Protocol Title

A Phase II Study of FOLFOX combined with Nab-Paclitaxel (FOLFOX-A) in the Treatment of Metastatic or Advanced Unresectable Gastric, Gastro-Esophageal Junction Adenocarcinoma.
Big Ten Cancer Research Consortium: BTCRC-GI15-015

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PROTOCOL SIGNATURE PAGE

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VERSION DATE: 15FEB2021

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

_____ _____
Signature of Site Investigator Date

_____
Site Investigator Name (printed)

_____
Site Investigator Title

_____
Name of Facility

_____
Location of Facility (City and State)

PLEASE EMAIL COMPLETED FORM TO BIG TEN CRC ADMINISTRATIVE HEADQUARTERS

SYNOPSIS

TITLE	A Phase II Study of FOLFOX combined with Nab-Paclitaxel (FOLFOX-A) in the Treatment of Metastatic or Advanced Unresectable Gastric, Gastro-Esophageal Junction Adenocarcinoma. Big Ten Cancer Research Consortium: BTCRC-GI15-015
SHORT TITLE	FOLFOX-A in the Treatment of Metastatic or Advanced Unresectable Gastric, Gastro-Esophageal Junction Adenocarcinoma
PHASE	II
OBJECTIVES	Primary Objective: • To estimate the overall objective response rate (CR+PR) of FOLFOX combined with nab-paclitaxel (FOLFOX-A) in patients with advanced gastric, gastroesophageal junction adenocarcinoma. Secondary Objectives: • To evaluate clinical efficacy by assessment of median OS, PFS, TTP as well as best ORR and disease control rate (DCR) • Describe the safety and toxicity profile of the combination of nab-paclitaxel and FOLFOX in this population
KEY ELIGIBILITY CRITERIA	Inclusion: 1. Histologically-confirmed advanced or metastatic unresectable gastric carcinoma, or adenocarcinoma of the gastroesophageal junction. 2. Prior neoadjuvant or adjuvant chemotherapy, hormonal therapy, immunotherapy, radiation or chemoradiotherapy must have been completed at least 6 months prior to documented recurrence or metastatic disease. **NOTE**: patients must not have received previous systemic treatment for metastatic disease. 3. Evaluable disease according to RECIST v1.1 for solid tumors, within 28 days prior to registration. 4. Demonstrate adequate organ function as described below. a. Bilirubin $\leq$ 1.5 mg/dL b. Patients must have adequate liver function: AST and ALT $\leq$ 2.5 $\times$ upper limit of normal, alkaline phosphatase $\leq$ 2.5 $\times$ upper limit of normal, unless bone or liver metastasis is present ($\leq$5 $\times$ upper limit of normal). c. Patients must have adequate bone marrow function: Platelets >100,000 cells/mm^3 (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to laboratory sample), Hemoglobin > 9.0 g/dL and ANC $\geq$ 1,500 cells/mm^3. d. Patients must have adequate renal function: creatinine $\leq$1.5 mg/dL or creatinine clearance $\geq$60 mL/min is recommended; however, institutional norms are acceptable. Exclusion: 1. Her-2 positive gastric tumor

	2. Preexisting peripheral neuropathy is not allowed from any cause. 3. Known history of Human Immunodeficiency Virus (HIV) or Hepatitis C (baseline testing is not required) 4. Patients with active sepsis or pneumonitis 5. Known hypersensitivity to fluorouracil (5-FU), oxaliplatin, or other platinum agents. 6. Known hypersensitivity to nab-paclitaxel or any of its excipients. 7. History of slowly progressive dyspnea and unproductive cough, or pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis or multiple allergies. See section 6.5.1. 8. Has known dihydropyrimidine dehydrogenase deficiency (DPD) deficiency (testing not required) 9. Ongoing or active infection requiring systemic treatment (must be afebrile for ≥ 48 hours prior to study registration) 10. Uncontrolled intercurrent illness including, but not limited to any of the following: a. Symptomatic congestive heart failure b. Unstable angina pectoris c. Cardiac arrhythmia
STATISTICAL CONSIDERATIONS	The primary endpoint will be the objective response rate (partial or complete response). A Simon (1989), optimal two-stage design will be employed. A 5% response rate precludes further study whereas a 20% response rate would indicate that further investigation of the treatment is warranted (i.e., P0=0.05 and P1=0.20 in the Simon terminology). Using α and β errors of 0.10 and 0.10, respectively, 12 patients will be enrolled in the first stage and if no responses are observed, the trial will be terminated. Otherwise, an additional 27 patients will be enrolled in the second stage and if ≤ 3 responses are observed among the 39 patients, the agent will not be considered worthy of further testing; whereas, if 4 or more responses are observed the drug will be considered sufficiently active to justify further study. This design has 90% power under the alternative hypothesis and provides a 54% probability of early stopping if the true response rate is only 5%.
TOTAL NUMBER OF SUBJECTS	39
ESTIMATED ENROLLMENT PERIOD	18 months
ESTIMATED STUDY DURATION	24 months

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SCHEMA

A Phase II Study of FOLFOX combined with Nab-Paclitaxel (FOLFOX-A) in the Treatment of Metastatic or Advanced Unresectable Gastric, Gastro-Esophageal Junction Adenocarcinoma.
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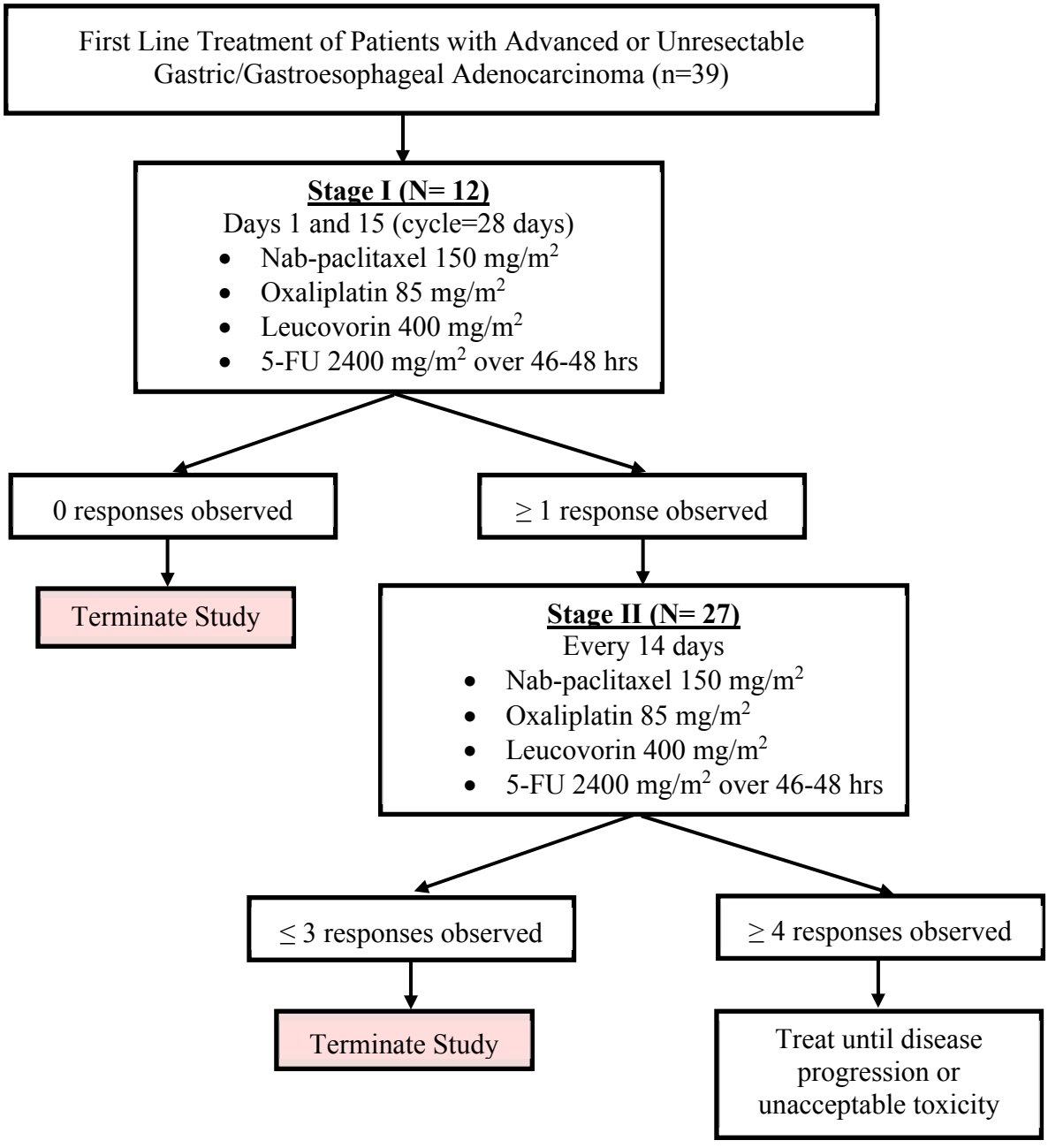

1. BACKGROUND AND RATIONALE

1.1 Gastric Cancer- Disease Overview

Gastric Cancer is one of the most common types of cancer, ranking third among the most prevalent malignancies. [1] Despite the introduction of new drugs and treatment strategies, the clinical outcomes for this malignancy remains poor, with a 5-year survival rate of only about 20 percent (all stages). The primary curative option in this clinical scenario is surgical excision. Unfortunately, most patients are diagnosed with advanced disease, making surgical resection either not feasible or available with purely palliative intent. While earlier diagnosis would help to improve outcomes for patients with gastric cancers, a significant unmet medical need exists because no effective therapy has yet been identified. The current standard chemotherapy regimens appear to have a marginal survival benefit. Hence newer agents and combinations are desperately needed.

Chemotherapy likely provides some benefit for patients with advanced gastric/gastroesophageal junction (GEJ) cancers. In a recent meta-analysis, it was concluded that chemotherapy produces superior survival as compared with best supportive care. [2] It was also concluded that combination chemotherapy (usually using a fluoropyrimidine, a taxane, an anthracycline, and a platinum agent) improves survival as compared with single-agent chemotherapy, but with additional toxicity. [3] Nonetheless, the prognosis for patients with advanced gastric cancer is dismal, with median survival typically being less than 10 months. [4]

1.2 Treatment of Gastric Cancer

A number of validated doublet and triplet chemotherapy combinations are available as first line therapy, although there is no consensus as to the best regimen for initial chemotherapy of advanced esophagogastric cancer. In general, combination chemotherapy regimens provide higher response rates than do single agents, but this translates into only modestly longer durations of disease control and survival that are measured in weeks to a few months. In randomized trials, the ECF (epirubicin, cisplatin, infusional 5-fluorouracil [5-FU]) and DCF ([TCF] docetaxel, cisplatin, infusional 5-FU) combinations have emerged as standard regimens for first-line treatment, unfortunately however adding increased toxicity and possible worsening patients' quality of life (QOL). Hence better-tolerated chemotherapy alternatives that can provide higher efficacy and better tolerability are urgently needed.

Platinum–taxane combinations like DCF are an established regimen for treatment in advanced gastric / GEJ adenocarcinoma. Docetaxel plus cisplatin and 5-FU (the DCF or TCF regimen), was compared with cisplatin and 5-FU alone in a multi-national TAX-325 trial that enrolled 457 patients with chemotherapy-naïve advanced gastric cancer. Patients received either 21-day cycles of cisplatin (75 mg/m^2 on day 1) plus infusional 5-FU (750 mg/m^2 daily, days 1 to 5) and docetaxel (75 mg/m^2 on day 1), or 28-day cycles of cisplatin (100 mg/m^2 on day 1) plus infusional 5-FU (1000 mg/m^2 per day days 1 to 5). The group receiving docetaxel did significantly better in terms of response rates (37 versus 25 percent), time to progression (TTP, 5.6 versus 3.7 months), and two-year survival (18 versus 9 percent). Although the incidence of grade 3 or 4 diarrhea (20 versus 8 percent) and neutropenia (30 versus 14 percent) was higher with triple therapy, rates of any grade 3 or 4 toxicity during therapy were high in both groups (81 and 75 percent, respectively). [5]

The support of oxaliplatin as an anchor drug in advanced gastric cancer comes from extensive data that suggest that oxaliplatin is at least as effective as cisplatin in combination regimens for patients with

advanced gastric and esophagogastric cancer. A meta-analysis of the Randomised ECF for Advanced and Locally Advanced Esophagogastric Cancer-2 (REAL-2) study in conjunction with two other randomized phase II trials showed that oxaliplatin was associated with significant improvements in PFS (HR 0.88, 95% I 0.80-0.98) and overall survival (HR for death 0.88, 95% CI 0.78-0.99), and fewer neutropenia, anemia, alopecia, and thromboembolic events, but more neurotoxicity and diarrhea. [6] [7] [8] Although oxaliplatin has been used in the backbone chemotherapy in a number of trials in combination with other cytotoxic agents in advanced gastric/esophagogastric tumors, overall there was not a significant improvement in efficacy.

The poor prognosis for patients diagnosed with metastatic gastric/esophagogastric cancer suggests the need for 1) a more effective agent to improve and expand treatment options and 2) to create a better-tolerated alternative to those standard regimens currently used as first line regimens.

1.3 Role of Nab-Paclitaxel

Paclitaxel is a hydrophobic molecule and is dissolved in a solvent, cremophor EL (CrEL), which has been associated with significant risk of hypersensitivity reactions and neuropathy. Moreover, CrEL is also known to impair free drug delivery to the tumor, limiting clinical effectiveness of paclitaxel [9]. Nab-paclitaxel (Abraxane®, Celgene, Summit, NJ) was developed as a solvent-free, albumin-bound colloidal formulation of paclitaxel for intravenous (IV) use allowing for shorter infusion time without pre-medications or specialized infusion sets. Comparative intra-tumoral and anti-tumoral activity of nab-paclitaxel has been demonstrated to be greater than CrEL-paclitaxel in multiple tumor types using preclinical models [10, 11]. In nude mice bearing human xenograft breast tumors, nab-paclitaxel treated mice showed more complete regressions, longer time to recurrence, longer doubling time and prolonged survival compared to paclitaxel [12]. Moreover, pharmacokinetic modeling has shown that nab-paclitaxel has lower risk for neutropenia when compared to equivalent dosing of paclitaxel due to shorter time of free paclitaxel concentration in serum [13, 14]. In a Phase III clinical trial in patients with metastatic breast cancer, nab-paclitaxel demonstrated higher response rates, better safety and side-effect profile compared to conventional paclitaxel, and improved survival in patients receiving it as second line therapy [15].

In pancreatic cancer, Von Hoff et al. published pre-clinical in vivo data showing that the aggregate tumor regression response in individual xenografts were 22/90 (24%), 34/95 (36%), and 53/96 (55%) for gemcitabine, nab-paclitaxel, and gemcitabine plus nab-paclitaxel, respectively [16]. The combination of nab-paclitaxel with gemcitabine was studied in a Phase I/II trial in patients with metastatic pancreatic cancer and showed promising clinical activity with improvement in median OS to 12.2 months [16] from 5.65 months with single agent gemcitabine [17]. The maximum-tolerated dose (MTD) for the combination was defined as gemcitabine 1000 mg/m2 IV and nab-paclitaxel 125 mg/m2 IV on days 1, 8, 15 every 28 days [16]. This led to the MPACT International Multi-Center Phase III Trial conducted in 861 patients comparing nab-paclitaxel plus gemcitabine to gemcitabine monotherapy as first line treatment of metastatic pancreatic adenocarcinoma. Results significantly favored the nab-paclitaxel plus gemcitabine arm of the trial with a median OS of 8.5 months (95% CI=7.89, 9.53) versus 6.7 months (95% CI=6.01, 7.23) in the gemcitabine arm. The HR of nab-paclitaxel plus gemcitabine/gemcitabine (HRA+G/G) was 0.72 (95% CI=0.617, 0.835) indicating a 28% overall reduction in the risk of death for patients receiving the combination of nab-paclitaxel and gemcitabine, $p<0.0001$, stratified log rank test [18]. The updated results from this trial were presented at the 2014 Gastrointestinal Cancers Symposium. The gemcitabine/nab-paclitaxel combination resulted in a statistically significant

improvement in OS (8.7 versus 6.6 months; HR, 0.72; p<0.0001) compared to gemcitabine alone in patients with advanced pancreatic cancer [9]. Nab-paclitaxel has also shown anti-tumor activity in other advanced cancer types, including breast [15], lung [20], and melanoma [21] and has received FDA approval for use in breast, non-small cell lung and pancreatic cancers.

1.4 Rationale for the Current Study and Dose Selection

Given the high toxicity associated with current standard platinum-taxane combination regimen (like DCF) and poor tolerability, alternative regimens of taxane-platinum combinations are urgently needed. Hence our rationale to explore our combination of FOLFOX and nab-paclitaxel (FOLFOX-A) in advanced gastric /GEJ adenocarcinoma. We hypothesize that this combination (FOLFOX-A) will have a higher efficacy, a better tolerability, and enhanced patient reported outcomes. Hence, our proposed phase II single arm trial of FOLFOX + nab-paclitaxel in chemotherapy –naïve unresectable, advanced gastric /GEJ adenocarcinoma.

Safran et al (ASCO 2014) reported the results of a phase I study of FOLFOX + Nab-paclitaxel in advanced pancreatic cancer that has established the MTD of the combination. The MTD for Nab-paclitaxel was 150 mg /m2 IV Q 2 weeks when combined with FOLFOX regimen. In this phase I study, 89% who received >10 cycles of the combination developed grade 2 neuropathy, 22% developed grade 3 neuropathy. The study recommended oxaliplatin dose reduction to 65 mg/m2 if patients developed grade 2 neuropathy. Hence our rationale for this dosage of nab-paclitaxel when combined with FOLFOX as proposed in our study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To estimate the overall objective response rate (CR+PR) of FOLFOX combined with nab-paclitaxel (FOLFOX-A) in patients with advanced gastric, gastroesophageal junction adenocarcinoma.

2.1.2 Secondary Objectives

- To evaluate clinical efficacy by assessment of median OS, PFS, TTP as well as best ORR and disease control rate (DCR)
- Describe the safety and toxicity profile of the combination of nab-paclitaxel and FOLFOX in this population

2.2 Endpoints

2.2.1 Primary Endpoint

- Objective response rate will be calculated by combining the number of subjects who achieve complete response and partial response per RECIST 1.1 criteria

2.2.2 Secondary Endpoints

- Assessment of median OS, PFS, TTP as well as best ORR and disease control rate (DCR)
- Grade 3 and 4 toxicities as defined by the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.

3. ELIGIBILITY CRITERIA

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. The target population for this study is patients with advanced gastric/GEJ adenocarcinoma. This will be a multicenter trial conducted at participating sites within the Big Ten Cancer Research Consortium (Big Ten CRC). Northwestern University will serve as the lead site.

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

2. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
3. Age ≥ 18 years at the time of consent.
4. ECOG Performance Status of 0-1 within 28 days prior to registration.
5. Histologically-confirmed advanced or metastatic unresectable gastric carcinoma, or adenocarcinoma of the gastroesophageal junction.
6. Prior neoadjuvant or adjuvant chemotherapy, hormonal therapy, immunotherapy, radiation or chemoradiotherapy must have been completed at least 6 months prior to documented recurrence or metastatic disease. **NOTE**: patients must not have received previous systemic treatment for metastatic disease.
7. Evaluable disease according to RECIST v1.1 for solid tumors, within 28 days prior to registration.
8. Demonstrate adequate organ function as described below; all screening labs to be obtained within 28 days prior to registration.
   a. Bilirubin ≤ 1.5 mg/dL
   b. Patients must have adequate liver function: AST and ALT ≤ 2.5 × upper limit of normal, alkaline phosphatase ≤ 2.5 × upper limit of normal, unless bone or liver metastasis is present (≤5 × upper limit of normal).
   c. Patients must have adequate bone marrow function: Platelets >100,000 cells/mm^3 (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to laboratory sample), Hemoglobin > 9.0g/dL and ANC ≥ 1,500 cells/mm^3.
   d. Patients must have adequate renal function: creatinine ≤1.5 mg/dL or creatinine clearance ≥60mL/min is recommended; however, institutional norms are acceptable.
9. Females of child-bearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:
   a. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis), or agree to use and be able to comply with effective contraception without

interruption 28 days prior to starting investigational product (IP), and while on study medication (including dose interruptions) and for 30 days following the last dose of IP; and

b. Have a negative serum pregnancy test (β -hCG) result at screening and agree to ongoing pregnancy testing prior to each treatment and after the end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

c. Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 6 months following IP discontinuation, even if he has undergone a successful vasectomy.

*NOTE: True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Her-2 positive gastric tumor.
2. Treatment with any investigational products within 28 days prior to study registration.
3. Preexisting peripheral neuropathy is not allowed from any cause.
4. Known history of Human Immunodeficiency Virus (HIV) or Hepatitis C (baseline testing is not required).
5. Patients with active sepsis or pneumonitis
6. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to trial registration and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial registration.
7. Known hypersensitivity to fluorouracil (5-FU), oxaliplatin, or other platinum agents.
8. Known hypersensitivity to nab-paclitaxel or any of its excipients.
9. History of slowly progressive dyspnea and unproductive cough, or pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis or multiple allergies. See section 6.5.1.
10. Has known dihydropyrimidine dehydrogenase deficiency (DPD) deficiency (testing not required)
11. Ongoing or active infection requiring systemic treatment (must be afebrile for ≥ 48 hours prior to study registration)
12. Uncontrolled intercurrent illness including, but not limited to any of the following:
    - Symptomatic congestive heart failure
    - Unstable angina pectoris
    - Cardiac arrhythmia

13. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).
14. Known additional malignancy within the past 3 years. Exceptions include treated localized basal cell or squamous cell carcinoma of the skin, in situ cervical or vulvar carcinoma that has undergone potentially curative therapy, superficial bladder tumors (Ta, Tis & T1), ductal carcinoma in situ (DCIS) of the breast and low grade prostate cancer (Gleason sore 6). Any cancer curatively treated > 3 years prior to registration with no clinical evidence of recurrence is permitted.
15. Psychiatric illness/social situations that would limit compliance with study requirements.
16. Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

4. SUBJECT REGISTRATION

All subjects must be registered through Big Ten CRC Administrative Headquarters' electronic data capture (EDC) system, OnCore. A subject is considered registered when an 'On Study' date is entered into the EDC system.

Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy within **5 business days** of registration.

5. TREATMENT PLAN

This is an open label, single-arm phase II, multi-institutional trial to evaluate the efficacy and safety of the combination of nab-paclitaxel and FOLFOX (FOLFOX-A) as first line therapy for patients diagnosed with histologically-confirmed advanced gastric/GEJ adenocarcinoma.

All patients will receive FOLFOX-A on days 1 and 15 of each cycle (1 cycle = 28 days). Nab-paclitaxel will be given at a dose of 150 mg/m^2 IV over 30 minutes, followed by oxaliplatin IV 85 mg/m^2 and leucovorin IV 400 mg/m^2 over 2 hours, and 5-FU as a continuous IV infusion over Day 1 and Day 2 (for a total dose of 2400mg/m^2 over 46-48 hours.). Radiographic assessment will be performed at baseline and every other cycle (starting with Cycle 3) to evaluate response to treatment by RECIST Version 1.1 guidelines. Patients may continue to receive treatment until disease progression or unacceptable toxicity. The primary endpoint will be objective response rate (partial or complete response). A maximum of 39 patients will be enrolled.

5.1 Pre-medication and Hydration

Patients may receive premedication with diphenhydramine (25-50 mg IV) 30 minutes prior to nab-paclitaxel or per institutional standards.

5.2 Dose Calculations

Body Surface Area (BSA)

BSA calculations will be used for dosing of all drugs. BSA should be calculated on Cycle 1 Day 1 based on the subject's current height and actual body weight using the DuBois formula. BSA will be recalculated per the site's standard of care, or if Day 1 body weight changes by more than 10%. Actual

heights and weights should be used to calculate surface areas (no downward adjustment to "ideal" weight). This principle applies to individuals whose calculated surface area is 2.2 m^2 or less. In those rare cases where a patient's surface area is greater than 2.2 m^2, the actual surface area or 2.2 may be used. Dosing BSA may be capped if the treating physician believes it is in the best interest of an obese patient.

5.3 Treatment Administration

Patients may receive premedication with dexamethasone 20 mg within 12 hours prior to the nab-paclitaxel. Diphenhydramine (25-50 mg IV) may be given 30 minutes prior to nab-paclitaxel or per institutional standards. Nab-paclitaxel will be administered first followed by FOLFOX over a period of 46-48 hours.

Agent	Full Dose Administration[1]	Days of Administration[2]
Nab-Paclitaxel[3]	150 mg/m^2 IV over 30-40 mins	D1, D15
Oxaliplatin	85 mg/m^2 IV over 2 hours (±15 min)	D1, D15
Leucovorin	400 mg/m^2 IV over 2 hours (±15 min). This may be given either concurrently with oxaliplatin (e.g. y-site or separate line) or after oxaliplatin has been infused, according to site standard procedures.	D1, D15
5-FU	2400 mg/m^2 IV continuously over 46-48 hours. Administer after oxaliplatin and leucovorin.	D1-2, D15-16

[1] Recalculate BSA per site standard of care or when Day 1 actual body weight changes by ≥ 10%.
[2] A window of +/- 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).
[3] Nab-Paclitaxel will be administered first, immediately followed by FOLFOX

Patients will be monitored by infusion center nursing staff every 15 minutes during infusions or per institutional standards, and treatment will be interrupted for any evidence of an infusion reaction. If hypersensitivity symptoms develop, the infusion will be stopped. Patients will be treated with additional H1 antagonist, as well as an H2 antagonist (such as famotidine 20 mg or ranitidine 50 mg IV) at the discretion of the treating investigator. If hypersensitivity symptoms are mild (grade 1 or 2) and resolve over 30-60 minutes of observation with administration of additional H1 and H2 blockers, the study drug infusion may resume with caution at a reduced rate (over approximately 60 minutes), at the discretion of the treating investigator. Additional supportive care measures should be available at each study site infusion center in case of severe hypersensitivity reaction.

5.4 Concomitant Medications

5.4.1 Allowed Concomitant Medications

All treatments the site investigator considers necessary for a subject's welfare may be administered at the discretion of the site investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded if associated with SAEs.

5.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial. The Exclusion Criteria describes other medications that are prohibited in this trial.

- Anti-cancer systemic chemotherapy or biological therapy
- Chemotherapy not specified in this protocol
- Investigational agents other than nab-paclitaxel
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with sponsor-investigator by contacting the Big Ten CRC project manager.

Subjects who, in the assessment by the site investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial treatment. Subjects may receive other medications that the site investigator deems to be medically necessary off trial treatment.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5 Supportive Care

Standard supportive care should be followed at each site per their guidelines. Patients should receive *full supportive care*, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The use of epoetin products is not allowed.

Supportive care measures may include but are not limited to the items outlined below:

Nausea/vomiting:
Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

Antimicrobials:
Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the site investigator for a given infectious condition, according to standard institutional practice.

Diarrhea/Colitis:
Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

A new cycle of FOLFOX-nab-paclitaxel **may not** be administered to the participant until the following criteria are met:

- the ANC has recovered according to Table 3;
- the platelet count has recovered according to Table 3;
- stomatitis or diarrhea have recovered to grade 1 or less;
- fatigue has recovered to grade 2 or less.
- All other study drug-related, clinically significant, non-hematological toxicity must have resolved to grade 1 or baseline. This does not include alopecia.

If the patient does not meet these criteria, delay Day 1 until recovery to above guidelines. Delay the cycle until these requirements are met. Patients who require a treatment delay of more than 6 weeks from the scheduled treatment day due to toxicity will be removed from protocol treatment.

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the

event requires expedited reporting **in addition** to routine reporting.

6.2 Dose Levels for Dose Reductions

The tables below indicate potential dose levels for each of the agents for which dose modifications will be allowed. It is recommended that treating investigators follow standard institutional practice guidelines for dose modification within the FOLFOX chemotherapy regimen. Dose adjustments of each agent may be made independently based on the specific types of toxicities observed. There will be no dose reduction of leucovorin.

The following adjustments in the table below should be made to the appropriate drug (depending on the attribution of toxicity) based on the dose reduction guidelines. In addition, please note:

- If more than one toxicity requiring dose reduction occurs, use lowest dose level required.
- If multiple toxicities are seen, the dose administered in subsequent cycle should be based on the most severe toxicity experienced in the current cycle.
- Patients not experiencing resolution of their neutropenia within 28 days (ANC $\geq 1.0 \times 10^3$ cells/L), despite uninterrupted Granulocyte-Colony Stimulating Factor (G-CSF) treatment, will be discontinued from all study treatment.

Table 2: FOLFOX-A Dose Modification Schedule

	Nab-paclitaxel	Oxaliplatin	Leucovorin	5-FU
Starting Dose level	150 mg/m^2	85mg/m^2	400 mg/m^2	2400mg/m^2
Dose level -1	120 mg/m^2	65 mg/m^2	400 mg/m^2	1920 mg/m^2
Dose level -2	95 mg/m^2	50 mg/m^2	400 mg/m^2	1600 mg/m^2

Each drug can be dose reduced a total of 2 times. All dose reductions are permanent.

6.3 Hematologic Toxicities

The following table describes the recommended dose modifications at the start of each course of therapy, based on the pretreatment labs for that cycle.

Table 3: FOLFOX Dose Modification Guidelines

Toxicity and Grade	Action to be Taken
Neutropenia (ANC)	
Grade 1: <LLN – 1.5 × 10^9/L **Grade 2**: 1.5 – 1.0 × 10^9/L	Maintain dose level
Grade 3: <1.0 - 0.5 × 10^9/L	Hold FOLFOX-A. When ANC has recovered to ≤ grade 2, resume treatment and decrease oxaliplatin by one dose level.
Grade 4: <0.5 × 10^9/L	Hold FOLFOX-A and check CBC weekly. When ANC has recovered to ≤ grade 2, resume treatment and decrease both 5-FU and oxaliplatin by one dose level. If ANC < 1.0 × 10^9/L after 4 weeks, discontinue therapy.
Thrombocytopenia (PLT)	
Grade 1: <LLN – 75.0 × 10^9/L	Maintain dose level.

Toxicity and Grade	Action to be Taken
Grade 2: <75.0 – 50.0 × 10^9/L **Grade 3**: <50.0 – 25.0 × 10^9/L	Hold FOLFOX-A. When PLT has recovered to ≤ grade 1, resume treatment and decrease oxaliplatin by one dose level.
Grade 4: <25.0 × 10^9/L	Hold FOLFOX-A and check CBC weekly. When PLT has recovered to ≤ grade 1, resume treatment and decrease both 5-FU and oxaliplatin by one dose level. If PLT < 75 × 10^9/L after 4 weeks, discontinue therapy.
Febrile Neutropenia	
Grade 3 or greater: ANC <1.0 × 10^9/L and fever 38.5°C (101°F)	Hold FOLFOX-A and check CBC weekly. When ANC has recovered to >1.0 × 10^9/L, and any infection is under control, resume treatment and decrease both 5-FU and oxaliplatin by one dose level. If ANC < 1.0 × 10^9/L after 4 weeks, and/or fever or infection has not resolved after 4 weeks, discontinue therapy.

6.4 Neuropathy

The goal of the following dose modifications are to prevent patients from developing grade 3/4 neuropathy during or after completion of FOLFOX-A. Fluorouracil and leucovorin will not be reduced for neuropathy.

6.4.1 For patients experiencing grade 2 neuropathy:

- Hold Oxaliplatin
- To reinstitute oxaliplatin in patients with a **first episode** of grade 2 neuropathy, neuropathy must have improved to Grade ≤ 1, however, nab-paclitaxel, 5-FU and leucovorin may be administered. Oxaliplatin should be permanently reduced to dose level - 1 (65mg/m^2). Nab-paclitaxel, 5-FU and leucovorin will not be reduced for grade 2 neuropathy.
- To reinstitute oxaliplatin in patients with a **second episode** of grade 2 neuropathy, neuropathy must have improved to Grade ≤ 1, however, nab-paclitaxel, 5-FU and leucovorin may be administered. Oxaliplatin should be permanently reduced dose level - 2 (50mg/m^2). Nab-paclitaxel, 5-FU and leucovorin will not be reduced for grade 2 neuropathy.
- Oxaliplatin should be permanently discontinued for patients developing a **third episode** of grade 2 neuropathy. However, nab-paclitaxel, 5-FU and leucovorin may be continued.
- At the investigator's discretion, FOLFOX-A may be held for up to six weeks secondary to patient's experiencing grade 2 neuropathy. The reason for hold (grade 2 neuropathy) must be documented in the eCRF.

6.4.2 For patients experiencing grade 3 neuropathy:

- Hold FOLFOX-A until neuropathy improves to ≤ grade 1.
- When treatment is resumed after the **first episode**, oxaliplatin and nab-paclitaxel should be permanently decreased to 65mg/m^2 and 120mg/m^2 respectively (dose level -1). 5-FU and Leucovorin will not be reduced for grade 3 neuropathy.
- When treatment is resumed after the **second episode,** oxaliplatin and nab-paclitaxel should be permanently decreased to 50mg/m^2 and 95mg/m^2 respectively (dose level -2).
- Patients developing a **third episode** of grade 3 neuropathy should be removed from study treatment. The reason for patient discontinuation must be documented as secondary to grade 3 neuropathy.

- At the investigator's discretion, FOLFOX-A may be held for up to six weeks secondary to patient's experiencing grade 3 neuropathy. The reason for hold (grade 3 neuropathy) must be documented in the eCRF.

6.4.3 Grade 4 neuropathy:

- For patients experiencing grade 4 neuropathy, patients must come off study treatment.

6.5 Interstitial Pneumonitis

Interstitial pneumonitis has been observed in < 1% during *nab*-paclitaxel monotherapy and in < 1% during combination treatment with *nab*-paclitaxel and carboplatin. However, the risk has been higher for the combination of *nab*-paclitaxel with gemcitabine. Pneumonitis has been reported at a rate of 4% with the use of *nab*-paclitaxel in combination with gemcitabine. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with *nab*-paclitaxel and promptly initiate appropriate treatment and supportive measures.

6.5.1 Prevention, Surveillance and Management of Interstitial Pneumonitis:

- Before starting treatment with *nab*-paclitaxel candidates should be evaluated for familial, environmental or occupational exposure to opportunistic pathogens: do not enroll patients with a history of slowly progressive dyspnea and unproductive cough, or pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis or multiple allergies.
- During treatment with *nab*-paclitaxel episodes of transient or repeated dyspnea with unproductive persistent cough or fever should be paid attention to. Radiographic evaluation with chest X-rays and computed tomography (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 microbiological and/or immunologic 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.
- Upon a diagnosis of interstitial pneumonitis *nab*-paclitaxel should be permanently discontinued. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. 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.

6.6 Sepsis:

Sepsis occurred in 5% in patients with or without neutropenia receiving *nab*-paclitaxel/gemcitabine. Biliary obstruction or presence of biliary stent, were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold *nab*-paclitaxel until fever resolves and ANC ≥ 1500, then resume treatment and reduce all drugs by one dose level.

6.7 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities, a subject will also be discontinued from protocol therapy and followed up per protocol under the following circumstances:

- Evidence of disease progression
- The treating physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In case a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 6 weeks.

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

6.8 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The treating investigator should contact the subject or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject's study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Cycle = 28 days	Screening	Cycle 1 and following		D1 every odd cycle[2,3]	Safety F/U	Long-term F/U[5]
	-28 days[1]	Day 1[2]	Day 15[2]		30 days[2,4]	Q 3mos (±14)
REQUIRED ASSESSMENTS						
Informed Consent	X					
Diagnosis and Staging[6]	X					
Medical history[6]	X					
Physical exam	X	X	X		X	
Vital signs, ECOG Performance status[8]	X	X	X		X	
AEs & concomitant medications	X	X	X		X	X[5]
LABORATORY ASSESSMENTS						
Complete Blood Cell Count with diff (CBC)	X	X	X		X	
Comprehensive Metabolic Profile (CMP)[9]	X	X	X		X	
Mg, Phos, Uric Acid, LDH	X	X	X			
PT/INR and aPTT[7]	X					
CA19-9	X			X	X	
Pregnancy test (serum or urine) WOCBP[10]	-7d[10]	X				
DISEASE ASSESSMENTS[11]						
CT of chest	X			X		X[11]
CT or MRI of abdomen and pelvis	X			X		X[11]
TREATMENT EXPOSURE						
Nab-paclitaxel		X	X			
FOLFOX[7]		X	X			
CORRELATIVE STUDIES (SPECIMEN COLLECTION)						
Tumor block or unstained slides[12] (if available)		C1				
Blood sample[13]		C1				
BANKING SAMPLES (SPECIMEN COLLECTION)						
Whole Blood		C1				
Unstained Slides (if available)		C1				
Serum and Plasma		C1			X	
FOLLOW-UP						
Survival status; Subsequent therapy						X

Footnotes

Screening evaluations are to be conducted within 28 days prior to study registration. Scans must be done <4 weeks prior to study registration. All laboratory and other assessments must be performed prior to administration of any study medication, however a window of +/- 7 days will be allowed to change patient schedule without PI or IRB approval.

[1]If screening (baseline) labs were performed within 7 days of D1 of treatment, these do not need to be repeated.

[2]A window of 3 days will be applied to all treatment study visits; for safety follow-up visit and every other cycle tumor imaging, imaging may take place within 7 days prior to the study visit.

[3]Tumor imaging to continue every odd numbered cycle until progression, starting with cycle 3.

[4]The safety follow-up visit should occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the site investigator.

[5]Long-term follow up will occur every 3 months from the last administration of protocol-directed therapy or until death, and may be conducted via telephone. Subjects who have ongoing Grade 4 AE or SAE at the time of discontinuation from treatment, and those who come off treatment prematurely for safety reasons will continue to be followed until the event is resolved or deemed irreversible by the site investigator.

[6]Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging. Medical history will include smoking history and trial awareness question (see Documents/Info tab of OnCore). Medical history will also include tumor mutational testing results, if previously performed (PD-L1; microsatellite instability [MSI]; mismatch repair [MMR]).

[7] Concomitant administration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time. Participants receiving both drugs should be followed with weekly INRs.

[8]Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status

[9]CMP to include Na, K, Cl, creatinine, BUN; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

[10]Women of childbearing potential (WOCBP) must have serum β-HCG testing within 7 days prior to Cycle 1 Day 1 of FOLFOX-A and prior to Day 1 of every Cycle thereafter (serum or urine). If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[11]Tumor response assessment will be performed every odd numbered cycle starting with cycle 3; tumor imaging to be done at treatment discontinuation at discretion of investigator. Additional imaging should be obtained at investigator's discretion if there is suspicion of other sites metastatic involvement. If imaging is positive at baseline, it should be included with subsequent tumor response assessments as noted above. If a patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment.

[12]Fixed paraffin-embedded blocks or unstained slides will be requested from tumor specimen in all subjects (optional). See Correlative Laboratory Manual (CLM) for additional details.

[13]Baseline pretreatment blood sample will be collected to support biomarker research. See CLM for additional details.

7.1 Safety Follow-up Visit Evaluations

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 7) after the last dose of study drug. Medical history, physical exam, performance status, review of medications, and assessment of adverse events will be documented.

7.2 Long Term Follow-up Evaluations

After treatment discontinuation, follow-up for survival and initiation of any other anti-cancer therapies will be documented every 3 months for up to 2 years from treatment discontinuation or until death, whichever comes first. The study will end 2 years after the final patient discontinues treatment or after all patients are deceased, whichever comes first. If a patient continues to do well on the study drug combination, follow-up will cease 3 years after first date of treatment but patient may continue to receive the combination treatment from the local investigator apart from this clinical trial.

If a patient is removed from treatment for reason(s) other than progression, follow with regular tumor assessments per standard of care until progression or start of new treatment.

8. BIOSPECIMEN STUDIES

8.1 Correlative studies

Baseline tissue and blood will be collected for future biomarker studies and next generation sequence analysis.

8.2 Samples for future studies

Subject consent will be obtained for additional samples collected for future Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the Big Ten CRC, will manage the banked samples. Samples will be banked indefinitely in the Hoosier Cancer Research Network Biorepository.

This includes:

- Whole blood: Whole blood will be collected prior to treatment on Cycle 1 Day 1.
- Pre- and Post-treatment plasma: Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Pre- and Post-treatment serum: Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at the 30-day Safety Follow-up visit.
- Unstained slides: Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions.

8.3 Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease

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

9.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.2 Non-measurable Lesions

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

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

9.4 Non-target Lesions

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

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

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

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

10. DRUG INFORMATION

10.1 Nab-Paclitaxel (Abraxane®)

Please see the current package insert for complete product information.

10.1.1 Classification

Antimicrotubular, Cytotoxic

10.1.2 Mode of Action

Nab-paclitaxel is a microtubule inhibitor 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.

10.1.3 Supplier/How Supplied

Celgene will supply nab-paclitaxel at no charge to subjects participating in this clinical trial.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of the product in accordance with the protocol and any applicable laws and regulations.

10.1.4 Preparation

Nab-paclitaxel is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling nab-paclitaxel. The use of gloves is recommended. If nab-paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If nab-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

Reconstitution of Nab-Paclitaxel

- Aseptically, reconstitute each vial of nab-paclitaxel by injecting 20 ml of 0.9% Sodium Chloride Injection, USP or equivalent into each vial.
- **Slowly** inject the 20 ml of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
- **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP directly onto the lyophilized cake as this will result in foaming.
- Once the injection is complete, allow the vial to sit for a **minimum of 5 minutes** to ensure proper wetting of the lyophilized cake/powder.
- **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. **Avoid** generation of foam.
- Each ml of reconstituted product will contain 5 mg of nab-paclitaxel.

1. The reconstituted suspension should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use.
2. Inject the calculated dosing volume of reconstituted nab-paclitaxel into an empty sterile, IV bag.
3. The use of in-line filters is not recommended.

Refer to Abraxane® Package Insert for full prescribing information.

10.1.5 Storage and Stability

Store the vials in original cartons at 20ºC to 25ºC (68ºF to 77ºF). Retain in the original package to protect from bright light. Unopened vials of nab-paclitaxel are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF) [excursions permitted between 15ºC to 30ºC (59ºF to 86ºF)], 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 8 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 stored at ambient temperature (approximately 25ºC) and lighting conditions for up to 4 hours. Discard any unused portion.

10.1.6 Dispensing
Nab-paclitaxel must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Nab-paclitaxel should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.7 Adverse Events
The most common adverse reactions (≥ 20%) with single-agent use of nab-paclitaxel in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea.

The most common adverse reactions (≥ 20%) of nab-paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. The most common serious adverse reactions of nab-paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of nab-paclitaxel are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of nab-paclitaxel are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in nab-paclitaxel dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of nab-paclitaxel in combination with gemcitabine for pancreatic adenocarcinoma, the most common (≥ 20%) selected (with a ≥ 5% higher incidence) adverse reactions of nab-paclitaxel are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common serious adverse reactions of nab-paclitaxel (with a ≥ 1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of nab-paclitaxel are peripheral neuropathy (8%), fatigue (4%) and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of nab-paclitaxel are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in nab-paclitaxel dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%) and diarrhea (5%).

10.2 5-Fluorouracil (5-FU, Fluorouracil, Adrucil)
Please see the current package insert for complete product information.

10.2.1 Supplier/How Supplied
Commercial supplies of 5-FU will be used in this study and billed to third party payers or the subject.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of the product in accordance with the protocol and any applicable laws and regulations.

10.2.2 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Slight yellow discolor does not usually indicate decomposition. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration, and diluent.

10.2.3 Compatibility

Leucovorin enhances the cytotoxicity of 5-FU by forming a more stable tertiary complex with thymidylate synthase. Concomitant administration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time. Participants receiving both drugs should be followed with weekly INRs.

10.2.4 Preparation

Inspect for precipitate; if found, agitate or gently heat in water bath.

46-48 hour infusion of 5-FU should be prepared for administration via ambulatory infusion pump according to the individual institution's standards. These solutions may be prepared in D5W or 0.9% NaCl. 5-FU should not be mixed in the same solution with most parenteral anti-emetics.

10.2.5 Availability

5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL, and 100 mL vials. 5-FU will not be provided by the study as it is considered standard of care.

10.2.6 Adverse Events

- Nausea, diarrhea, vomiting (mild)
- Stomatitis: 5-8 days after treatment initiation
- Myelosuppression: granulocytopenia (9-14 days)
- Thrombocytopenia (7-14 days)
- Alopecia
- Loss of nails
- Hyperpigmentation
- Photosensitivity
- Maculopapular rash
- Palmar–plantar erythrodysesthesias: (42-82% receiving continuous infusion)
- CNS effects: cerebral ataxia (rare)
- Cardiotoxicity: MI, angina
- Asymptomatic S–T changes 68%
- Ocular effects: excessive lacrimation and less commonly, tear duct stenosis

10.3 Leucovorin (Leucovorin Calcium, Folinic Acid, Citrovorum Factor, N 5-Formyltetrahydrofolate, 5-Formyl-FH4)

Please see the current package insert for complete product information.

10.3.1 Supplier/How Supplied

Commercial supplies of leucovorin will be used in this study and billed to third party payers or the subject.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of the product in accordance with the protocol and any applicable laws and regulations.

10.3.2 Preparation

Leucovorin may be reconstituted with BWI or with sterile water for injection. Solutions should be further diluted in D5W, 0.9% NaCl, or Ringers solution for infusion over two hours.

10.3.3 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with BWI are stable for at least 7 days at room temperature. Solutions diluted for infusion are stable for 24 hours at room temperature and 4 days under refrigeration.

10.3.4 Adverse Events

The only adverse reactions associated with leucovorin are allergic reactions. These are extremely uncommon.

10.4 Oxaliplatin (Eloxatin)

Please see the current package insert for complete product information.

10.4.1 Supplier/How Supplied

Commercial supplies of oxaliplatin will be used in this study and billed to third party payers or the subject.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of the product in accordance with the protocol and any applicable laws and regulations.

10.4.2 Preparation

The calculated dose of oxaliplatin should be diluted for infusion with 250 mL to 500 mL in D5W. Oxaliplatin should not be diluted with a sodium chloride solution. Needles, syringes, catheters, or IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

10.4.3 Storage and Stability

Intact vials should be stored at room temperature. Solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration.

10.4.4 Administration

Oxaliplatin must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Oxaliplatin should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to

subjects. Oxaliplatin is injected into a vein [intravenous (I.V.) infusion] over 2 hours (±15 min). Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.

10.4.5 Adverse Events

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression.

Three neurotoxicity syndromes have been seen: acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include paresthesias, dysesthesias, and hypoesthesia of the hands, feet, and perioral region. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain and a sensation of chest pressure have also been noted. Acute sensory neuropathy symptoms may be exacerbated by exposure to cold temperature or cold objects. Symptoms are reversible, usually resolving within 14 days and commonly recurring with further dosing. This syndrome has been observed in about 56% of patients receiving oxaliplatin with 5-FU and leucovorin.

Acute pharyngolaryngeal dysesthesia is reported to occur in 1-2% of patients. This syndrome is characterized by a subjective sensation of difficulty breathing or swallowing without laryngospasm or bronchospasm or objective evidence of hypoxia. Avoidance of cold drinks, food and air is suggested in order to minimize pharyngolaryngeal dysesthesia. Antianxiety agents (e.g., lorazepam) may be used to treat pharyngolaryngeal dysesthesias once oxygen saturation has been documented to be normal.

Peripheral neuropathy persisting > 14 days is characterized by paresthesias, dysesthesias, and hypoesthesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea.

Neutropenia is reported in 73% of patients receiving oxaliplatin with 5-FU and leucovorin (44% grade 3 or 4). Grade 3 or 4 thrombocytopenia is reported to occur in 4% of patients receiving the combination.

Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis.

Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, dysphagia) or pulmonary infiltrates until interstitial lung disease or pulmonary fibrosis have been ruled out.

Recent reports of oxaliplatin extravasation suggest that tissue necrosis may result and that oxaliplatin should be considered a vesicant. No standard treatment exists for oxaliplatin extravasation although heat and sodium thiosulfate have both been suggested.

Veno-occlusive disease (VOD) of the liver is a rare complication associated with oxaliplatin and 5-FU. Clinical manifestations of VOD include hepatomegaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver. Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices. A recent analysis of resected liver metastases in 153 patients indicated histological findings consistent with VOD in 6/27 patients who received 5-FU alone, 4/17 patients who received 5-FU and irinotecan, 20/27 patients who received 5-FU and oxaliplatin, and 14/16 who received 5-FU, oxaliplatin and irinotecan. The remaining 66 patients had not received chemotherapy prior to resection. There were no such findings in these patients.

For more information on toxicities associated with oxaliplatin, please see the package insert.

11. ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in OnCore (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject
- Abuse, withdrawal, sensitivity or toxicity to an investigational product
- An overdose (defined as 10% over the protocol-specified dose), accidental or intentional, whether or not it is associated with an AE, should be recorded. Any sequela of an accidental or intentional overdose of an investigational product should be recorded as an AE. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and as an AE. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

Abnormal laboratory values or diagnostic test results constitute AEs only if it:

- results in discontinuation from the study
- requires treatment, modification/ interruption of study drug(s), or any other therapeutic intervention
- or is judged to be of significant clinical importance, e.g., one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

An SAE is any adverse event that:

- Results in death. NOTE: Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert or when it is not included in the informed consent

document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Causality

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Not suspected: Means a causal relationship of the adverse event to IP administration is unlikely or unrelated, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Unrelated	The Adverse Event is ***clearly not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)

Suspected: Means there is a reasonable possibility (possible, probable, definite) that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s).
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

11.2.2 Serious Adverse Events (SAEs)

Site Requirements for Reporting SAEs to Big Ten CRC Administrative Headquarters

- SAEs will be reported from time of signed informed consent until 30 days after discontinuation of study drug(s) and those SAEs made known to the investigator at any time thereafter that are suspected of being related to the study drug(s).
- SAEs will be reported on the SAE Submission Form **within 24 hours** of discovery of the event.
- SAEs include events related and unrelated to the study drug(s).

- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The completed SAE Submission Form must be submitted to Big Ten CRC AHQ **within 24 hours** of discovery of the event. The form may be submitted to Big Ten CRC AHQ electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines above), sites must electronically submit a follow-up SAE Submission Form within a reasonable timeframe to Big Ten CRC AHQ at safety@hoosiercancer.org.

Big Ten CRC AHQ Requirements for Reporting SAEs to Celgene Corporation

Expedited Reporting by Big Ten CRC to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to nab-paclitaxel based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. Big Ten CRC must inform Celgene in writing using a SAE Submission Form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-GAS-PI-006239) and the institutional protocol number (BTCRC-GI15-015) should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the study records.

Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
556 Morris Avenue, Building S12
Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com
Telephone: 1-908-673-9667
Toll Free: 1-800-640-7854

Sponsor-Investigator Responsibilities to Big Ten CRC AHQ
Big Ten CRC AHQ will send an SAE summary to the sponsor-investigator within 1 business day of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

Big Ten CRC AHQ Requirements for Reporting SAEs to FDA
The FDA has concluded that this protocol is exempt from the requirements of an IND. Big Ten CRC AHQ will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21CFR50.20 informed consent, 21CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.2.3 Reporting Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test, regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 30 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately. The female subject should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Male Subjects
If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Site Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

Site Requirements for Reporting Pregnancies to Big Ten CRC Administrative Headquarters
The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Big Ten CRC AHQ immediately.

The Site Investigator will follow the female subject until completion of the pregnancy and must notify Big Ten CRC AHQ immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy meets any of the serious criteria (including spontaneous or therapeutic abortion, fetal and neonatal death or congenital anomaly), it must be reported as an SAE. Any death of an infant which occurs in connection with *in utero* exposure to the Study Drug within 28 days of birth must be reported as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the IP should also be reported immediately. The Investigator will also document any congenital anomaly detected in an aborted fetus.

Send reports to Big Ten CRC AHQ by emailing the Celgene Pregnancy Reporting Form or SAE Submission Form to safety@hoosiercancer.org within 24 hours of the Investigator's knowledge of the event.

Big Ten CRC AHQ Requirements for Reporting Pregnancies to Celgene Corporation

Big Ten CRC AHQ will submit all pregnancy reports received from sites to Celgene within 24 hours of receipt of the Celgene Pregnancy Reporting Form or SAE Submission Form. The Celgene tracking number (AX-CL-GAS-PI-006239) and the institutional protocol number (BTCRC-GI15-015) should be included on report (or on the fax cover letter) sent to Celgene.

Big Ten CRC AHQ will submit all pregnancy reports and any other relevant safety information to:

Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
556 Morris Avenue, Building S12
Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com
Telephone: 1-908-673-9667
Toll Free: 1-800-640-7854

Follow-up information will be provided to Celgene as reasonably requested.

11.3 IND Safety Reports Unrelated to this Trial

Celgene will provide IND safety reports from external studies that involve the study drug(s) per their guidelines to Big Ten CRC AHQ. Big Ten CRC AHQ will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. Big Ten CRC AHQ will forward these reports to participating sites **within 1 business day** of receiving sponsor-investigator's review. Based on sponsor-investigator's review, applicable changes will be made to protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from Big Ten CRC AHQ, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

IND safety reports determined by the sponsor-investigator to be serious, unexpected, and possibly related (UPIRSO) will also be submitted to the Northwestern DMC for review (croqualityassurance@northwestern.edu).

12. STATISTICAL METHODS

12.1 Endpoints

Endpoints are described in Section 2.2 and include the primary endpoint which is the objective response rate (partial or complete response). All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of objective response. Secondary endpoints include overall survival, progression-free survival, time to progression and disease control rate. Safety endpoints include toxicities.

12.2 Sample Size and Accrual

A Simon [1989] optimal two-stage design [16] will be employed. A 5% response rate precludes further study whereas a 20% response rate would indicate that further investigation of the treatment is warranted (i.e., P0=0.05 and P1=0.20 in the Simon terminology). Using α and β errors of 0.10 and 0.10, respectively, 12 patients will be enrolled in the first stage and if no responses are observed, the trial will be terminated. Otherwise, an additional 27 patients will be enrolled in the second stage and if ≤ 3 responses are observed among the 39 patients, the agent will not be considered worthy of further testing; whereas, if 4 or more responses are observed the drug will be considered sufficiently active to justify further study. This design has 90% power under the alternative hypothesis and provides a 54% probability of early stopping if the true response rate is only 5%. The baseline of ORR probability is based on existing data from a couple of platinum -5-FU combinations phase II, TTT trials with a minimum ORR of 16% [6-8, 24-31].

A maximum of 39 patients will be enrolled to attain 37 eligible/evaluable patients (total target sample size has been inflated by 5% to allow for patient ineligibility/inevaluability). Patients will be followed until the minimum of the time to progression, time to death before the patient's data will be included in the decision rule.

12.3 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Intention-to-treat (ITT)	This will comprise all subjects who meet the eligibility criteria and are registered onto the study irrespective of their compliance to the planned course of treatment. (See IIT principle below*).
Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample)	This will comprise all subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. This population should be specifically defined in the protocol.
Safety	This will comprise all subjects that contribute data to the safety analysis. This population should be specifically defined in the protocol.
Treated	This will comprise all subjects who have been exposed to the planned course of treatment to any extent.

*IIT Principle - The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject with the planned treatment regimen rather than on the basis of the actual treatment given.

12.4 Assessment of Safety

Any subject who receive at least one dose of treatment will be evaluable for toxicity. Safety will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.

In addition to continuous monitoring of adverse events through expedited reporting and routine tabulations of toxicities being reported through case report forms, the trial will include two formal evaluations of toxicity before the completion of accrual. It is expected that the true proportion of any grade 3 or higher treatment-related adverse event (exclusive of hematologic toxicity, nausea/vomiting, fatigue, alopecia and liver function abnormalities) will be no higher than 30% in this patient population (most events would be expected to have true rates quite lower than 30%). True proportions higher than 30% would be reason to evaluate the regimen for possible modification. Given these assumptions, the following plan will be followed.

After 10 patients have been treated through at least 2 cycles, all treatment-related adverse event information will be compiled and tabulated by toxicity grade. If any observed grade 3 or higher treatment-related adverse event proportion (exclusive of hematologic toxicity, nausea/vomiting, fatigue, alopecia and liver function abnormalities) is higher than 40% (4 or more out of 10 patients), a detailed review of all treatment-related adverse events will be conducted and the study team may decide that treatment modification is necessary. If the true proportion of any adverse event is 50% (or higher) there is at least 87% probability of exceeding the observed adverse event boundary whereas if the true proportion is 30% there is only 11% probability of crossing the toxicity boundary. The above decision boundary (40% or more observed events) will be followed for grade 4 or higher toxicities in the above exclusion list (hematologic toxicity, nausea/vomiting, fatigue, alopecia and liver function abnormalities) in order to evaluate those events that might be expected to have relatively high event rates at grade 3, but not at grade 4.

12.5 Data Analysis Plan.

Analyses will be performed for all patients having received at least one dose of study drug after the first and second stage of the study. Response rate and disease control rate and their 95% confidence intervals will be estimated using exact binomial methods. Safety data summaries will describe the incidence of adverse events (including severity and relationship to drug or treatment), serious adverse events, adverse events leading to early withdrawal or death, and Grade 3 or 4 toxicities. Median duration of response and its 95% confidence interval will be calculated. Kaplan-Meier curves will be used to summarize the time-to-event endpoints of PFS and OS. All event times will be calculated relative to the start of FOLFOX-A combination. Distributions of PFS, TTP and OS will be estimated using the method of Kaplan-Meier [17] and univariate testing will be done via the log rank test [18]. Descriptive statistics will be performed for all on-study and clinical-demographic data. Chi-square or Fisher's exact tests will be used as appropriate for categorical associations and Wilcoxon rank tests or t-tests for continuous measures. All event times will be calculated relative to the start date of the study drug combination. ORR and DCR will be

summarized by count and percent of subjects with each ordinal response analyzed by Cochran-Mantel-Hanzel test [19] for comparison between groups. Correlation of change in CA 19-9 to ORR, PFS, TTP, DCR and OS will be completed as described above. Binary outcome regression modeling will be accomplished via standard logistic regression and time-to-event models (which will be largely exploratory) will be done using the Cox proportional hazards model. The safety data summaries will describe the incidence of adverse events (including severity and relationship to drug or treatment), serious adverse events and those leading to early withdrawal or death, as well as grade 3 or 4 toxicities. These analyses will be largely descriptive. Efficacy and safety analyses will be completed by intention to treat. Statistical analyses will be completed using SAS®.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring

The Data Monitoring Committee (DMC) of the Robert H. Lurie Comprehensive Cancer Center will provide study oversight activities for this study. They will review and monitor study progress, toxicity, safety, and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician, and study team members. Should any major concerns arise; the DMC will offer recommendations regarding whether or not to suspend the trial.

Big Ten CRC AHQ must submit all SAEs to the Quality Assurance Managers (QAMs) in real time, as defined below.

- Big Ten CRC AHQ will compile data summary reports for this trial and submit these reports monthly to the sponsor-investigator.
  - Big Ten CRC AHQ will report all SAEs to the DMC Quality Assurance (QA) office within one business day of receipt and formally present them at each DMC meeting.
  - Submit data summary reports to the lead institution DMC and attend DMC reviews:
    - as applicable, following any new reports of protocol deviations or SAEs, or, if overall study data delinquency that exceeds 10% incomplete forms or sites with data delinquency that are not responding sufficiently to the Big Ten CRC AHQ data delinquency escalation process
    - throughout the study, semi-annual comprehensive DMC review

  Any data set the PI wants to use to publish the trial will be presented to and approved by the DMC.

13.1.1 Data Safety Monitoring Committee

The Northwestern DSMC will review the following:

- Adverse event summary report
- Monitoring and/or audit reports as applicable
- Study accrual pattern
- Data delinquency
- Protocol deviations

The Robert H. Lurie Comprehensive Cancer Center's DMC will conduct a comprehensive study review semi-annually. Documentation of DMC reviews will be provided to sponsor-investigator and Big Ten CRC AHQ. Issues of immediate concern by the DSMC are brought to the attention of the sponsor-

investigator (and other regulatory bodies as appropriate) and a formal response from the sponsor-investigator is requested.

13.2 Data Quality Oversight Activities

Remote validation of OnCore data will be completed on a continual basis throughout the life cycle of the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel.

If at any time, Big Ten CRC AHQ or the sponsor-investigator determines a site is not compliant with recording and reporting of data, a "for-cause" audit will be initiated.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For-cause visits may occur as necessary. During an onsite visit, source documents will be reviewed for verification of agreement with data entered into OnCore. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by Big Ten CRC AHQ or its designee.

The trial site may also be subject to quality assurance audit by Celgene or its designee as well as inspection by appropriate regulatory agencies.

13.3 Amendments

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol (amended protocol) and/or the revised informed consent will be generated by Big Ten CRC AHQ and must be approved by the sponsor-investigator, Celgene, and each site's IRB.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The sponsor-investigator has delegated responsibility to Big Ten CRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

Big Ten CRC AHQ will serve as the Clinical Research Organization for this trial. Data will be collected through a web-based clinical research platform, OnCore, a system compliant with Good Clinical Practices and Federal Rules and Regulations. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Big Ten CRC AHQ personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in OnCore. If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in OnCore, according to study-specific objectives. Please see the Data and Safety Oversight Process (DSOP) guidelines for further details.

The completed dataset is housed at Big Ten CRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and Big Ten CRC AHQ. After the initial publication, the complete data set will be available to all Big Ten CRC institutions.

Trials that use the Lurie Cancer's DSMP are not permitted to publish trial data in any capacity until the data has been approved by the DMC. If a PI anticipates that he or she will publish data prior to three months after the Clinicaltrials.gov primary completion date, they must notify the assigned QAM as soon as possible. QAMs can prepare the data summary for DMC approval upon PI request, but must have a minimum six weeks' notification.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/ Big Ten CRC AHQ, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with Big Ten CRC AHQ. No records will be destroyed until Big Ten CRC AHQ confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations, including the sponsor-investigator and his/her research associates, Big Ten CRC AHQ, Celgene, IRB, or government agencies like the FDA, may inspect their medical records to verify the information collected, and that all personal information

made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subjects' identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to Big Ten CRC AHQ before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16. REFERENCES

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