess, therefore, is a 10% rate of failure to reach resection due to toxicities from preoperative chemotherapy. The study will be suspended pending further review if there is sufficient evidence to suggest that the true probability of failing to reach surgery due to toxicity from preoperative chemotherapy exceeds 10% in the combined study cohort.

Sufficient evidence will be taken to be an observed failure rate whose lower one-sided 90% confidence limit exceeds the threshold. Of the first 45 evaluable patients, 3 (7%) failed to reach surgery due to toxicity from preoperative chemotherapy. The observed failure rates will be examined again after the 80th enrolled patient becomes evaluable. Operationally, these limits will be met if 17 failures in 80 patients are observed. Based on 5,000 simulated datasets, and given a true failure rate of 5%, study suspension would occur with probability of less than 1%. Given a true failure rate of 25%, the probability of study suspension is 98% after 80 patients.

Furthermore, we will evaluate various subsets of patients based on outcomes. There may be a subset of patients who go to surgery but are found to have unresectable or metastatic disease intra-operatively. This is due to the inability of even the best cross-sectional imaging modalities (CT and MRI) to detect occult peritoneal or hepatic metastases. Data on such patients are poor – from historical series, this number is expected to be at least around 10%. (37,38*)* Another subset of patients may experience progression of disease during preoperative chemotherapy. This will be duly noted but is not a safety concern. In fact, an important advantage of this approach is identification of aggressive biology that is not responsive to the best current systemic chemotherapy regimens. These patients are unlikely to benefit – and may even be harmed – by surgical resection. We estimate ~20% of patients experiencing disease progression, based on the pivotal studies of these regimens. *(39,40)* Therefore, 1 in 3 patients may not be able to undergo surgical resection.

11.4 Other Analyses

Secondary endpoints will include overall resection rate, R0 resection rate, pathological response rates, patterns of recurrence, disease-free survival (DFS), overall response rate per RECIST 1.1, and toxicity.

With 50 patients, rates of resection and response can be estimated to within 14% (95% confidence interval). It is assumed that R0 resection and pathological response has not been achieved for patients who do not receive surgery or for whom a surgical specimen is lacking. These patients will be included in the denominator.

Patients who undergo surgical resection (R0/R1) will be included in analyses of patterns of recurrence and DFS. Both locoregional (in the pancreatic bed) and distant (liver, lungs, etc.) recurrence rates will be estimated in each arm. If we assume 85% of patients (n=43 in each arm) will reach resection, recurrence rates can be estimated to within 15% (95% confidence interval). Distributions of DFS in each arm will be estimated using the method of Kaplan-Meier.

Patients receiving at least one dose of drug will be included in the assessment of adverse events by treatment arm. Adverse event monitoring is conducted by the study coordinators, disease committee chair, Adverse Event Coordinator and study statistician on an ongoing basis, with notification to the DSMC and CTEP should any concerns arise. Any events reported through the CTEP-AERS system are reported immediately, and reports are sent to the above group for all other AEs on a monthly basis. Fifty eligible patients in each arm are sufficient to estimate the probability of a particular toxicity to within 14% (95% confidence interval). Any toxicity occurring with at least a 6% probability is likely (95% chance) to be seen at least once.

11.5 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

12.1 Central Imaging Review

Central imaging review will be performed by Dr. Namita Gandhi on baseline CT or MRI for all patients to confirm resectability for eligibility. See Section 15.1 for submission guidelines.

12.2 Surgical Review and Quality Assurance

All surgeries performed as part of this study will undergo a central review. The goal of this review is to verify that the resection was done according to the criteria specified in the protocol (Section 7.4). The surgical quality monitoring will be completed by the Surgical Study Chair (Dr. Syed Ahmad) within 30 days after surgery. Surgical data including operative notes and pathology reports will be reviewed. Any deviations in surgical quality that are identified will be addressed by the study chairs, Drs. Sohal and Ahmad.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing
Patients must be registered prior to initiation of treatment (no more than three working days prior to planned start of treatment).

13.2 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

- Institution CTEP ID
- Protocol Number
- Registration Step
- Treating Investigator
- Credit Investigator
- Patient Initials
- Patient's Date of Birth
- Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)
- Country of Residence
- ZIP Code
- Gender (select one):
    - Female Gender
    - Male Gender
- Ethnicity (select one):
    - Hispanic or Latino
    - Not Hispanic or Latino
- Unknown

a. Method of Payment (select one):

- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)

- Other
- Unknown

b. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.3 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

a. Prior to accessing OPEN site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

b. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.

- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

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

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

13.4 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.

2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1505 Onstudy Form

Baseline Tumor Assessment Form (RECIST 1.1)

Pathology Report *

S1505 Local Radiology Review Checklist

Radiology reports from all scans performed to assess disease at baseline. *

Images from scans performed to assess disease at baseline as specified in Section 15.1. Submit via TRIAD for Central Imaging Review.

*(NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.)

b. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT

Submit the following:

S1505 Treatment Summary Form

S1505 Adverse Event Summary Form

c. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (both pre-operative re-staging and post-operative surveillance scans):

Submit the following:

Follow Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease. (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®.)

d. WITHIN 14 DAYS AFTER PROTOCOL SURGERY:

Submit the following:

S1505 Surgical Summary Form

Operative report (NOTE: Upload reports via the Source Documentation: Surgery form in Rave®.)

Pathology report corresponding to the surgical specimen (NOTE: Upload reports via the Source Documentation: Surgery form in Rave®.)

Tissue from protocol surgery as specified in Section 15.2

e. AFTER PROTOCOL SURGERY AND PRIOR TO POST-OPERATIVE TREATMENT:

Submit the **S1505** Surgical Adverse Event Summary Form

f. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1505 Treatment Form

S1505 Adverse Event Form

If patient went off protocol treatment prior to surgery, also submit the **S1505** Surgical Summary Form

g. WITHIN 14 DAYS OF PROGRESSION/RECURRENCE:

Follow Up Tumor Assessment Form (RECIST 1.1) documenting date, site and method for determining progression/recurrence.

Radiology reports from all scans performed to assess disease. (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®.)

h. AFTER OFF TREATMENT, EVERY 3 MONTHS FOR THE FIRST YEAR, EVERY 6 MONTHS FOR THE SECOND AND THIRD YEARS, THEN ANNUALLY UNTIL 4 YEARS FROM REGISTRATION
Submit the following:

S1505 Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported)

i. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information. In addition, if the patient was still on protocol treatment, submit materials specified in Section 14.4b, or if the patient was no longer on treatment, submit a final Follow-Up Form.

15.0 SPECIAL INSTRUCTIONS

15.1 Imaging Submission for Central Review (required for patient)

CT or MRI images must be locally read and interpreted by the local site radiology service. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for central data collection and quality control (QC) check as well as central review.

CT or MRI images must be submitted to IROC Ohio for central review at Baseline.

a. The following are recommended guidelines for CT scan quality:

1. Neutral contrast

a. Water or Volumen

b. NO POSITIVE ORAL CONTRAST

2. 16- 64-detector MDCT

3. INTRAVENOUS CONTRAST :

a. 150 ml (or weight based), 60ml saline

b. Bolus Tracking technique

c. Rate of contrast: at least 3-4 ml/sec

4. 4. Minimum two post-contrast phases (non-contrast is optional):

a. Arterial phase – ideally bolus track (delayed arterial phase)

b. Portal venous phase – 70-80 seconds

5. 0.6 mm collimation (thinnest collimation)

6. Diagnostic Images:

a. 3 mm slice thickness, 3 mm recon interval

b. 2 recon: 1 mm x 0.8 mm recon (smallest slice with overlap)

c. Reconstructions: 3 mm x 3 mm coronal MPRs for all phases.

b. The following are recommended guidelines for MRI scan quality:

1. **MAGNET:** 1.5 OR 3 T Magnet

2. **SURFACE COIL:** Phased array torso coil

3. **SEQUENCES**

a. Breath-hold T2-weighted imaging with a single/multishot fast spin-echo sequence or a half-Fourier acquisition single-shot turbo spin-echo sequence with or without fat saturation

b. MRCP sequence: 2 D and/ or 3D. Breath-hold two-dimensional single-projection turbo spin-echo MR cholangiopancreatography performed at various angles to the coronal plane OR navigator-triggered three-dimensional turbo spin-echo MR

c. DW imaging performed by using respiratory-triggered single-shot echo-planar imaging with b values of 0, 100, and 800 sec/mm2

d. Axial T1-weighted imaging with in-phase and opposed phase spoiled 3D gradient-echo sequences

e. T1 W 3D GRE sequences (: Effective slice thickness 2 mm) : unenhanced, arterial phase (AP), portal venous phase (PVP), 3-minute late-phase.

f. Subtraction images

c. TRIAD Digital Image Submission

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see Section 13.2).
- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

Questions regarding image submissions, including TRIAD, should be directed to SWOG1505@irocohio.org or call IROC Ohio at 614-293-2929.

15.2 Translational Medicine and Banking

Specimens for translational medicine and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201 (optional for patient):

a. With patient's consent, specimen must be submitted (see Sections 9.1 and 9.2):

1. FFPE tissue from surgical resection (1 block OR tissue section equivalent of at least 10 unstained slides OR 10 unstained slides).

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare event when internet connectivity is disrupted an electronic report MUST be submitted immediately upon re-establishment of internet connection.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. The commercial agents used in both arms of this study are fluorouracil, gemcitabine, nab-paclitaxel, oxaliplatin, and pegfilgrastim. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients Arm 1 or Arm 2 within 30 days of the last administration of the commercial agent(s). All of the agents used in the study are commercial agents.

	Grade 4		**Grade 5[a]**	
ATTRIBUTION	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

f. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

   Death Neonatal Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the fir**st 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.**

   A neonatal death should be reported expeditiously as Grade 4 "General disorders and administration – Other (neonatal loss)" under the General disorders and administration SOC.

Fetal death and neonatal death should NOT be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects/htm

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Informed Consent Model for S1505

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	60 (targeted above 55)
Flesch-Kincaid Grade Level	8.8 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term **should be used instead of "study doctor".**
- **The dates of protocol updates in the header and in the text of the consent is for** reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is

through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Consent Form

Study Title for Study Participants: Testing two approved chemotherapy combinations before and after surgery for pancreatic cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

S1505, "A Randomized Phase II Study of Perioperative mFOLFIRINOX versus Gemcitabine/nab-Paclitaxel as Therapy for Resectable Pancreatic Adenocarcinoma."

What is the usual approach to my resectable pancreatic cancer?

You are being asked to take part in this study because you have pancreatic cancer that can be removed by surgery. People who are not in a study are usually treated with surgery first and then with chemotherapy drugs approved by the Food and Drug Administration (FDA). Sometimes radiation is also used and your doctor can explain which may be best for you. For patients who receive the usual approach for this cancer, about 20 out of 100 are cancer-free at five years.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this study is to compare the effects of two different combinations of FDA-approved chemotherapy drugs. These two combinations are called mFOLFIRINOX (oxaliplatin, irinotecan, and fluorouracil) and gemcitabine plus nab-paclitaxel. These chemotherapy drugs will be given before and after surgery. The addition of these chemotherapy drugs before surgery is a new approach that is being tested in this study. This new approach could prevent your cancer from returning, but it could also cause side-effects. This study will allow the researchers to know if it is a good idea to treat pancreatic cancer with chemotherapy drugs before surgery, and if so, to see which of the two drug combinations is better. To be better, the study approach should increase the number of people alive at 2 years from about 40% with the usual approach to about 58% with the newer approach. There will be about 150 people taking part in this study. *(05/9/17)*

What are the study groups?

This study has two study groups.

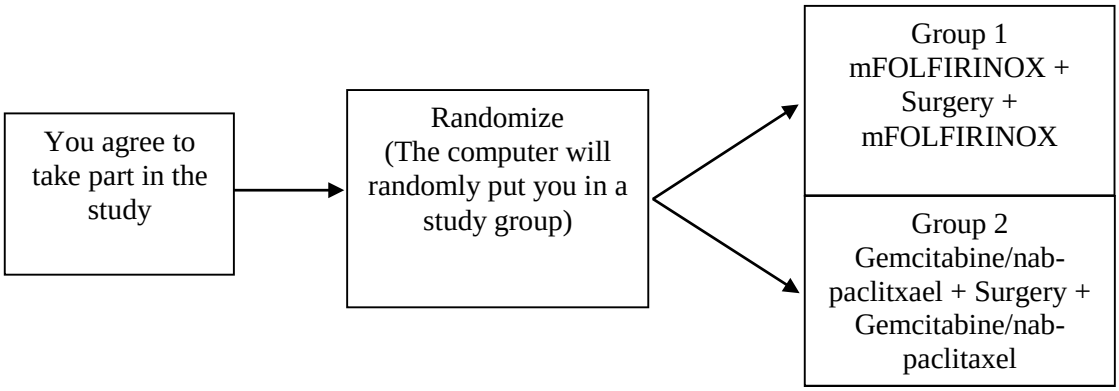
- Group 1 will get the drug combination mFOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin) given through a vein on Day 1 and 15 of every 28-day cycle. Fluorouracil is given continuously on Days 1-3 and 15-17 of each cycle. After 3 cycles of treatment (about 3 months), you will have a recovery period of about 1 month, and then you will have surgery to remove your cancer. Then 4-8 weeks after surgery, you will begin another 3 cycles of mFOLFIRINOX on the same schedule.
- Group 2 will get the drug combination of gemcitabine and nab-paclitaxel through a vein on Days 1, 8, and 15 of every 28-day cycle. After 3 cycles of treatment (about 3 months), you will have a recovery period of about 1 month, and then you will have surgery to remove your cancer. Then 4-8 weeks after surgery, you will begin another 3 cycles of gemcitabine and nab-paclitaxel on the same schedule.

Below is a timeline for patient treatment during the study.

3 months	Up to 4 weeks	4 to 8 weeks	3 months
Chemotherapy treatment Group 1: On Days 1 and 15 of each 28 day cycle for 3 cycles. Group 2: On Days 1, 8, & 15 of each 28 day cycle for 3 cycles	Both groups: Undergo surgery after completion of Cycle 3	Both groups: Recovery after surgery, timeframe will vary by patient	Chemotherapy treatment Group 1: On Days 1 and 15 of each 28 day cycle for 3 cycles. Group 2: On Days 1, 8, & 15 of each 28 day cycle for 3 cycles

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



How long will I be in this study?

You will receive the study treatment for up to 8 months. After you finish study treatment, your doctor will continue to watch you for side effects and follow your condition for four years.

What extra tests and procedures will I have if I take part in this study?

The exams, tests, and procedures you will have are part of the usual approach for your cancer. Therefore, there are not any extra exams and tests that you will need to have if you take part in this study.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **You may be asked sensitive or private questions which you normally do not discuss**
- **The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.**
- **The study approach of chemotherapy before surgery may prevent you from getting the surgery if your cancer continues to grow during chemotherapy**
- **The study approach of adding combination chemotherapy before surgery may result in increased side-effects from the surgery**

The chemotherapy and surgery used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 - Possible Side Effects of mFOLFIRINOX (5-Fluorouracil, Irinotecan, and Oxaliplatin)

COMMON, SOME MAY BE SERIOUS In 100 people receiving mFOLFIRINOX (5-Fluorouracil, Irinotecan, and Oxaliplatin), more than 20 and up to 100 may have:
• **Severe diarrhea** • **Constipation, nausea, vomiting, diarrhea, loss of appetite** • **Weakness** • **Infection, especially when white blood cell count is low** • **Hair loss** • **Loss of appetite, weight loss** • **Anemia which may require a blood transfusion** • **Fever, pain** • **Dizziness, tiredness** • **Cough, shortness of breath** • **Rash, increased risk of sunburn, itching** • **Bruising, bleeding** • **Sores in mouth which may cause difficulty swallowing** • **Redness, pain or peeling of palms and soles** • **Numbness and tingling of the arms and legs** • **Feeling of "pins and needles" in arms and legs** • **Heartburn** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving mFOLFIRINOX (5-Fluorouracil, Irinotecan, and Oxaliplatin), from 4 to 20 may have:

- **A tear or hole in internal organs that may require surgery**
- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**
- **Blood clot which may cause swelling, pain, shortness of breath**
- **Scarring of the lungs**
- **Chest pain**
- **Abnormal heartbeat which may cause fainting**
- **Hoarseness**
- **Abnormal eye movement, watering eyes, discomfort from light, blurred vision with chance of blindness**
- **Swelling and redness of the eye**
- **Problem with eyelid**
- **Hearing loss**
- **Dry eye, mouth, skin**
- **Fluid in the belly**
- **Difficulty walking, opening mouth, talking, with balance and hearing, smelling, eating, sleeping, emptying the bladder**
- **Swelling of the body which may cause shortness of breath**
- **Blockage of the airway which may cause shortness of breath, cough, wheezing**
- **Bleeding from multiple sites including vaginal bleeding, bleeding of the testis, or bleeding of the brain**
- **Internal bleeding which may cause black tarry stool, blood in vomit or urine, or coughing up blood**
- **Damage to organs which may cause shortness of breath**
- **Chills**
- **Swelling and redness at the site of the medication injection**
- **Liver damage which may cause yellowing of eyes and skin**
- **Kidney damage which may require dialysis**
- **Weight gain, dehydration, passing gas**
- **Changes in taste, voice**
- **Stroke which may cause paralysis, weakness**
- **Inability to move shoulder or turn head**
- **Muscle weakness**
- **Seizure**
- **Worry, confusion, depression**
- **Increased urination**
- **Stuffy nose, hiccups, sinus problems**
- **Increased sweating, flushing, hot flashes**
- **High blood pressure**
- **Low blood pressure which may cause feeling faint**

RARE, AND SERIOUS In 100 people receiving mFOLFIRINOX (5-Fluorouracil, Irinotecan, and Oxaliplatin), 3 or fewer may have:
• **A new cancer resulting from treatment of earlier cancer** • **Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness**

Study Group 2 - Possible Side Effects of Gemcitabine

COMMON, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, more than 20 and up to 100 may have:
• **Flu-like symptoms of muscle pain, fever, headache, chills and fatigue** • **Nausea, vomiting** • **Rash** • **Hair loss** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may require a blood transfusion** • **Muscle weakness** • **Blood in urine** • **Feeling of "pins and needles" in arms and legs** • **Numbness and tingling of the arms and legs** • **Tiredness** • **Difficulty sleeping** • **Hearing loss** • **Swelling of arms, legs**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, from 4 to 20 may have:
• **Diarrhea, constipation** • **Sores in mouth which may cause difficulty swallowing** • **Shortness of breath** • **Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles** • **Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness**

RARE, AND SERIOUS In 100 people receiving Gemcitabine, 3 or fewer may have:
• **Abnormal heartbeat** • **Heart failure or heart attack which may cause shortness of breath, swelling of ankles, and tiredness** • **Blisters on the skin** • **Sores on the skin** • **Blood clot** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Damage to organs which may cause shortness of breath** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Kidney damage which may require dialysis** • **Scarring of the lungs** • **Fluid around lungs** • **Blockage of the airway which may cause cough**

Study Group 2 – Possible Side Effects of nab-Paclitaxel

COMMON, SOME MAY BE SERIOUS In 100 people receiving nab-Paclitaxel, more than 20 and up to 100 may have:
• **Anemia, which may cause tiredness, or may require blood transfusions** • **Infection, especially when white blood cell count is low** • **Diarrhea, nausea** • **Pain** • **Numbness and tingling of the arms and legs** • **Tiredness** • **Hair loss**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving nab-Paclitaxel, from 4 to 20 may have:
• **Abnormal heartbeat** • **Heart stops beating** • **Cloudiness of the eye, visual disturbances** • **Vomiting** • **Swelling of the body** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Mini stroke** • **Paralysis, weakness, headache** • **Stroke** • **Blood clot which may cause swelling, pain, shortness of breath** • **Hoarseness**

RARE, AND SERIOUS In 100 people receiving nab-Paclitaxel, 3 or fewer may have:
• **Bruising, bleeding** • **Lung collapse which may cause chest pain**

Study Group 1 and 2 – Possible Side Effects of Surgery

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving surgery, from 4 to 20 may have:
• **Leakage around site of pancreatic repair** • **Infection inside the belly** • **Infection at the surgical incision** • **Pneumonia** • **Digestive problems related to food passage through stomach**

RARE, AND SERIOUS In 100 people receiving surgery, 3 or fewer may have:
• **Leakage of bile inside the belly** • **Post-operative bleeding requiring blood transfusion** • **Blood clot which may cause swelling, pain, shortness of breath**

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The chemotherapy drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study and for three months after the last dose of chemotherapy.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor (SWOG)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21CFR50.25 (c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Sample Collection for Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, tissue from your surgery will be collected. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) A sample from the tissue will be collected at the time of your surgery will be sent to the Biobank.
    a) Your sample and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
2) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer

3) Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial).*

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

Future Contact:

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).