PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG

A PHASE III RANDOMIZED TRIAL OF GEMCITABINE, CISPLATIN, AND NAB-PACLITAXEL VERSUS GEMCITABINE AND CISPLATIN IN NEWLY DIAGNOSED, ADVANCED BILIARY TRACT CANCERS

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by SWOG with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and NRG.

NCT#03768414

STUDY CHAIRS:

Rachna T. Shroff, MD, MS (Medical Oncology)
University of Arizona
1515 N. Campbell Ave
Tucson, AZ 85724
Phone: 520/626-4175
FAX: 520/626-2225
E-mail: rshroff@email.arizona.edu

Aaron J Scott, M.D. (Medical Oncology)
University of Arizona
1515 N. Campbell Ave
Tucson, AZ 85724
Phone: 520/626-2224
E-mail: ajscott@email.arizona.edu

ALLIANCE STUDY CHAMPION:

Mitesh J. Borad, M.D.
Mayo Clinic
13400 East Shea Boulevard
Scottsdale, Arizona 85259
Phone: 480-301-8335
Fax: 507-284-5280
E-mail: borad.mitesh@mayo.edu

ECOG-ACRIN STUDY CHAMPION:

Laura Goff, M.D.
Ingram Cancer Center
Vanderbilt University
2220 Pierce Avenue
Nashville, TN 37232
E-mail: laura.goff@vanderbilt.edu

AGENTS:

Commercially Available Agents:
Gemcitabine (NSC 613327)
Cisplatin (NSC 119875)

Supplied Agent:
Nab-paclitaxel (NSC 736631)

BIOSTATISTICIANS:

Katherine A. Guthrie, Ph.D.
Shay Bellasea, M.S.

SWOG Statistics and Data Management Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: kguthrie@fredhutch.org
E-mail: smcdonou@fredhutch.org

NRG STUDY CHAMPION:

Khalid Matin, M.D.
Professor of Medicine
Medical Director, Community Oncology
& Clinical Research
Massey Cancer Center
McGlothlin Medical Education Center
1201 E Marshall Street, Room 11-212
Box 980070
Richmond, Virginia 23298-0070
Phone: 804-828-9654
Fax: 804-628-5920
E-mail: khalid.matin@vcuhealth.org

PARTICIPANTS

U.S.-Only Participants:

ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG

TABLE OF CONTENTS

PROTOCOL CONTACT INFORMATION

Eligibility, RAVE, Data Submission:	SWOG Statistics and Data Management Center E-mail: GIquestion@crab.org or Phone: 206/652-2267
Medical Queries (treatment or toxicity related questions):	Email: giquestion@crab.org and rshroff@email.arizona.edu or call: Dr. Shroff or the Data Management Center at Phone: 520/626-4175 or 206/652-2267
Investigational Drug questions: Requests for Investigator's Brochures:	See Protocol Section 3.0 See Protocol Section 3.0
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	technicalquestion@crab.org
Regulatory, Protocol, Informed Consent:	SWOG Operations Office E-mail: protocols@swog.org or Phone: 210/614-8808
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM)	To review CTEP-IAM account (new requests, reset passwords): https://ctepcore.nci.nih.gov/iam/index.jsp
Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Section 13.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Serious Adverse Event Reporting questions:	See Protocol Section 8.5 Email: adr@swog.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	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. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench via the SWOG website (www.swog.org).

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. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

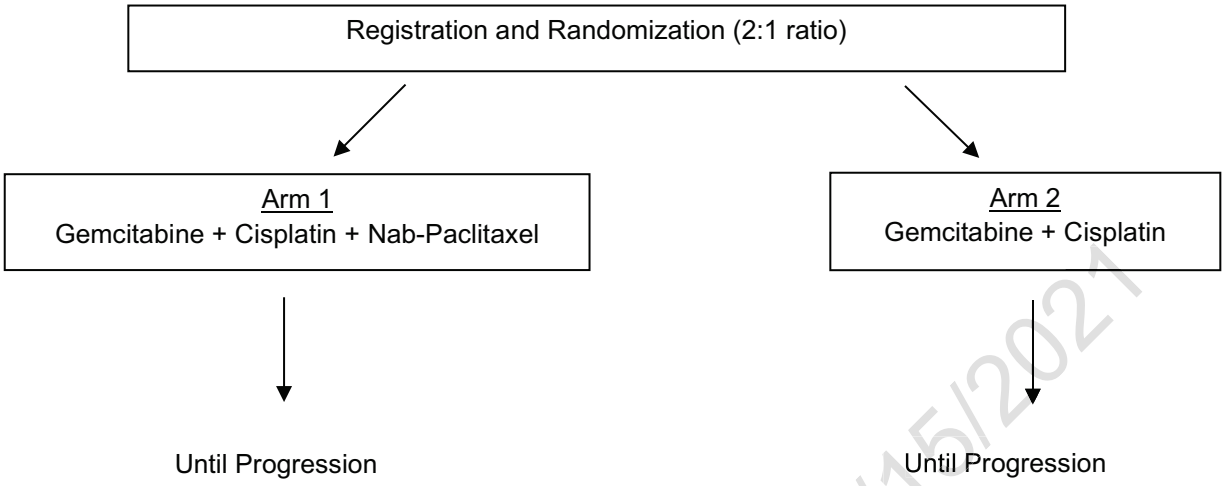
For patient eligibility or data submission questions contact the SWOG Data Operations Center by phone or email:
206/652-2267
GIquestion@crab.org

For treatment or toxicity related questions contact the Study Chair by phone or email: Dr. Rachna Shroff at 520-626-4175 or via email at rshroff@email.arizona.edu

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org.

SCHEMA



1 cycle = 21 days

1.0 OBJECTIVES

1.1 Primary Objective

a. To compare overall survival (OS) in patients with untreated, advanced biliary cancers treated with gemcitabine and cisplatin (GC) versus those treated with gemcitabine, cisplatin, and nab-Paclitaxel (GCN).

1.2 Secondary Objective

a. To compare progression-free survival (PFS) in patients treated with GC versus GCN.

b. To compare overall response rate (ORR), complete and partial, confirmed and unconfirmed, in the subset of patients with measurable disease treated with GC versus GCN.

c. To compare disease control rate [confirmed and unconfirmed; complete response + partial response + stable disease] (DCR) in patients treated with GC versus GCN.

d. To evaluate the frequency and severity of toxicity associated with GC and GCN in the patient population.

e. To explore the correlation between change in CA 19-9 levels from baseline to post-treatment (after 3 cycles) and overall response rate, in each treatment arm separately and in the total cohort.

1.3 Additional Objective

a. To bank tissue and blood for future translational medicine studies.

2.0 BACKGROUND

2.1 Background / Rationale

Biliary cancers are a heterogeneous group of malignancies with a limited number of chemotherapeutic options in advanced disease. Nab-Paclitaxel is FDA-approved for treatment of metastatic pancreatic cancer and is presumed to enhance delivery of chemotherapy by modifying the dense stromal barrier that is thought to surround pancreatic cancer cells. Biliary cancers are often treated similarly to pancreatic cancers given their equally strong desmoplastic response creating dense stromal barriers that play a role in the chemoresistance seen in these malignancies. Furthermore, like pancreatic cancers, gemcitabine has been the mainstay of chemotherapy in these diseases. Currently, the chemotherapy standard of care in advanced biliary cancers is the combination of gemcitabine and cisplatin (GC). Based on the landmark ABC-02 study, this regimen significantly improved median overall survival (11.7 months vs. 8.1 months) and progression-free survival (8.0 months vs. 5.0 months) compared to gemcitabine alone. No other Phase III study that has included gemcitabine and cisplatin as a backbone has demonstrated a significant improvement in overall survival over this chemotherapy combination. As a group of rare diseases, there are no FDA-approved therapies for advanced biliary tract cancers, limiting therapeutic options for these patients.

A single-arm multi-center Phase II study has been completed at MD Anderson Cancer Center and Mayo Arizona. The preliminary efficacy data was presented at the 2017 ASCO Annual Meeting as a poster discussion presentation. A total of 60 patients were enrolled with data available on 59 at the time of presentation. Patients with newly diagnosed, advanced biliary tract cancers (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer) received gemcitabine, cisplatin and nab-Paclitaxel IV on Days 1 and 8 of a 21-day cycle with restaging performed every 3 cycles. The primary endpoint was PFS with secondary endpoints including safety, OS, ORR. Using a Bayesian hypothesis test-based design, we assumed median PFS of 8 mos under the null hypothesis (H0), 10 mos under the alternative hypothesis (H1). The initial dosing of gemcitabine at 1000 mg/m^2, cisplatin at 25 mg/m^2, and nab-Paclitaxel at 125 mg/m^2 resulted in significant Grade 3-4 hematological toxicities including febrile neutropenia, anemia, and thrombocytopenia. As a result, after enrolling 30 patients, the starting doses were reduced to gemcitabine at 800 mg/m^2, cisplatin at 25 mg/m^2, and nab-Paclitaxel at 100 mg/m^2 with improved tolerance in the remaining 29 patients. In the first 59 patients, 50 patients were evaluable for efficacy having completed > 1 cycle of treatment. In this population, the median PFS was 11.8 months (95% CI 7.9, 16.1). One-year overall survival rate was 70.2% (95% CI 57.1%, 86.3%) with a median OS of 18.8 months (95% CI 13.6, NR). ORR in 50 evaluable patients was 34% with a disease control rate (DCR) of 84%. These PFS and OS results are unprecedented in the published experience for treatment of cholangiocarcinoma. At the initial dose level, 6 patients discontinued treatment due to hematologic toxicities including neutropenia, thrombocytopenia and anemia. At the reduced dose level, only 3 patients experienced Grade 4 hematologic toxicities. Non-hematologic toxicities were mild at only Grade 3. Most patients received growth factor support to mitigate neutropenia.

Based on preliminary efficacy data from a multi-institution single-arm Phase II study of the combination of gemcitabine, cisplatin, and nab-Paclitaxel, a randomized, Phase III study comparing this combination to the standard of care GC will determine if the addition of nab-Paclitaxel improves survival in patients with newly diagnosed advanced biliary tract cancers. This study has the potential to be practice-changing for this disease.

2.2 Inclusion of Women and Minorities and Planned Enrollment Report

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.

DOMESTIC PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	3	3	0	0	6
Asian	20	3	0	0	23
Native Hawaiian or Other Pacific Islander	2	2	0	0	4
Black or African American	31	16	0	0	47
White	168	132	38	18	356
More Than One Race	3	2	0	0	5
Total	227	158	38	18	441

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 these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources

3.1 Cisplatin (CDDP, Platinol®, Platinol-AQ) (NSC-119875)

a. PHARMACOLOGY

Mechanism of Action:

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central platinum atom surrounded by two chloride atoms and two ammonia molecules in the cis position. It is water soluble and acts as a bifunctional alkylating agent with cell cycle nonspecific characteristics. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Although cisplatin seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents and that cisplatin does not exhibit cross-resistance with other alkylating agents or nitrosoureas.

b. PHARMACOKINETICS

1. Absorption: Following rapid IV injection of cisplatin over up to one hour, peak plasma drug and platinum concentrations occur immediately. When cisplatin is administered by IV infusion over 6 or 24 hours, plasma concentrations of total platinum increase gradually during the infusion and peak immediately following the end of the infusion.

2. Distribution: Following intravenous dosing, cisplatin distributes rapidly into tissues, with highest concentrations in the liver, prostate and kidney. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90%. Cisplatin penetrates poorly into the CNS.

3. Metabolism: Cisplatin is non-enzymatically transformed to one or more metabolites that are extensively protein bound and have minimal cytotoxic activity. The non-protein bound (unchanged) fraction is cytotoxic.

4. Elimination: Urinary excretion is incomplete. Following bolus injection or infusion over a dose range of 40-140 mg/m^2 varying in length from 1-24 hours, from 10 to about 40% of the administered platinum is excreted in the urine in 24 hours. Renal clearance of free platinum exceeds the glomerular filtration rate, indicating that cisplatin or other platinum-containing molecules are actively secreted by the kidneys. Renal clearance of free platinum is nonlinear and variable, and is dependent on

dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption.

c. ADVERSE EFFECTS

1. Possible Side Effects of cisplatin: Adverse effects reported in 10% or more of patients receiving cisplatin include peripheral neuropathy, nausea, vomiting, diarrhea, myelosuppression, liver enzymes elevation, nephrotoxicity (acute renal failure and chronic renal insufficiency), alopecia, tissue irritation, and ototoxicity.

   Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, serum uric acid and impairment of endogenous creatinine clearance, as well as renal tubular damage), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Raynaud's phenomena and digital ischemia has been described. Anaphylactic-like reactions including facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Alopecia, malaise and asthenia have been reported. Rare complications are alopecia, seizures, loss of taste and allergic reactions. Tetany may occur due to hypomagnesemia and/or hypocalcemia. Other electrolyte disturbances may occur. At high doses patients have experienced optic neuritis, papilledema, cerebral blindness, blurred vision, and altered color perception. Patients have also experienced cardiac abnormalities, elevated aspartate aminotransferase and rash. Subsequent courses should not be given until serum creatinine returns to normal if elevated. Audiometric analyses should be monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

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

2. Pregnancy and Lactation: Category D. Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. This drug has been found to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, patients receiving cisplatin should not breast feed.

3. Drug Interactions: During cisplatin therapy, plasma levels of anticonvulsant agents may become sub-therapeutic and should be monitored. For complete information refer to the current FDA-approved package insert.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Refer to the current FDA-approved package insert for drug administration.

e. PREPARATION, STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

Cisplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

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, myelosuppression including 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/m2. 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 Nab-Paclitaxel (Abraxane®) (NSC 736631)

a. PHARMACOLOGY

Mechanism of Action: 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, secreted protein acidic and rich in cysteine (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: The bioavailability of nab-paclitaxel is 100% as it is administered intravenously.

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 22% 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. Adverse Effects:

Adverse Events with Possible Relationship to *Nab-paclitaxel*		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		Hemorrhage

Adverse Events with Possible Relationship to *Nab-paclitaxel*		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
Neutropenia		Febrile neutropenia
Thrombocytopenia		
CARDIAC DISORDERS		
ECG abnormality	Cardiac failure	Arrhythmia
	Hypotension	Cardiac arrest
	Hypertension	Ischemic heart disease
	Tachycardia	Myocardial infarction
	Chest Pain	Supraventricular tachycardia
CONGENITAL, FAMILIAL AND GENETIC DISORDERS		
EAR AND LABYRINTH DISORDERS		
ENDOCRINE DISORDERS		
	Hypokalemia	
EYE DISORDERS		
	Visual disturbances	
	Cystoid macular edema	
GASTROINTESTINAL DISORDERS		
Diarrhea	Constipation	
Nausea		
Vomiting	Mucositis	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema	Paralysis	
Fatigue	Weakness	
Pyrexia		
HEPATOBILIARY DISORDERS		
Increased ALT	Increased gamma-glutanyl transferase	Increased serum bilirubin
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
INFECTIONS AND INFESTATIONS		
Respiratory tract infection	Urinary tract infection	
	Oral candidiasis	
	Pneumonia	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
INVESTIGATIONS		
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	Dysgeusia	
Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		

Adverse Events with Possible Relationship to *Nab-paclitaxel*		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
Asthenia		
Musculoskeletal pain		
Myalgia/arthralgia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (incl cysts and polyps)		
NERVOUS SYSTEM DISORDERS		
Paresthesia	Headache	
Peripheral neuropathy	Depression	
PSYCHIATRIC DISORDERS		
RENAL AND URINARY DISORDERS		
	Increased serum creatinine	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Epistaxis	
	Dyspnea	
	Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		
Rash including generalized		
SOCIAL CIRCUMSTANCES		
SURGICAL AND MEDICAL PROCEDURES		
VASCULAR DISORDERS		
		Pulmonary thromboembolism
		Thrombosis
		Transient ischemic attack

Adverse events occurring in < 1%, post marketing, and/or case reports:

Arrhythmia, sinus bradycardia, atrioventricular block, supraventricular tachycardia, hypersensitivity, dermatitis allergic, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, cystoid macular edema, maculopathy, conjunctivitis, keratitis, malaise, lethargy, skin exfoliation, erythema multiform, urticaria , facial paralysis, cranial nerve palsies.

2. Pregnancy and Lactation:

Pregnancy Category D. There are no adequate and well-controlled studies in pregnant women using nab-paclitaxel. Females of reproductive potential should have a pregnancy test prior to starting treatment with nab-

paclitaxel. 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 nab-paclitaxel. Advise females of reproductive potential to use effective contraception during treatment with nab-paclitaxel and for at least 1 month after the last dose. Nab-paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Like other genotoxic cytostatics, nab-paclitaxel can have genotoxic effects. Male patients treated with nab-paclitaxel are advised to use effective contraception and to avoid fathering a child during and up to 6 months after treatment.

Nursing Mothers: Paclitaxel and/or its metabolites were excreted into the milk of lactating rats (Taxol US prescribing information). It is not known whether paclitaxel is excreted in human milk. 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 must be discontinued when receiving nab-paclitaxel 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 or inducing these enzymes. Pharmacokinetic drug-drug interactions between nab-paclitaxel and inhibitors or inducers of CYP2C8 or CYP3A4 have not been evaluated in humans. Caution should be exercised when administering nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

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

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

1. Nab-paclitaxel is supplied by Celgene and distributed by McKesson Specialty Pharmacy, LP. Nab-paclitaxel is supplied as a white-to-off-white, sterile, lyophilized cake containing 100 mg and 250 mg of paclitaxel and human albumin as a stabilizer in a 50 mL and 100 mL vial, respectively.

f. STORAGE, PREPARATION & STABILITY

1. Storage: Store the vials in original cartons at 20º C to 25º C (68º F to 77º F). Retain in the original package to protect from bright light. Contact supplier for temperature excursion information.

2. Preparation: Nab-paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use. Using a sterile syringe, slowly inject the appropriate volume of 0.9% sodium chloride solution for injection to a vial of nab-paclitaxel; 20 mL for 100 mg/vial and 50 mL for the 250 mg/vial. Each mL of the reconstituted formulation will contain 5 mg/mL of nab-

paclitaxel. Direct the solution flow onto the inside wall of the vial. Do not inject the solution directly onto the lyophilized cake as this will result in foaming. Once the addition is complete, allow the vial to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs avoiding the generation of foam. The reconstituted sample should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient and slowly withdraw the dosing volume of the reconstituted nab-paclitaxel suspension from the vial(s) into a syringe. The exact total dosing volume of 5 mg/mL suspension required for the patient is calculated using the following formula:

Dosing volume (mL) = Total dose (mg) / 5 (mg/mL)

Inject the appropriate amount of reconstituted nab-paclitaxel into an empty, sterile, intravenous bag (PVC or non-PVC type IV bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer nab-paclitaxel infusions. Visually inspect the reconstituted nab-paclitaxel suspension in the IV bag prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever the solution and container permit. Following administration of nab-paclitaxel, the intravenous line should be flushed with 0.9% sodium chloride solution for injection to ensure administration of the complete dose, according to local practice.

Unopened vials of nab-paclitaxel are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial: Reconstituted nab-paclitaxel in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag: The suspension for infusion when prepared as recommended in an infusion bag should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours. The total combined refrigerated storage time of reconstituted nab-paclitaxel in the vial and in the infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours.

3. Specific dispensing requirements: DO NOT SUBSTITUTE nab-paclitaxel for or with other paclitaxel formulations. Nab-paclitaxel is an albumin-bound formulation of paclitaxel, which may have substantially different

functional properties compared to those of solution formulations of paclitaxel.

g. DRUG ORDERING & ACCOUNTABILITY

1. McKesson Specialty Pharmacy, LP:

Drug orders may be requested by the principal investigator (or their authorized designee) at each participating site must by completing the McKesson Drug Order Request Form for **S1815** and must be submitted by faxing the Drug Order Form – **S1815** to McKesson at the number listed on the order form. This form can be found on the SWOG website (http://swog.org).

Authorized and completed orders will be processed and shipped "same day" of receipt if received before 2:00 p.m. EST Monday through Thursday. Authorized and completed orders received after 2:00pm EST Monday through Thursday or on Friday will be processed and shipped the next business morning. All drug orders are shipped via FedEx Priority Overnight delivery. McKesson distribution team monitors packages throughout duration of transit via FedEx One Call Solution (live support) and delivery exceptions are managed at the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator.

Drug deliveries are restricted during weekends and holidays. McKesson Specialty Pharmacy, LP observes the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

Sites must allow up to 5 business days for study drug to arrive once the Drug Order Request Form is submitted to McKesson. The Drug Order Request Form should be faxed to 919/256-0794.

2. Drug return and/or disposition instruction (include forms if needed)

Drug returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

3. Contact Information

Questions about drug orders, transfers, returns, or accountability should be addressed to protocols@swog.org.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this study.

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. 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 SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or GIquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

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 28 or 42 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 confirmed intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer.

NOTE: Pathology report must be uploaded in Rave. Histology report must be consistent with an adenocarcinoma with pancreaticobiliary primary assuming there are no pancreatic lesions and other primaries are ruled out per local standard.

b. Patients must have documented metastatic or locally advanced unresectable disease on CT or MR imaging. CT scans or MRIs used to assess measurable disease (as defined in Section 10.1) must have been completed within 28 days prior to registration. CT scans or MRIs used to assess non-measurable disease must have been completed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

c. Patient must not have a current diagnosis of ampullary cancer.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must not have received prior systemic therapy for the current metastatic or locally advanced biliary cancer.

b. Patient must not have received adjuvant therapy within 6 months prior to registration.

5.3 Clinical/Laboratory Criteria

a. Patients must have a complete medical history and physical exam within 28 days prior to registration.

b. Patients must be ≥ 18 years of age.

c. Patients must have a Zubrod Performance Status of 0 or 1. (See Section 10.4)

d. Patients must not have a history of peripheral neuropathy of Grade 2 or greater by Common Terminology Criteria for Adverse Events (CTCAE) 5.0. In CTCAE version

5.0 Grade 2 sensory neuropathy is defined as “moderate symptoms; limiting instrumental activities of daily living (ADLs)”

e. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500/mcL; platelets ≥ 100,000/mcL; Hemoglobin ≥ 8 g/dL, and serum albumin ≥ 2.8 g/dL. These results must be obtained within 28 days prior to registration.

f. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except patients with Gilbert’s Syndrome, who must have a direct bilirubin < 1.5 mg/dL), and SGOT (AST) and SGPT (ALT) ≤ 8 x IULN. These results must be obtained within 28 days prior to registration.

g. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ IULN OR calculated creatinine clearance ≥ 60 mL/min. This serum creatinine result must have been obtained within 28 days prior to registration.

Calculated creatinine clearance = $\frac{(140 - \text{age}) \times \text{wt}^{*} \text{ (kg)} \times 0.85 \text{ (if female)}}{72 \quad \text{Creatinine}^{**} \text{ (mg/dl)}}$

* The kilogram weight is the patient’s actual body weight with an upper limit of 140% of the IBW.

** Actual lab serum creatinine value with a minimum of 0.8 mg/dL

h. Patients must have CA19-9 obtained within 42 days prior to registration.

i. Patients must have sodium, potassium, bicarbonate, chloride, BUN, calcium, total protein, magnesium, and alkaline phosphatase obtained within 28 days prior to registration.

j. Patients must not have an active infection requiring systemic therapy.

k. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for two years.

l. Patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method. 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.

5.4 Specimen Submission Criteria

a. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.1. If patient consents to participation, specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.1.

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 13.3 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 randomized in a 2:1 ratio (GCN:GC) using a dynamic balancing algorithm with stratification based on :

6.1 Disease site: gallbladder adenocarcinoma versus intrahepatic cholangiocarcinoma versus extrahepatic cholangiocarcinoma

6.2 Disease stage: Locally advanced versus Metastatic

6.3 Zubrod Performance Status: 0 versus 1

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Rachna Shroff at 520/626-4175 or e-mail rshroff@email.arizona.edu. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/about/policies-procedures,

7.1 Pre-medication and supportive care

Pre-medications and concomitant medicines should be administered to counter the expected common side effects of chemotherapy. These will be ordered by the treating physician per institutional standards and tailored to the patient's condition.

The following is recommended prior to treatment:

- Adequate hydration per institutional standards.
- Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with ASCO guidelines (see Section 8.5).
- In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel. In the rare event of a severe hypersensitivity reaction, discontinue nab-paclitaxel.

7.2 Treatment

Patients assigned to Arm 1 will receive the following treatment until meeting one of the criteria in Section 7.3.

a. Arm 1: Gemcitabine, Cisplatin, and nab-Paclitaxel (GCN)

Patients assigned to Arm 1 will receive the following treatment every 21 days until meeting one of the criteria in Section 7.3.

Agent	Dose	Route	Day*	Schedule
nab-Paclitaxel	100 mg/m^2	IV over 30 min (+/- 5 minutes)	1, 8	Administer first
Gemcitabine	800 mg/m^2	IV over 30 min (+/- 5 minutes)	1, 8	Following nab-paclitaxel
Cisplatin	25 mg/m^2	IV over 60 min (+/- 5 minutes)	1, 8	Following Gemcitabine

* Note: One cycle = 21 days

Preparation and administration details are located in Section 3.0.

b. Arm 2: Gemcitabine and Cisplatin (GC)

Patients assigned to Arm 2 will receive the following treatment every 21 days until meeting one of the criteria in Section 7.3.

Agent	Dose	Route	Day*	Schedule
Gemcitabine	1000 mg/m^2	IV over 30 min (± 5 minutes)	1, 8	Prior to cisplatin
Cisplatin	25 mg/m^2	IV over 60 min (± 5 minutes)	1, 8	Following gemcitabine

* Note: One cycle = 21 days

Preparation and administration details are located in Section 3.0.

7.3 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Unacceptable toxicity.

c. Treatment delay for any reason > 4 weeks

d. The patients may withdraw from the study at any time for any reason.

7.4 Discontinuation of Treatment

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

7.5 Follow-Up Period

All patients will be followed until death or 3 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 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 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 5.0.

8.2 General Considerations

- Dose modifications and treatment delays based on observed drug-related toxicity will be performed as described below.
- Any toxicity associated or possibly associated with gemcitabine, cisplatin, and nab-paclitaxel treatment should be managed according to standard medical practice.
- The maximum dose delay for any reason is 4 weeks.
- Where several toxicities with different grades or severity occur at the same time, the dose modification applied should be the greatest reduction applicable.
- No dose re-escalations are permitted. If the patient experiences toxicity requiring a dose reduction, the dose will remain lowered for subsequent cycles
- Patients on either arm may continue protocol treatment as long as all drugs do not need to be discontinued for toxicities.

8.3 Dose Modifications for Arm 1: gemcitabine/nab-paclitaxel/cisplatin

a. Dose Levels

Drug	Initial Dose	Dose Reduction Level 1	Dose Reduction Level 2**
Gemcitabine	800 mg/m^2	600 mg/m^2	500 mg/m^{2**}
nab-Paclitaxel	100 mg/m^2	75mg/m^2	50 mg/m^{2**}
Cisplatin*	25 mg/m^2	20 mg/m^2	15 mg/m^2

*Cisplatin should be held for the entire cycle if creatinine clearance is less than 45 ml/min on day 1.

**If a patient experiences a hematologic toxicity while nab-paclitaxel is at a dose -2 level, only decrease gemcitabine per table 8.3.b if gemcitabine is not at dose -2 level. If a patient experiences a hematologic toxicity while gemcitabine is at a dose -2 level, only decrease nab-paclitaxel per table 8.3.b if nab-paclitaxel is not at dose -2 level.

NOTE: If, for a particular drug, a dose reduction is required below Dose Reduction Level 2, that drug must be discontinued.

Dose reductions may or may not be concomitant. Please refer to the tables below for day of cycle and toxicity, respectively.

NOTE: If a Dose Reduction Level 1 is required of gemcitabine and nab-paclitaxel for an ANC <1000 at Day 1 or Day 8, the use of G-CSF is strongly encouraged on Day 8 or 9 to avoid any further dose reductions due to neutropenia. The investigators recommend pursuing this approach at the first occurrence of ANC < 1000.

NOTE: If Day 1 requires a delay physicians may consider adding G-CSF 5 mcg/kg/day (Neupogen® or filgrastim biosimilar depending on patient's insurance) starting Day 2 for 3- 5 days per physician discretion

b. Hematologic toxicities

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of nab-paclitaxel, cisplatin, and gemcitabine may be adjusted as detailed below.

NOTE: The tables below apply only to Arm 1. For dose modifications of Arm 2, please see Section 8.4.

Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

ANC *		Platelets	Modification
< 1,000 cells/mm^3*	OR	< 75,000/uL	Delay treatment by 1 week intervals until recovery *

* First occurrence: Delay treatment by 1 week intervals until count recovery. Once recovered treat with initial dose levels. Second or beyond occurrence: Delay treatment by 1 week intervals until count recovery. Once recovered treat with decreased dose by 1 level for gemcitabine and nab-paclitaxel. This will be a permanent dose reduction (no dose escalation) for day 1.

Dose Modifications for Day 8 of Each Cycle (Hematologic Toxicity)

Day 8 Laboratory Results	Day 8 Nab-Paclitaxel	Day 8 Cisplatin	Day 8 Gemcitabine
ANC > 1000 and Platelets ≥ 75,000	No modification	No modification	No modification
ANC 500-1000[a] or Platelets 50,000-74,000	Decrease dose by 1 level (treat on time) and consider adding G-CSF support to prevent further toxicity. See below for examples of adding G-CSF.*	No modification	Decrease dose by 1 level (treat on time) and consider G-CSF support to prevent further toxicity. See below for examples of adding G-CSF.*
ANC < 500 or Platelets < 50,000	Hold until ANC > 500 and Platelets	Hold until ANC ≥ 500 and Platelets	Hold until ANC > 500 and Platelets >50,000. Once

Day 8 Laboratory Results	Day 8 Nab-Paclitaxel	Day 8 Cisplatin	Day 8 Gemcitabine
	>50,000. Once recovered, treat at dose reduction by 1 level and consider adding G-CSF support to prevent further toxicity. See below for examples of adding G-CSF after Day 8.*	≥ 50,000, then resume at current dose level	recovered, treat at dose reduction by 1 level and consider adding G-CSF support to prevent further toxicity. See below for examples of adding G-CSF after Day 8.*
Febrile Neutropenia (Grade 3 or 4)[b]	Hold until ANC > 500 and fever-free for 48 hours, then decrease dose by 1 level and add G-CSF support to prevent further toxicity. See below for examples of adding G-CSF.*	Hold until ANC > 500 and fever-free for 48 hours, then decrease dose by 1 level.	Hold until ANC > 500 and fever-free for 48 hours, then decrease dose by 1 level and add G-CSF support to prevent further toxicity. See below for examples of adding G-CSF.* .

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

[b] Patients with febrile neutropenia should have their chemotherapy treatment held. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to non-neutropenic levels before resuming chemotherapy treatment.

* In order to prevent neutropenia, it is strongly recommended to use growth factor after Day 8 of each cycle.

The exact dosage amount and schedule for G-CSF support will be left to the treating physician's discretion. Examples below on recommendations for adding G-CSF. The prior Phase II study investigating Arm 1 offer GM-CSF support on Day 8 to prevent neutropenia at the start of the subsequent cycle and would be the suggested schedule for growth factor support

G-CSF support addition after day 8 examples are as follows:

If a patient has ANC < 1000 cells/mm^3 on Day 8, it is strongly encouraged to use G-CSF to prevent future treatment modifications and delays due to neutropenia. Patient's with episodes of febrile neutropenia should have G-CSF added. These examples are listed in no particular order or preference. Patient's insurance plan is to be considered for best selection or drug and day administered.

- Neulasta® Onpro- 6 mg subcutaneous administer on day 8 to activate on day 9 of chemotherapy cycle
- Pegfilgrastim (Neulasta® or a pegfilgrastim biosimilar): 6 mg subcutaneous administer on day 9 of chemotherapy cycles
- Filgrastim (Neupogen® or a filgrastim biosimilar): 5 mcg/kg/day (rounded to nearest syringe size of 300 mcg or 480 mcg) starting on day 9 for 3-7 days per physician discretion.

c. Non-hematologic toxicities

All treatment related non-hematological toxicities (with the exception of hair loss and nausea and vomiting that can be controlled with antiemetics) should resolve to ≤ Grade 2 prior to starting next cycle of therapy.

Dose modification or delay may occur in the setting of lower Grade toxicity if the treating physician believes that it is in the interest of a subject's safety.

Alopecia and nausea and/or vomiting that can be controlled by antiemetics do not require dose modification. No dose modification will be required for anemia as it can be satisfactorily managed by transfusions.

Dose Modifications for Nab-Paclitaxel, Cisplatin, and Gemcitabine on Day 1 or Day 8 of Each Cycle (Non-Hematologic Toxicity)*

CTCAE Grade	Treatment Modification
Grade 0-2 toxicity	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of nab-paclitaxel and gemcitabine should be reduced to next lower dose level – see below)
Grade 3 toxicity[a,c]	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level for all drugs[a].
Grade 4 toxicity[ab]	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level for all drugs.

* Except peripheral neuropathy and nephrotoxicity (see below)

*Except for cisplatin induced ototoxicity which should be evaluated when suspected via an audiology consult and recommendations

[a] If the toxicity only affects neuropathy, then only *nab*-paclitaxel and cisplatin should be reduced (see below). If the specific toxicity is attributed to only one drug (i.e. cisplatin hypomagnesemia; nab-paclitaxel myalgias), okay to hold only that drug. When toxicity resolves to ≤ grade 1, then resume treatment at the next lower dose level of only that specific drug.

[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (see below).

[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

1. Sensory Neuropathy

Modify cisplatin and nab-paclitaxel treatment per below. Gemcitabine administration can continue during this period. Patients experiencing peripheral neuropathy that requires a delay in scheduled cisplatin and nab-paclitaxel dosing for ≥ 28 days will discontinue study treatment. The time to resolution to Grade ≤ 2 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 sensory neuropathy, both cisplatin and nab-paclitaxel should be withheld, and treatment resumed at a reduction of 2 dose levels for nab-paclitaxel (dose level -2) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 2. Note: the investigator may elect to dose modify for grade 2 sensory neuropathy.

Grade 2 If persistent between cycles: decrease cisplatin and nab-paclitaxel at next lowest dose level. *If peripheral sensory neuropathy stays at grade 2 after dose reduction, dosing can continue at the same dose level if toxicity remains grade 2

Grade 3: hold cisplatin and nab-paclitaxel until grade <2 then restart cisplatin and nab-paclitaxel at next lowest dose level

Grade 4: Discontinue nab-paclitaxel and cisplatin until grade < 2 then restart cisplatin at 2 dose level reduction and nab-paclitaxel at 2 dose level reduction

2. Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity. The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent dose. Cisplatin should not be given unless adequate renal function is confirmed with a calculated creatinine clearance of ≥ 45 mL/min

3. Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have the dose reduced of the drug the local investigator deems most contributory to the next lower dose level as per table in 8.3a. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

4. Gastrointestinal Toxicity

Patients who develop Grade 2 or 3 gastrointestinal toxicity should have their dose reduced to the next lower dose level as per Table 3. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 gastrointestinal toxicity should have treatment discontinued

5. Pulmonary Embolism

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

6. Interstitial Pneumonitis

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e. Episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Administration of study drugs will be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

Prevention, Surveillance and Management of Interstitial Pneumonitis

- During study treatment, episodes of transient or repeated dyspnea with unproductive persistent cough or fever should be paid attention to. Radiographic evaluation with chest X-rays and CT scans (normal or high resolution) may be indicated to look for infiltrates, ground-glass opacities or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.
- Infections should be ruled out with routine immunological/ microbiological methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.
- Study drug administration should be interrupted upon diagnosis of interstitial pneumonitis and patients permanently discontinued from further study drug treatment. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy and secondary pathogen coverage should be instituted without delay. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

7. Sepsis

The increased risk of sepsis in the setting of advanced or metastatic cancer in combination with gemcitabine could be managed with prophylactic antibiotic treatment in febrile patients (regardless of neutrophil count) and dose reduction, and with G-CSF treatment in neutropenic patients. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Nab-Paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels.

Prophylaxis Against Sepsis

Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever ≥ 38.5°C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily) or amoxicillin/clavulanate (500 mg orally, 2-3

times daily) in patients with allergy to fluoroquinolones should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 °C (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts and to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation. If hospitalization is required, this should be reported as a Serious Adverse Event (SAE).

8. Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience severe hypersensitivity reactions to nab-paclitaxel should not be re-challenged. It is not recommended to administer Nab-Paclitaxel to patients with prior hypersensitivity to a taxane. If mild to moderate cisplatin hypersensitivity develops (per NCI CTCAE), the patient may be desensitized using the standard desensitization protocol of the institution. In the setting of a severe hypersensitivity reaction, cisplatin should be discontinued.

8.4 Dose Modifications for Arm 2: Gemcitabine/cisplatin

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
Cisplatin*	25 mg/m^2	20 mg/m^2	15 mg/m2

*Cisplatin should be held for the entire cycle if creatinine clearance is less than 45 ml/min on day 1.

NOTE: If, for a particular drug, a dose reduction is required below the corresponding value listed, that drug must be discontinued.

NOTE: If a dose reduction level 1 is required of gemcitabine for an ANC <1000 at day 1 or day 8, the use of G-CSF is strongly encouraged on day 9 to avoid any further dose reductions due to neutropenia. The investigators recommend pursuing this approach at the first occurrence of ANC < 1000.

b. Hematologic toxicities

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of cisplatin, and gemcitabine may be adjusted as detailed below.

Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

ANC		Platelets	Modification
< 1,000 cells/mm^3	OR	< 75,000/uL	Delay treatment by 1 week intervals until recovery*

* First occurrence: Delay treatment by 1 week intervals until count recovery. Once recovered treat with initial dose levels. Second or beyond occurrence: Delay treatment by 1 week intervals until count recovery. Once recovered treat with decreased dose by 1 level for gemcitabine. This will be a permanent dose reduction (no dose escalation) for Day 1.

Dose Modifications for Day 8 of Each Cycle (Hematologic Toxicity)

Day 8 Laboratory Results	Day 8 Cisplatin	Day 8 Gemcitabine
ANC > 1000 and Platelets ≥ 75,000	No modification	No modification
ANC 500-1000[a] or Platelets 50,000-74,000 *	No modification	Decrease dose by 1 level (treat on time) and consider G-CSF support to prevent further toxicity. See below for examples of adding G-CSF.*
ANC < 500 or Platelets < 50,000	Hold until ANC ≥ 500 and Platelets ≥ 50,000, then resume at current dose level	Hold until ANC > 500 and Platelets >50,000. Once recovered, treat at dose reduction by 1 level and consider adding G-CSF support to prevent further toxicity. See below for examples of adding G-CSF after day 8.*
Febrile Neutropenia (Grade 3 or 4)[b]	Hold until ANC > 500 and fever-free for 48 hours, then decrease dose by 1 level.	Hold until ANC > 500 and fever-free for 48 hours, then decrease dose by 1 level and add G-CSF support to prevent further toxicity. See below for examples of adding G-CSF.* .

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

[b] Patients with febrile neutropenia should have their chemotherapy treatment held. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to non-neutropenic levels before resuming chemotherapy treatment.

* In order to prevent neutropenia, it is strongly recommended to use growth factor after Day 8 of each cycle.

The exact dosage amount and schedule for G-CSF support will be left to the treating physician's discretion. Examples below on recommendations for adding G-CSF. The prior Phase II study investigating Arm 1 offer GM-CSF support on Day

8 to prevent neutropenia at the start of the subsequent cycle and would be the suggested schedule for growth factor support.

G-CSF support addition after day 8 examples are as follows:

If a patient has ANC < 1000 cells/mm^3 on day 8, it is strongly encouraged to use G-CSF to prevent future treatment modifications and delays due to neutropenia. Patient's with episodes of febrile neutropenia should have G-CSF added. These examples are listed in no particular order or preference. Patient's insurance plan is to be considered for best selection or drug and day administered.

- Neulasta® Onpro- Administer on Day 8 to activate on Day 9 of chemotherapy cycle
- Pegfilgrastim (Neulasta® or a pegfilgrastim biosimilar): Administer on day 9 of chemotherapy cycles
- Filgrastim (Neupogen® or a filgrastim biosimilar): 5 mcg/kg/day (rounded to nearest syringe size of 300 mcg or 480 mcg) starting on Day 9 for 3-7 days per physician discretion.

c. Peripheral Sensory Neuropathy – Dose modifications for cisplatin 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 cisplatin*
3	Next lowest dose level for cisplatin	Next lowest dose level for cisplatin	Discontinue
Peripheral Sensory Neuropathy Grade 4	Discontinue	Discontinue	Discontinue

*If peripheral sensory neuropathy stays at grade 2 after dose reduction, dosing can continue at the same dose level if toxicity remains grade 2

d. Non-hematologic toxicities

Dose Modifications for Cisplatin, and Gemcitabine on Day 1 or Day 8 of Each Cycle (Non-Hematologic Toxicity)*

CTCAE Grade	Treatment Modification
Grade 0-2 toxicity	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine should be reduced to next lower dose level – see below)
Grade 3 toxicity[a,c]	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level for all drugs.[a]
Grade 4 toxicity[ab]	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level for all drugs.

* Except peripheral neuropathy and nephrotoxicity (see below)
* Except for cisplatin induced ototoxicity which should be evaluated when suspected via an audiology consult and recommendations

[a] If the toxicity only affects neuropathy, then only cisplatin should be reduced (see below). If the specific toxicity is attributed to only one drug (i.e. cisplatin hypomagnesemia), okay to hold only that drug. When toxicity resolves to ≤ grade 1, then resume treatment at the next lower dose level of only that specific drug.

[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (see below).

[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

1. Sensory Neuropathy

Modify cisplatin treatment per below. Gemcitabine administration can continue during this period. Patients experiencing peripheral neuropathy that requires a delay in scheduled cisplatin dosing for ≥ 28 days will discontinue study treatment. The time to resolution to Grade ≤ 2 should be the adverse event duration used for adverse event reporting. In those patients who experience. Note: the investigator may elect to dose modify for grade 2 sensory neuropathy.

Grade 2 If persistent between cycles: decrease cisplatin at next lowest dose level

Grade 3: hold cisplatin until grade <2 then restart cisplatin at next lowest dose level

Grade 4: Discontinue cisplatin until grade < 2 then restart cisplatin at 2 dose level reduction.

2. Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity. The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Cisplatin should not be given unless adequate renal function is confirmed with a calculated creatinine clearance of ≥ 45 mL/min

8.5 White blood Cell Growth Factors

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines (http://jco.ascopubs.org/content/24/19/3187.full) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

8.6 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Rachna Shroff at rshroff@email.arizona.edu or 520-626-4175

8.7 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: Gemcitabine/ cisplatin / nab-Paclitaxel/(GCN)

REQUIRED STUDIES	Pre-Registration	Cycle 1 Wks 1-3			Cycle 2 Wks 4-6			Cycle 3 Wks 7-9			Cycle 4 [M] Wks 10-12			F/U prior to prog or recur[A]	F/U after prog or recur[L]
		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 [H]	X		X		X	X		X	X		X	X		X	X
Wt; Perform. Status [H]	X		X		X	X		X	X		X	X			
Toxicity Assessment [H]			X		X	X		X	X		X	X			
Disease Assessment [F]	X										X			X	
LABORATORY															
CBC [B]	X	X[E]	X		X	X		X	X		X	X			
Comprehensive Metabolic Panel [C]	X	X[E]			X			X			X				
CA19-9[K]	X										X				
AST & ALT	X	X[E]			X			X			X				
Serum albumin	X	X[E]													
Serum creatinine	X	X[E]			X			X			X				
SCANS															
CT or MRI for disease assessment [F]	X										X			X	
SPECIMEN SUBMISSION															
Tissue for Banking [D]		X													
Blood for ctDNA [D]		X									X			X	
TREATMENT															
nab-Paclitaxel [I]		X	X		X	X		X	X		X	X			
Gemcitabine hydrochloride [I]		X	X		X	X		X	X		X	X			
Cisplatin [I]		X	X		X	X		X	X		X	X			

Note: 1 cycle = 21 days **Click here for Footnotes.**

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://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf

9.2 Arm 2: Gemcitabine/cisplatin (GC)

REQUIRED STUDIES	Pre-Registration	Cycle 1 Wks 1-3			Cycle 2 Wks 4-6			Cycle 3 Wks 7-9			Cycle 4 [M] Wks 10-12			F/U prior to prog or recur[A]	F/U after prog or recur[L]
		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 [H]	X		X		X	X		X	X		X	X		X	X
Wt; Perform. Status [H]	X		X		X	X		X	X		X	X			
Toxicity Assessment [H]			X		X	X		X	X		X	X			
Disease Assessment [F]	X										X			X	
LABORATORY															
CBC [B]	X	X	X		X	X		X	X		X	X			
Comprehensive Metabolic Panel [C]	X	X [E]			X			X			X				
CA19-9[K]	X										X				
AST & ALT	X	X [E]			X			X			X				
Serum albumin	X	X [E]													
Serum creatinine	X	X [E]			X			X			X				
SCANS															
CT or MRI for disease assessment [F]	X										X			X	
SPECIMEN SUBMISSION															
Tissue for banking [D]		X													
Blood for ctDNA [D]		X									X			X	
TREATMENT															
Cisplatin [I]		X	X		X	X		X	X		X	X			
Gemcitabine hydrochloride [I]		X	X		X	X		X	X		X	X			

Note: 1 cycle = 21 days **Click here for Footnotes.**

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://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf

Footnotes for Arm 1 and Arm 2 Calendars:

A After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating physician) should take place every 9 weeks until progression. Exception: For patients who have come off of protocol treatment due to resection (curative surgery), these procedures should take place every 12 weeks until progression).
B CBC (Hemoglobin, WBC, platelet count, and ANC).
C Sodium, potassium, bicarbonate, chloride, BUN, calcium, total protein, magnesium, total bilirubin, and alkaline phosphatase.
D See Section 15.1 for information.
E Labs do not need to be repeated if pre-study labs were done within 14 days prior to Cycle 1 Day1.
F Disease assessment to be performed every 9 weeks (+/- 1 week) until progression using the same method as pre-study. CT or MRI must include chest, abdomen, and pelvis. For patients who have come off of protocol treatment due to resection (curative surgery), disease assessment scans and physical exams should be performed every 12 weeks until progression or recurrence using the same method as pre-study.
H Assessment must be performed prior to treatment on Days 1 and 8 of each cycle. For Cycle 1, assessment does not need to be performed on Day 1.
I Treatment on Days 1 and 8 of each cycle. No treatment on Day 15 (see Section 7.2).
K CA 19-9 must be performed at baseline and after 3 cycles of treatment have been completed.
L Follow-up performed every 6 months for 2 years and then at the end of Year 3.
M Treatment continues until one of the criteria in Section 7.3 is met.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

This study will use the RECIST 1.1. guidelines.

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.

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).

b. **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.

c. **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 **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 10.2e).

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.

10.3 **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.

10.4 **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.

10.5 **Disease Control Rate**

This is calculated based on best response as defined in Section 10.3. Disease control includes confirmed and unconfirmed complete response, confirmed and unconfirmed partial response, and stable disease. In patients with non-measurable disease, disease control will be defined as those who are alive without disease progression.

10.6 **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.

10.7 **Progression-Free Survival**

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a prospective randomized Phase III open label (not blinded) trial. The primary objective of the study is to compare overall survival (OS) between the two treatment arms. As originally planned, assuming a null hypothesis of 11.7 months median OS for the GC arm, we targeted a HR of 0.61 (experimental arm vs. control arm; median OS of 19.3 months for the GCN arm) with 34 months of accrual, 24 months of follow-up, 90% power and a 1-sided alpha of 0.025. Randomization will be assigned in a 2:1 ratio favoring the experimental arm. This required 228 eligible patients for analysis, 152 in the GCN arm and 76 in the GC arm. A total sample size of 268 patients will allow for 15% ineligible patients. The estimated monthly average accrual rate for this study is 8 patients per month with participation across the NCTN.

Prior to the first interim analysis and 14 months post-activation, 231 of 268 patients were accrued to the study at a rate of approximately 27 patients per each of the last six months. Given this rapid accrual, it was determined that a more clinically meaningful improvement in median OS could be targeted. A HR of 0.7 signifies a difference in median OS of 5 months (11.7 months in the GC arm vs. 16.7 months in the GCN arm) and requires 384 eligible patients, assuming 24 months of follow-up, 85% power and a 1-sided alpha of 0.025. To account for an ineligibility rate of 13% (based on the observed rate), this design requires enrollment of a total of 441 patients and one additional year of accrual.

11.2 Analysis Plan for Primary Endpoint

The primary analysis of OS will be conducted in all eligible patients according to the modified intent-to-treat principle, using the log-rank test with stratification by disease site (gallbladder adenocarcinoma vs. intrahepatic cholangiocarcinoma vs. extrahepatic cholangiocarcinoma), disease stage (locally advanced vs. metastatic), and Zubrod Performance Status (0 vs. 1). Distributions of overall survival by treatment arm will be estimated using the method of Kaplan-Meier.

In addition to regular study monitoring, there will be two formal interim analyses, after approximately 40% and 70% of the total expected OS events have occurred (under the alternative hypothesis). See the table for number of events and expected time when events will occur. The interim analyses will be conducted based on the total number of events specified, not the calendar time. We will apply an adaptation of the Haybittle-Peto interim spending function for both efficacy and futility stopping. At each interim analysis, evidence suggesting early termination of the trial and a conclusion that the addition of nab-paclitaxel does not improve OS would be if the alternative hypothesis of a 43% increase in median OS in the experimental arm is rejected at the 1-sided p=0.005 level. This test will use an extension of the stratified log-rank test that allows for testing a relative risk not equal to one. In addition, the null hypothesis of no difference in OS will be tested at the 1-sided 0.005 level. If the decision is to continue the study for the full specified period, we estimate that the final analysis will occur approximately 2 years after completion of accrual.

The final OS analysis will be conducted upon the observation of approximately 308 deaths (112 on the control arm and 196 on the experimental arm, assuming the alternative hypothesis), with hypothesis testing at the one-sided 0.023 significance level to account for multiple testing. The HR and 95% confidence interval will be estimated via stratified Cox regression model.

Analysis Time Point (% events)	Time from start of trial	Expected deaths		1-sided critical p-value for efficacy and futility	HR* for efficacy	HR* for futility
		Control arm	Experimental arm			
40%	21 months	45	78	0.005	0.61	1.15
70%	32 months	78	137	0.005	0.69	1.02
100%	48 months	112	196	0.023	0.79	–

*HR: experimental arm vs. control arm

11.3 Analysis Plan for Secondary Endpoints

Secondary endpoints include PFS, ORR, DCR, toxicity, and change in CA19-9 from baseline to post-treatment (after 3 cycles) in the GCN arm. Distributions of PFS will be described using cumulative incidence estimates with differences in these estimates between treatment arms assessed by a stratified Cox regression model.

The chi-square test will be used to compare ORR, DCR, and rates of toxicity events across arms. ORR will be assessed in the subset of patients with measurable disease. At least 128 eligible patients in each arm are sufficient to estimate the disease response rate to within 9% (95% confidence interval). Correlations between changes in CA19-9 levels from baseline to post-treatment and ORR will be estimated via logistic regression models, both within each treatment arm and in the overall cohort. Analyses will explore the prognostic and predictive values of CA19-9 for disease response.

Patients receiving at least one dose of any drug on any arm will be included in the assessment of adverse events. Adverse event monitoring is conducted by the study chairs, 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.

Since there is limited clinical experience with the triplet regimen, rates of serious toxicities will be compared between arms after 24 patients in the GCN arm and 12 patients in the GC arm have completed their first cycle, to inform discussions of protocol modification or early closure if required. At least 128 eligible patients in each arm are sufficient to estimate the probability of a particular toxicity to within 9% (95% confidence interval). Any toxicity occurring with at least a 3% probability is likely (98% chance) to be seen at least once.

11.4 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 Statistics and Data Management 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

This section does not apply to this protocol.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than seven calendar days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

b. CTSU Registration Procedures

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

1. **IRB Approval:**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).
Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;

- If *using NCI CIRB, rostered on the NCI CIRB Signatory record;*
- *Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and*
- *Holds* the appropriate CTEP registration type for the protocol.

Additional Requirements
Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

2. **Downloading Site Registration Documents:**

Site registration forms may be downloaded from the **S1815** protocol page located on the CTSU members' website. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol **S1815**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. **Requirements For S1815 Site Registration:**

- • IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations, access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

4. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

5. **Checking Your Site's Registration Status:**

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

- Log on to the CTSU members' website;
- Click on Regulatory at the top of your screen;
- Click on Site Registration;
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 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.

The Oncology Participant Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of participant registration/randomization assignment. OPEN will populate the participant enrollment data in NCI's clinical data management system, Medidata Rave.
Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to participant enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a participant transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.
Prior to accessing OPEN, site staff should verify the following:

- Participant has met all eligibility criteria 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 participants have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. 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

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

13.4 Registration Procedures

a. All site staff will use OPEN to enroll participants to this study. Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org, https://open.ctsu.org, or from the OPEN Participant Registration link on the SWOG CRA Workbench. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

b. 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).

13.5 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 below for details.

14.3 Data Submission Procedures

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

- To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
- To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

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

a. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

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

b. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

c. Data Quality Portal
   The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

   The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

   The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

   To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS OF REGISTRATION:

Submit the following:

S1815 Onstudy Form

Baseline Tumor Assessment Form (RECIST 1.1)

Pathology Report* (This submission is in addition to the pathology report submission to the SWOG Specimen Repository that is required by Section 15.1).

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

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

b. WITHIN 28 DAYS AFTER REGISTRATION:

If the patient consents, submit tissue and blood specimens (including pathology report) as described in Section 15.1.

c. WITHIN 15 DAYS AFTER EACH CYCLE OF TREATMENT

Submit the following:

S1815 Treatment Form

S1815 Adverse Event Form

d. WITHIN 15 DAYS AFTER EACH DISEASE ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION):

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®.)

e. WITHIN 15 DAYS AFTER 3 CYCLES OF TREATMENT:

Submit the **S1815** CA 19-9 Form

f. WITHIN 15 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1815 Treatment Form

S1815 Adverse Event Form

g. WITHIN 15 DAYS OF PROGRESSION/RELAPSE:

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®.)

Off Treatment Notice (if the patient was still on protocol treatment)

Final **S1815** Treatment Form (if the patient was still on protocol treatment)

Final **S1815** Adverse Event Form (if the patient was still on protocol treatment)

Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

h. AFTER OFF PROTOCOL TREATMENT, EVERY 6 MONTHS FOR 2 YEARS FROM REGISTRATION, AND THEN AT THE END OF YEAR 3

Submit the following:

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 **and final S1815** Treatment Form and **S1815** Adverse Event Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for Banking (***OPTIONAL FOR PATIENT***)

Sites must seek additional patient consent for banking. Specimens for banking are submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma, and Lymphoma Division, Lab #201.

An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked tissue or blood samples

will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

a. With patient's consent, the following baseline specimens must be submitted within 28 days of registration:

1. FFPE block or 10 unstained, air-dried slides (10-micron on charged slides preferred; either fresh or archival samples will be acceptable).

2. Whole Blood for ct-DNA: Collect 10 mL of blood in cfDNA Streck collection tube prior to protocol treatment.

b. With patient's consent, the following specimens must be submitted at the following timepoints until progression.

Whole Blood for Ct-DNA: Collect 10 mL of blood in cfDNA Streck collection tube.

Timepoints
- Every imaging assessment: every 9 weeks, or every 12 weeks if patient is off protocol treatment due to resection.
- When patient comes off protocol treatment.

c. Specimen Collection and Submission Instructions

Streck Cell-Free DNA Collection Tube Collection Guidelines
- Fill tube completely (10 mL)
- Immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in inaccurate test results.
- **After collection, blood in cfDNA Streck tubes should never be refrigerated**, as this will compromise the specimen. Blood collected in cfDNA Streck tubes is stable at room temperature.

If blood in Streck tube cannot be shipped the day of collection, then it must be kept at **room temperature** and shipped on the next working day to the SWOG Biospecimen Bank (Lab #201). Do not process.

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources). If collection/submission instructions differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

d. Specimen Labeling

Label blood tubes with the following:

- SWOG patient number
- Patient initials
- Collection date (date the specimen was collected from the patient)
- Specimen type (i.e., whole blood)

Include the following on FFPE tissue labels:

- SWOG patient number
- Patient initials

- Collection date (date the specimen was collected from the patient)
- Site of collection (e.g., Lymph node, left breast, liver, etc.)
- Specify whether tissue is from primary (P), metastatic (M), or normal/uninvolved (N) site
- The Surgical Pathology ID # (Accession#) and block number (e.g., A2, 3E, 2-1, B, etc.) that corresponds with the pathology report
- Note: if submitting slides, then also include the thickness (in µm).

e. Specimen collection kits

Specimen collection kits will be provided for the cfDNA Streck tubes. Kits may be ordered with the SWOG Biospecimen Bank Kit Management Application at https://ricapps.nationwidechildrens.org/KitManagement.

f. Refer to https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures for additional instructions.

15.2 SHIPPING SAMPLES

a. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org). Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

(NOTE: If a specimen had an incomplete submission, this must be documented in the Specimen Tracking System under "Special Instructions" at time of specimen submission. If no specimen was available, this must be documented in the Specimen Tracking System by choosing "Notify that Specimen Cannot be Submitted").

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue and blood samples samples for SWOG Repository Submission is identified as follows:

Lab #201: SWOG Specimen Repository
Solid Tissue, Myeloma, and Lymphoma Division

Phone: 614-722-2865
FAX: 614-722-2897
E-mail: bpcbank@nationwidechildrens.org

b. Federal guidelines for the shipment of blood products:

1. The tube must be wrapped in an absorbent material.

2. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and tube in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

Mark the box "Biohazard".

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 to SWOG Operations Office 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

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

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 as specified in Table 16.1.

In the rare event when Internet connectivity is disrupted notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

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 agent(s) used in this study is/are gemcitabine, cisplatin, and nab-paclitaxel. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 16.1 (Section 16.1.f).

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

ATTRIBUTION	Grade 4		Grade 5[a]	
	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, Pregnancy Loss, 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. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.**

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** "Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth." A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal" under the General disorders and administration SOC.**

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

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 210-614-0006. 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

17.0 BIBLIOGRAPHY

1. Valle J, Wasan H, Palmer DH, et al: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362:1273-81, 2010.

2. Shroff RT, et al. A phase II trial of gemcitabine (G), cisplatin (C), and nab-paclitaxel (N) in advanced biliary tract cancers (aBTCs). J Clin Oncol 35, 2017 (suppl; abstr 4018).

18.0 APPENDIX

18.1 Specimen Banking Instructions for the SWOG Biospecimen Bank

18.1 Specimen Banking Instructions for the SWOG Biospecimen Bank

The SWOG Bank will receive formalin-fixed, paraffin-embedded (FFPE) tumor tissue as either blocks or unstained slides at one time point. Upon receipt, the Bank will accession, barcode, and bank all FFPE specimens at room temperature until distribution.

The SWOG Bank will receive fresh whole blood in cfDNA Streck tubes at ambient temperature approximately every 9-12 weeks. Upon receipt, blood in cfDNA Streck tubes will be processed for plasma and buffy coat. Plasma will be divided into 1-mL aliquots, both buffy coat and plasma will be stored in a -80°C freezer for future studies.

Research Study Informed Consent Document

Study Title for Participants: Gemcitabine, Cisplatin, and Nab-Paclitaxel or Gemcitabine and Cisplatin in Newly Diagnosed Advanced Biliary Tract Cancers

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

S1815, A Phase III Randomized Trial of Gemcitabine, Cisplatin, and Nab-Paclitaxel Versus Gemcitabine and Cisplatin in Newly Diagnosed Advanced Biliary Tract Cancers

(NCT#03768414)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have advanced biliary tract cancer (cholangiocarcinoma or gallbladder cancer) that is newly diagnosed.

Taking part in this study is your choice.

You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

How does treating newly diagnosed, advanced biliary tract cancer (cholangiocarcinoma or gallbladder cancer) with the drugs gemcitabine and cisplatin differ when adding the study drug nab-paclitaxel?

We are doing this study because we want to find out which approach is better for newly diagnosed advanced biliary tract cancer.

What is the usual approach to my newly diagnosed advanced biliary tract cancer?

There are several treatment options for newly diagnosed advanced biliary tract cancer. Patients who are not in a study are usually treated with chemotherapy that is already FDA approved. The standard treatment for patients with newly diagnosed advanced biliary tract cancer is currently a combination of two chemotherapies, gemcitabine and cisplatin. Please talk with your doctor about alternatives before finalizing your decision to take part in this study.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above without joining this study.
- You may choose to take part in a different research study, if one is available.
- You may choose to get only comfort care to help relieve your symptoms and not get treated for your cancer. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get treatment with gemcitabine, cisplatin, and nab-paclitaxel or gemcitabine and cisplatin alone.

After you finish your study treatment, your doctor will continue to follow your condition for up to three years after you register to the study. Your doctor will watch you for side effects and to see how your cancer affects you. You will have clinic visits every six months from the time you stop taking treatment until two years after you register to the study, and then once again, at the end of the 3rd year.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that receiving the additional study drug nab-paclitaxel may not be as good as receiving the standard treatment.

There is also a risk that you could have side effects from any of the drugs on this study.

Some of the most common side effects that the study doctors know about are:

- Kidney Damage
- Abnormal blood tests
- Dehydration

If you are randomly assigned to receive nab-paclitaxel with gemcitabine and cisplatin, it is possible that side effects could worsen or become dangerous.

There may be some risks that the study doctors do not yet know about.

Benefits

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

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your 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.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your cancer or your symptoms get worse
- You have unacceptable side effects to the study drug.
- Your health changes and the study is no longer in your best interest.
- Your treatment is delayed for more than 3 weeks.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (SWOG). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the effects of adding the drug nab-paclitaxel to the standard of care drugs cisplatin and gemcitabine versus cisplatin and gemcitabine alone. Nab-paclitaxel is an FDA-approved drug, but it is not approved for use in this disease setting. The addition of the study drug nab-paclitaxel could shrink your cancer but it could also cause side effects. This study will allow researchers to know whether this different approach is better, the same, or worse than the common approach. In this study, you will get either cisplatin and gemcitabine, or nab-paclitaxel with cisplatin and gemcitabine.

There will be about 441 people taking part in this study of which 1/3 will be in the standard of care group and 2/3 will be in the study group.

Talk to your doctor about your choices before you decide if you will take part in this study.

What are the study groups?

This study has 2 study groups. You will be told which group you are in, but you and your doctor will not get to choose which group you go into if you join this study.

- **Group 1**

  If you are in this group, you will receive gemcitabine, cisplatin, and nab-paclitaxel by IV in your arm. You will receive nab-paclitaxel first over about 30 minutes followed by gemcitabine over about 30 minutes, and then cisplatin for about 60 minutes. You will receive these infusions on Day 1 and Day 8 every 21 days until you no longer receive benefit from the drug. You will not need to be admitted to the hospital for the treatment.

  There will be about 294 people in this group.

- **Group 2**

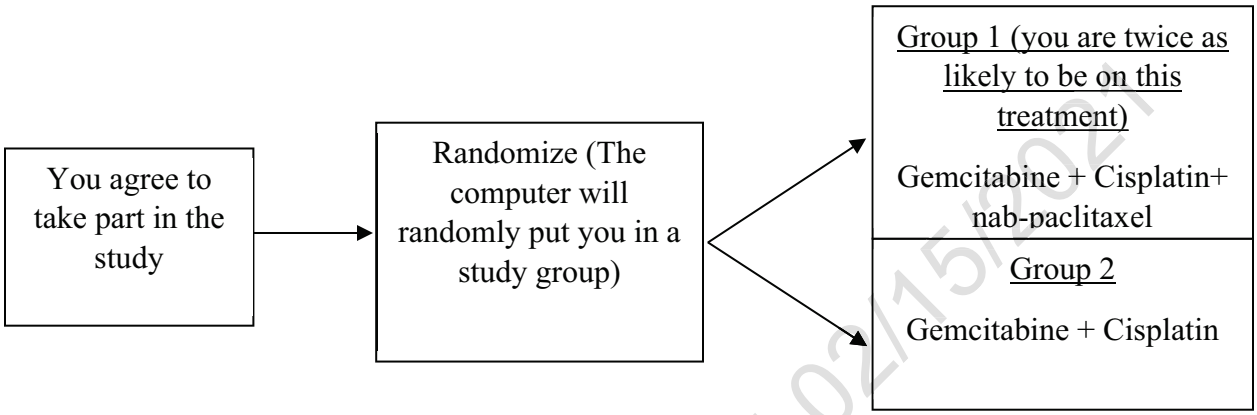
  If you are in this group, you will receive gemcitabine and cisplatin by IV in your arm. You will receive gemcitabine first over about 30 minutes and then cisplatin for about 60 minutes. You will receive these infusions on Day 1 and Day 8 every 21 days until you no longer receive benefit from the drug . You will not need to be admitted to the hospital for the treatment.

  There will be about 147 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose, and you cannot choose which study

group you are in. You will be put into a group by chance. You will have a higher chance of being in Group 1 than being in Group 2.

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



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Tumor markers
- CT or MRI every 9 weeks until your cancer worsens. If your cancer has shrunk or gone away and you have undergone surgery, you will then receive a CT or MRI every 12 weeks until your cancer worsens or returns.
- blood counts done weekly during the first 2 weeks of every treatment cycle
- Physical exams done weekly during the first 2 weeks of every treatment cycle

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

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 6 weeks after you have completed the study.

Side Effect Risks

The drugs 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 test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

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

Study Group 1 Risk Profile for Nab-Paclitaxel

You may have side effects while you are in the study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study drug that are unknown at this time. You should tell the study doctor/staff about anything that is bothering you or any side effects you have, even if you do not think they are related to the study drug.

The following is a list of the most medically significant or most common side effects reported in completed studies considered to be related to nab-paclitaxel albumin. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/therapy, and some may never go away. The study doctor may alter the dosage regimen of nab-paclitaxel (per study criteria) or give you medicines to help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

Possible side effects of Nab-paclitaxel

(*Table Version Date: October 30, 2019*)

COMMON, SOME MAY BE SERIOUS In 100 people receiving nab-paclitaxel more than 20 and up to 100 may have:
• **Swelling of the body** • **Infection, especially when white blood cell count is low which can be serious** • **Bruising, bleeding** • **Anemia, which may cause tiredness, or may require blood transfusions** • **Diarrhea, nausea, vomiting, or loss of appetite** • **Numbness and tingling of the arms and legs, muscle weakness** • **Fever** • **Tiredness** • **Dehydration** • **Hair loss, rash** • **Abnormal EKG** • **Cold symptoms such as stuffy nose, sneezing, sore throat** • **Pain in muscles and/or joints**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving nab-paclitaxel from 4 to 20 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Damage to the lungs which may cause shortness of breath** • **Pain** • **Constipation** • **Paralysis, weakness, headache** • **Abnormal heartbeat** • **Low blood pressure, which may cause feeling faint** • **High blood pressure, which may cause headaches, dizziness, blurred vision** • **Visual disturbances, blurred, or decreased vision** • **Sores in the mouth which may cause difficulty swallowing** • **Cough, shortness of breath, infection** • **Nosebleed** • **Depression** • **Infection which may cause painful and frequent urination** • **Changes in taste**

RARE, AND SERIOUS In 100 people receiving nab-paclitaxel, 3 or fewer may have:
• **Bleeding** • **Heart stops beating** • **Heart attack, which may cause chest pain, shortness of breath** • **Heart Disease** • **Blood clot which may cause swelling, pain, shortness of breath** • **Mini stroke** • **Abnormal heartbeat**

Study Group 1 and Group 2

GEMCITABINE

Possible Side Effects of Gemcitabine *(Table Version Date: January 19, 2016)*

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** • **Swelling of arms, legs**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Gemcitabine, from 4 to 20 may have:
• **Swelling and redness of the area of radiation** • **Blisters on the skin** • **Diarrhea, constipation** • **Sores in mouth which may cause difficulty swallowing** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Scarring of the lungs** • **Shortness of breath** • **Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles** • **Brain damage, brain swelling, which may cause headache, seizure, blindness**

RARE, AND SERIOUS In 100 people receiving Gemcitabine, 3 or fewer may have:
• **Severe blood Infection** • **Anemia, kidney problems which may require dialysis** • **Blood clot** • **Blockage of the airway which may cause cough**

Possible Side Effects of Cisplatin (Table Version Date: April 10, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may cause tiredness, or may require blood transfusions** • **Kidney damage which may cause swelling, may require dialysis** • **Nausea, vomiting** • **Confusion** • **Numbness and tingling of the arms and legs**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• **Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness** • **Change in taste** • **Diarrhea** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Difficulty with hearing and balance** • **Hair loss**

RARE, AND SERIOUS In 100 people receiving Cisplatin, 3 or fewer may have:
• **Seizure**

Additional Drug Risks

- A very rare condition known as Posterior Reversible Encephalopathy Syndrome has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your study doctor if you have one or more of the following symptoms; headache, abnormal shaking of body, sleepiness, increased blood pressure, feeling confused, abnormal vision including loss of vision, loss of muscle control or muscle weakness, numbness or tingling in extremities.
- A very rare condition known as Capillary Leak Syndrome that causes leaking of fluid outside of blood vessels has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your study doctor if you have one or more of the following symptoms: fatigue; lightheadedness or fainting; pain in arms, legs, or stomach or all over body; swelling in face or body; difficulty breathing; low blood pressure.
- an inflammation of the small blood vessels described as pain, heat, and redness to the affected part of the body.
- dying tissue due to lack of blood supply described as skin discoloration, severe pain, foul smelling leakage from a sore, and may include swelling, and increased temperature to the affected region of the body.

The study drugs could interact with other drugs and foods. You should avoid grapefruit juice and any other drugs your doctor discusses with you.

Rarely, there are problems getting enough supplies of the study drugs. If that happens, your doctor will talk with you about your options.

Risks of Venipuncture/Intravenous Needle Insertion:

Occasional, some may be serious: Mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Rare: Severe pain, swelling, infection from the actual injection, and fainting.

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.

What are my responsibilities in this study?

If you choose to take part in this study, you will need to

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.

For Women: Do not get pregnant or breastfeed while taking part in this study. Tell your doctor right away if you think that you or your partner have become pregnant during the study or up to 1 month after your last dose of study drug. **For men:** Do not father a baby while taking part in this study and up to 6 months after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your biliary tract cancer. This includes

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- your insurance co-pays and deductibles.
- the cost of gemcitabine, and cisplatin

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

You or your insurance provider will not have to pay for the nab-paclitaxel while you take part in this study.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are

- The study sponsor and any company supporting the study now or in the future.
- The Institutional Review Board (IRB), which 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 (FDA) and the groups it works with to review research
- The National Cancer Institute (NCI) and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

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.

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, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or 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. ^

Optional studies that 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. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading this optional study hope the results will help other people with your type of 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.

Taking part in this optional study is your choice. You can still take part in the main study even if you say "no" to this optional study. There is no penalty for saying "no." You and your insurance company will not be billed for this optional study. If you sign up for, but cannot complete this study for any reason, you can still take part in the main study.

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

1. Contact for Future Research

Occasionally, researchers working with SWOG may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to 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**

2. Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, blood and tissue (from a previous biopsy) will be collected and stored.

Storing samples for future studies is called "biobanking." The biobank is being run by Nationwide Children's Hospital and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

We don't know what research may be done in the future using your tumor tissue, or blood samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- Future research studies may include sequencing of all or part of your DNA called genomic sequencing. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems.
- You will not get reports or other information about any research that is done using your samples.

What is involved in this optional sample collection?

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

1. About 2 tablespoons of blood will be collected from a vein in your arm. A sample from the tissue that was collected will be sent to the biobank before you start treatment. A sample from the tissue that was collected at the time of your biopsy (or the entire block of tissue) will be sent to the biobank for use in future studies.
2. About 4 teaspoons of blood will be taken at the same time blood is being collected for your treatment on the study. You will have this extra blood taken before you begin treatment and every time you have a scan for your disease (either a CT or MRI), which is about every 9 weeks if that happens.
3. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
4. Researchers can only get samples from the biobank after their research has been approved by experts.
5. Researchers will not be given your name or contact information.
6. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

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

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

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 to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

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 biobank know. Samples that remains in the biobank will not be used. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

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 below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

I agree that my samples and related information may be kept in a Biobank for use in future health research.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the 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 and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature _____

Date of signature _____

Signature of person(s) conducting the informed consent discussion

Date of signature_____