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FOLFOX-A For Locally Advanced Pancreatic Cancer: A Phase II Brown University Oncology Research Group Trial

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1.0 OBJECTIVES

1.1 Primary Objective

1.1.1. To evaluate the response rate of FOLFOX-A for patients with locally advanced pancreatic cancer.

1.2 Secondary Objective

1.2.1 To evaluate the disease-free and overall survival for patients with locally advanced pancreatic cancer treated with FOLFOX-A.

2.0 BACKGROUND

Locally Advanced Pancreatic Cancer: Pancreatic cancer is the fourth most common cause of cancer death in the United States.[1] Only those patients who have undergone resection have the potential to be cured.[2] However, only 15 to 20 percent of patients have potentially resectable disease at diagnosis; approximately 40 percent have distant metastases, and another 30 to 40 percent have locally advanced unresectable tumors.[2] Typically, patients with locally advanced unresectable pancreatic cancer have tumor invasion into adjacent critical structures, particularly the celiac and superior mesenteric arteries.[3] The optimal management of these patients is controversial, and there is no internationally-embraced standard approach. Therapeutic options include radiation therapy (RT) alone, chemoradiotherapy, and chemotherapy alone.[4,5] Rarely, a response to initial therapy will be sufficient to permit an attempt at subsequent resection.

The Efficacy of Radiation for Locally Advanced Pancreatic Cancer Is Uncertain: The LAP 07 trial evaluated the use of gemcitabine alone versus gemcitabine followed by radiation in patients with locally advanced pancreatic cancer.[6] In this trial, 442 patients were first randomized to gemcitabine alone or gemcitabine plus erlotinib for 4 months. Patients without progression (60%) were then randomized to 2 additional months of chemotherapy or chemoradiation. There was no improvement in survival with the addition of radiation following gemcitabine for patients with locally advanced pancreatic cancer. In contrast, a phase 3 trial by ECOG showed a survival advantage to the combination of radiotherapy and gemcitabine over gemcitabine alone.[7] The study was closed early because of slow accrual; however, in the 74 patients enrolled, median survival improved from 9.2 to 11.1 months (p=0.017).

Chemotherapy for Locally Advanced Resectable Pancreatic Cancer: Systemic chemotherapy is often given prior to radiation in patients with locally advanced pancreatic cancer.[2] Chemotherapy has 2 goals – to produce responses in radiographically assessable locally advanced disease and to target unsuspected micrometastases reducing the extremely high risk of systemic recurrence with locoregional therapy such as radiation. The most commonly used systemic regimens are gemcitabine, gemcitabine + abraxane and FOLFIRINOX.[2]

FOLFIRINOX: The PRODIGE 4/ACCORD 11 trial compared FOLFIRINOX (oxaliplatin, leucovorin, irinotecan and fluorouracil) to gemcitabine for first-line treatment of metastatic pancreatic cancer. The trial enrolled 342 patients between 01/2005 and 10/2009. The median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (P<0.001).[8]Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group. The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group. Grade 3/4 toxicities increased with FOLFIRINOX including neutropenia (18.7% versus 45.7%), febrile neutropenia (0.6% versus 5.4%), diarrhea (1.2% versus 12.7%) and neuropathy (0% to 9%), respectively.

FOLFIRINOX is being investigated in the locally advanced and borderline resectable settings. In a study from France, 77 patients were enrolled.[9] Patients received a median number of five cycles (1-30). Grade 3-4 toxicities were neutropenia (11 %), nausea (9 %), diarrhea (6 %), fatigue (6 %), and anemia (1 %).

Grade 2-3 sensory neuropathy occurred in 25 % of patients. The response rate was 28 %. Seventy-five percent of patients received a consolidation therapy: 70 % had radiotherapy and 36 % underwent a surgical resection, with a curative intent. Within the whole cohort, 1-year OS rate was 77 % (95 % CI 65-86) and 1-year progression-free survival rate was 59 % (95 % CI 46-70).[9] FOLFIRINOX was also investigated in 22 patients at the Massachusetts General Hospital Cancer Center in patients.[10] The response rate was 27.3%, and the median progression-free survival was 11.7 months. Five of 22 patients were able to undergo R0 resections following neoadjuvant FOLFIRINOX and chemoradiation. Three of the five patients have experienced distant recurrence within 5 months. Thirty-two percent of patients required at least one emergency department visit or hospitalization while being treated with FOLFIRINOX. This study showed that FOLFIRINOX possesses substantial activity inpatients with LAPC and the use of FOLFIRINOX was associated with conversion to resectability in>20% of patients. However, the recurrences following R0 resection in three of five patients and the toxicities observed with the use of this regimen were concerning.

The studies in France and MGH showed that, due to substantial toxicity of FOLFIRINOX, administering > 6 cycles of FOLFIRINOX is difficult. The ability to administer multiple cycles of highly effective chemotherapy is important in reducing the risk of systemic relapse. In the cooperative group ALLIANCE, only 4 cycles of FOLFIRINOX are administered in the neoadjuvant setting for borderline resectable patients. A more active, less toxic regimen with the ability to receive more than 6 cycles of therapy is needed to improve overall outcome in locally advanced patients.

Irinotecan is not an effective agent in pancreatic cancer: Single agent irinotecan is without significant activity in pancreatic cancer.[11] Furthermore, the combination of irinotecan and gemcitabine does not improve survival as compared to gemcitabine alone.[12] While irinotecan may be synergistic with oxaliplatin and fluorouracil, it's overall contribution to FOLFIRINOX efficacy may be modest. However, the inclusion of irinotecan adds substantially to the toxicity of FOLFIRINOX.

Abraxane: Abraxane is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form.[13] This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intraluminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium.[14] A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane.[15]Abraxane is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.[15] Pancreatic cancer cells and surrounding stroma are known to overexpress SPARC (secreted protein acid rich in cysteine), which is associated with poor clinical outcomes.[16] The albumin-bound nanoparticle form of paclitaxel increases tumor accumulation of paclitaxel through binding of albumin to SPARC.[16]

Abraxane + gemcitabine in pancreatic cancer: The regimen of Abraxane, 125mg/m^2, and gemcitabine, 1gm/m^2, weekly x 3 weeks in 28 day cycles, was developed by Von Hoff et al in a phase I/II study for patients with metastatic pancreatic cancer.[16] A phase III study of 861 patients demonstrated that the combination of Abraxane and gemcitabine was superior to gemcitabine alone. As shown in the table 1 below, overall survival (OS), progression-free survival (PFS), time to treatment failure (TTF), and response rate (RR) were significantly improved in the Abraxane + gemcitabine arm.[17]

	Abraxane + Gemcitabine n = 431	Gemcitabine n = 430	P =
Median survival	8.5 months	6.7 months	0.000015
1-yr survival	35%	22%	0.000200
2-yr survival	9%	4%	0.021234
PFS	5.5 months	3.7 months	0.000024
TTF	5.1 months	3.6 months	<0.0001
Response rate	23%	7%	

Table 1: Abraxane + gemcitabine is superior to gemcitabine alone

Phase I Study of FOLFOX-Abraxane (FOLFOX-A): Irinotecan is responsible for much of the toxicity of FOLFIRINOX but may its contribution in FOLFIRINOX may be modest. The addition of irinotecan to gemcitabine was not superior to gemcitabine alone. In contrast, the addition of Abraxane to gemcitabine increased survival. Therefore, the Brown University Oncology Research Group initiated a protocol to remove irinotecan from FOLFIRINOX and substitute Abraxane – this new regimen is called FOLFOX-A. All patients received oxaliplatin, 85 mg/m^2, leucovorin 400 mg/m^2 and 5-FU 2400 mg/m^2 IV over 46 hours with Abraxane. Cycles were repeated every 14 days. Three dose-levels of Abraxane were evaluated:

- Level 1: Abraxane 125mg/m2
- Level 2: Abraxane 150 mg/m2
- Level 3: Abraxane 175 mg/m2

This study has been completed. Thirty-five patients were entered: Dose level 1 (n=6), dose level 2 (N=26), dose level 3 (N=3). The median age was 64 (35-81). [18] The maximum tolerated dose of Nab-paclitaxel was 150 mg/m^2 every 2 weeks with FOLFOX. Twenty-one of the 35 patients have had a partial response (60%). The median survival for patients with metastatic disease is 15 months. Since implementing a dose reduction of oxaliplatin for patients developing grade 2 neuropathy, no patients have developed grade 3 neuropathy and most patients have been able to receive 10 cycles of therapy.

Current proposal - A phase II study of adjuvant FOLFOX-A: Our preliminary data suggests that FOLFOX-A may have equal or superior activity as compared to FOLFIRINOX for patients with metastatic pancreatic cancer and appears to be better tolerated with the ability to administer at least 10 cycles of therapy. We therefore will evaluate FOLFOX-A in a phase II study for patient with locally advanced pancreatic cancer.

3.0 PATIENT ELIGIBILITY

3.1 Conditions for Patient Eligibility

1. Pathologically or cytologically confirmed pancreatic ductal adenocarcinoma. Patients with pathology or cytology showing carcinoma of pancreas or adenosquamous of the pancreas are also eligible.
2. Locally advanced pancreatic cancer, including patients defined by Callery[19] as "unresectable" and "borderline resectable" are eligible:[19]

Unresectable tumors:

a. Major venous thrombosis of the portal vein or SMV extending for several centimeters (precluding vein resection and reconstruction).

b. Encasement (>180°) of the SMA or, proximal hepatic artery.
c. Abutment of the celiac trunk

Tumors considered borderline resectable:

a. Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
b. Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
c. Tumor abutment of the SMA not to exceed >180° of the circumference of the vessel wall.

Tumors that are localized and resectable, defined by Callery[19] as no radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement; and clear fat planes around the celiac axis, hepatic artery, and SMA, are not eligible.

Required to submit to BrUOG, treating physician documentation of which criterion patient meets (ie: borderline resectable, criterion a).

3. Measurable disease as per RECIST 1.1
4. No prior chemotherapy for pancreatic cancer.
5. No major surgery within 3 weeks of the start of study treatment. Patients must have recovered from the side effects of any major surgery at the start of study treatment. For questions on if a surgery is deemed "major," definition by surgeon can be used for clarification. Laparoscopy and central venous catheter placement are not considered major surgery.
6. No prior invasive malignancy within the prior two years. However, patients with an early stage malignancy that is not expected to require treatment in the next 2 years (such as early stage, resected breast cancer or asymptomatic prostate cancer) are eligible.
7. ECOG performance status 0 or 1.
8. Age ≥ 18
9. Not pregnant and not nursing. Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to beginning of treatment. Post-menopausal women (surgical menopause or lack of menses ≥24 months) do not need to have a pregnancy test, please document status.
10. Women of childbearing potential and sexually active males must use an effective contraception method 28 days prior to treatment, during treatment and for three months after completing treatment (men are to use contraception for six months post last dose of drug). Documentation of this being discussed required.
11. Required Initial Laboratory Values:

- Neutrophils ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm3 (transfusion independent, defined as not receiving platelet

transfusions within 7 days prior to laboratory sample)

- Hemoglobin > 9.0g/dL, transfusional support allowed
- Creatinine ≤ 1.5 mg/dL -or- creatinine clearance ≥ 60 mL/min
- Total bilirubin ≤1. 5 x ULN
- AST (SGOT) & ALT (SGPT) ≤ 2.5 x ULN
- Alkaline phosphatase ≤ 2.5xULN. (Patients with elevated alkaline phosphatase, total bilirubin, AST and ALT, who have subsequently undergone biliary stenting and their liver tests are improving, do not need to wait for their alkaline phosphatase to become ≤ 2.5x ULN if their total bilirubin, AST and ALT have improved to within required study levels and the alkaline phosphatase is decreasing.)

3.2 Exclusion Criteria

1 Patients with metastatic disease
2 Prior hypersensitivity to Oxaliplatin or Abraxane ® that in the investigators opinion would put the patient at risk if re-exposed
3 Preexisting neuropathy is not allowed from any cause.
4 Patients with serious medical risk factors involving any of the major organ systems such that the investigator considers it unsafe for the patient to receive FOLFOX-A
5. Patients with unstable biliary stents or with plastic stents. Information on type of stent is required at registration.
6. Patients with active infection or fever (no fever for 48hrs) (patients on antibiotics for infection or patients getting over a cold or seasonal virus are not excluded), or known historical or active infection with HIV, hepatitis B, or hepatitis C.
7. Patients with active sepsis or pneumonitis.
8. Patients with a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies that in the investigator's opinion would put the patient at an increased risk.
9. Patients on concurrent anticancer therapy
10. Uncontrolled diabetes. If patient has diabetes, confirmation on status (controlled or uncontrolled) required at registration.

3.3 Re-screen:

If a patient signs consent and then screen fails (does not meet the eligibility criteria) and the treating MD requests that the patient be re-screened outside of the 28 day screening window, sites are to contact BrUOG who will assess patients on a case by case basis. Depending on many diverse factors including the conditions that are being evaluated, the reasons why patient initially screen failed, and the nature of the initial results, re-screening may or may not be medically/scientifically appropriate. BrUOG should be made aware of such a situation with at least 72 hours and provided with information on screen-failure.

4.0 TREATMENT

4.1 Schema:

1 cycle = 14 days
It will not be considered a deviation if a cycle or pre-cycle assessment must be adjusted to accommodate scheduling or holidays. Adjustment must be documented with reason to BrUOG

Abraxane ®: 150mg/m^2 IV over 30 minutes, day 1 (administered first) every 14 days.
Oxaliplatin: 85mg/m^2, IV over 2 hours, day 1 every 14 days
Leucovorin: 400mg/m^2, IV over 2 hours, day 1 every 14 days
5-FU infusion: 1200mg/m^2/day, as a continuous IV infusion over 2 days, day 1 and day 2 (for a total dose of 2400mg/m^2 over 46 hours.)

- It is at the discretion of the treating physician to give Neulasta, 6 mg sq x 1 post treatment
- Antiemetics will be administered as per standard institutional policy.

Patients may receive up to 10 cycles of FOLFOX-A as part of this study as long as their cancer does not progress. After 10 cycles of FOLFOX-A, patients will come off study treatment and additional treatment/management will be as per institutional standards of care. It is recommended that patients receive radiation with concurrent capecitabine as per institutional standard policy after completion of FOLFOX-A. It is recommended that patients who become potentially resectable proceed to attempted surgical resection after completion of FOLFOX-A, either before or after standard capecitabine and radiation as per institutional standard of care. Information on type of treatment/management post FOLFOXA will be collected by BrUOG.

Patients who are borderline resectable may stop FOLFOX-A treatment at 6 cycles to then receive off-study radiation or surgery as per institutional practice, however this is at the discretion of the investigator. Borderline resectable patients may be kept on FOLFOX-A treatment for up to 10 cycles at the discretion of the investigator.

5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (CTCAE) version 4.03 (Appendix C). **For patient's experiencing neuropathy please refer to section 5.3**

	Starting Dose level	Dose level -1	Dose level -2
Abraxane ®	150 mg/m^2	120 mg/m^2	96 mg/m^2
Oxaliplatin	85mg/m^2	68 mg/m^2	54 mg/m^2
Leucovorin	400 mg/m^2	400 mg/m^2	400 mg/m^2
5-FU	1200mg/m^2	960 mg/m^2	768 mg/m^2

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

Doses of chemotherapeutic agents do not need to be recalculated if weight change is less than 10% of total body weight. Weight gain secondary to edema does not require dose re-calculation even if $\geq$10%.

Please note that if a patient has experienced a reduction for neuropathy (section 5.3) they will be receiving doses of drugs from different dose levels

5.1 A new course of treatment should not begin until the following criteria are met:

- Platelets $\geq$ 100x10^9/L (100,000/mm^3)
- ANC $\geq$1.5x10^9/L (1500/mm^3)
- Recovery from other treatment related, non-hematologic toxicities to $\leq$ Grade 2, this does not included 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.

5.2 A 1 dose-level reduction is required for the following:

- Grade 4 neutropenia (ANC < 500/mm^3) lasting for > 7 days
- ANC <1000/mm^3 with fever (temp > 101) or infection
- Platelets <25,000/mm^3
- Platelets <50,000/mm^3 requiring transfusion
- Grade 3 or 4 treatment related non-hematologic toxicities excluding alopecia. Grade 3 nausea and vomiting and Grade 3 or 4 electrolyte abnormalities do not require a dose modification if the nausea, vomiting and/or electrolyte disorder can be corrected to grade 2 or less within 72 hours.
- Delay of treatment for > 2 weeks due to treatment related toxicity, not applicable for neuropathy, for neuropathy refer to section 5.3

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

5.3 Neuropathy

The goals of the following dose modification rules are to prevent patients from developing grade 3/4 neuropathy during or after completion of FOLFOX-A and to facilitate patients being able to receive 10cycles of FOLFOX-A without grade 3/4 neuropathy. Fluorouracil and leucovorin are not reduced for neuropathy.

5.3.1 For patients experiencing grade 2 neuropathy:

- Hold Oxaliplatin
- For patients developing a **first episode** of grade 2 neuropathy, to reinstitute oxaliplatin, neuropathy must have improved to Grade $\leq$1, however, Abraxane ®, 5-FU and leucovorin may be administered. For patients developing a first episode of grade 2 neuropathy, oxaliplatin should be permanently decreased to oxaliplatin –by 1 dose level (for example a patient who is on the starting dose level would have Oxaliplatin reduced to dose level -1: 68mg/m2). Abraxane ®, 5-FU and Leucovorin doses are not reduced for grade 2 neuropathy.
- For patients developing a **second episode** of grade 2 neuropathy, to reinstitute oxaliplatin, neuropathy must have improved to Grade $\leq$1, however, Abraxane ®, 5-FU and leucovorin may be administered.
- For patients developing a **second episode** of grade 2 neuropathy, oxaliplatin should be permanently decreased to oxaliplatin by 1 dose level (for example a patient who had no other total dose reductions, but was reduced for their first episode of neuropathy grade 2, would now

have their Oxaliplatin reduced to dose level - 2 (54mg/m2)). Abraxane ® and 5-FU and Leucovorin doses are not reduced for grade 2 neuropathy.

- For patients developing a **third episode** of grade 2 neuropathy, oxaliplatin should be permanently discontinued, however, Abraxane ®, 5-FU and leucovorin may be continued.
- It is the investigators discretion to hold FOLFOX-A treatment for up to six weeks secondary to patient's experiencing grade 2 neuropathy. Hold for neuropathy must be documented.

5.3.2 For patients experiencing grade 3 neuropathy:

- For patients developing grade 3 neuropathy, FOLFOX-A should be held until neuropathy improves to ≤ grade 1. When treatment is resumed oxaliplatin and Abraxane ® doses should be permanently decreased to 68mg/m^2 and 120mg/m^2 respectively (reduction by 1dose level, (for example a patient who is on the starting dose level would have Oxaliplatin reduced to dose level -1: 68mg/m2)). 5-FU and Leucovorin are not reduced for grade 3 neuropathy.
- For patients developing a **second episode** of grade 3 neuropathy, FOLFOX-A should be held until neuropathy improves to ≤ grade 1. When treatment is resumed oxaliplatin and Abraxane ® dose should be permanently decreased by 1 dose level (for example a patient who had no other total dose reductions, but was reduced for their first episode neuropathy grade 3, would now have their Oxaliplatin and Abraxane reduced to 54mg/m^2 and 96mg/m^2 respectively (dose level -2)).
- For patients developing a **third episode** of grade 3 neuropathy they should be removed from study treatment. Reason for patient discontinuing treatment must be documented as secondary to grade 3 neuropathy.
- It is also at the investigator's discretion to hold FOLFOX-A treatment for up to six weeks secondary to patient experiencing grade 3 neuropathy. Hold for neuropathy must be documented on treatment and AE forms.

5.3.3: Grade 4 neuropathy:

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

Examples:

For patients who experience neuropathy grade 2 or worse and thus require a dose reduction to drugs as per 5.3.1 and 5.3.2 and then require a dose reduction per the criteria in section 5.2, please note that patients will be reduced per the dose modification table under section 5.0 per drug.

Grade 2 neuropathy: For example if a patient experiences grade 2 neuropathy, per section 5.3.1, Oxaliplatin is to be held until neuropathy is ≤ grade 1 but Abraxane, Leucovorin and 5_FU are to be administered. Oxaliplatin will then be reduced by 1 dose level. However, if they then subsequently experience a toxicity per section 5.2 which prompts a dose reduction per the dose modification table in section 5.0, the Abraxane ® and 5-FU would be reduced per Dose level -1 and the Oxaliplatin would be reduced per Dose level -2 (Oxaliplatin would be reduced per Dose level -2 as this patient would have experienced a dose reduction to Oxaliplatin per the neuropathy grade 2). Please note that investigators can hold treatment for 6 weeks secondary to neuropathy and this will not count as another reason for dose reduction, the grade 2 neuropathy is the event that would prompt the dose modification per section 5.3.1.

Grade 3 neuropathy: For patients who experience neuropathy grade 3, per section 5.3.2, FOLFOX-A will be held and when neuropathy is ≤ grade 1, Abraxane ® and Oxaliplatin will then be reduced by 1 dose level and 5-FU and Leucovorin are not reduced. However, if they then subsequently experience a toxicity per section 5.2 which prompts a dose reduction per the dose modification table in section 5.0, the 5-FU will be reduced per Dose level -1 and the Oxaliplatin and Abraxane ® will be reduced per Dose level -2. Leucovorin is not reduced. Please note that investigators can hold treatment for 6 weeks secondary to neuropathy and this will not count as another reason for dose reduction (as noted above in bullet 6 of section 5.2).

There are no further reductions past Dose level -2

5.4 Hypersensitivity reactions

Patients with severe (defined as grade ≥ 3) hypersensitivity reactions from oxaliplatin or Abraxane ® must be removed from protocol treatment. Patients with hypersensitivity reactions, including pneumonitis, cannot be re-challenged.

Examples of medications to reduce risk of hypersensitivity reactions to oxaliplatin and Abraxane ® include:

Dexamethasone 20 mg PO or IV, 12 and 6 hours prior to the oxaliplatin or Abraxane ® dose;
Dexamethasone 20 mg PO or IV, as well as diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30-60 minutes prior to oxaliplatin or Abraxane ® administration.

If these prophylactic measures or institutional practices fail to prevent severe oxaliplatin or Abraxane ® related hypersensitivity, therapy with oxaliplatin and Abraxane® should be discontinued and the patient should be removed from protocol treatment.

5.5 Pulmonary Fibrosis

In the case of unexplained respiratory symptoms such as nonproductive cough, dyspnea or radiological pulmonary infiltrates, Abraxane ® and oxaliplatin should be held until further investigation excludes interstitial pulmonary fibrosis. If interstitial pulmonary fibrosis is confirmed, both Abraxane ® and oxaliplatin therapy should be terminated and the patient removed from protocol treatment. If pulmonary fibrosis is not confirmed and the investigator believes the patient can continue on study, the patient will begin treatment at their next scheduled cycle at a 20% dose reduction. If this is their third episode of dose reduction, patient will be removed from study.

Interstitial Pneumonitis

Interstitial pneumonitis has been observed in < 1% during *Abraxane* ® monotherapy and in < 1% during combination treatment with *Abraxane* ® and carboplatin. 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 *Abraxane* ® and promptly initiate appropriate treatment and supportive measures.

Prevention, Surveillance and Management of Interstitial Pneumonitis

a. Before starting treatment with *Abraxane* ® 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.

b. During treatment with *Abraxane* ® 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.
c. 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.
d. Upon a diagnosis of interstitial pneumonitis *Abraxane* ® 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.

5.6 Sepsis

Sepsis has been reported in less than 1% during monotherapy and fatalities attributed to these events have been rare. However, the risk was appreciably higher in patients with advanced or metastatic pancreatic cancer receiving *Abraxane* ® in combination with gemcitabine with a rate of 5% in patients with or without neutropenia receiving *Abraxane* ® /gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. The increased risk of sepsis in the setting of advanced or metastatic cancer in combination with gemcitabine could be managed with prophylactic antibiotic treatment in febrile patients (regardless of neutrophil count) and dose reduction, and with G-CSF treatment in neutropenic patients. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold *Abraxane* ® and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels (as per sections 5.1 and 5.2).

5.7 Drug Interactions

While no drug interactions have been studied, the metabolism of paclitaxel is enhanced by CYP2C8 and CYP3A4. Therefore patients should be informed about the potential of a drug interaction if they are also taking drug that induce or inhibit CYP2C8 (antifungals, erythromycin, cimetidine etc) or CYP3A4 (rifampicin, phenytoin, etc).

6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR*The day an assessment (PE, labs, scan etc) is completed is day 0 for counting for example labs drawn on a Friday can be used for dosing Monday as they are within 3 days*

Parameter	Pre-study (to be sent to BrUOG with results prior to registration)	Within 3 days prior to each Day 1 of Each Cycle (Every 2 weeks) F**	Prior to Cycle 6 of FOLFOX A (post cycle 5)	After completion of that last FOLFOX A cycle (ie: post the 14 day cycle and within (+) 1 week)	30 days post last dose of drug (+1 week)	FU[D]
Informed Consent (within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window	X					
History , Demographics (baseline only)	X					
Physical examination	X	X		X	X[H]	
Weight	X	X		X	X[H]	
Vital signs	X	X		X		
Toxicity Assessment	X	X		X	XHG	
Performance Status	X	X		X	X[G]	
CBC, diff, platelet count	X (within 14 days)	X				
Na, K, BUN, Cr	X (within 14 days)	X				
AST, ALT, TBili	X (within 14 days)	X				
Mg, Calcium, phosphorus, Alk Phos	X(within 14 days)		X			
Serum Pregnancy[E]	X (within 7 days of drug)					
CA19-9	X(within 14 days)		X	X		
CT scan of Chest/abd cAID RECIST for assessment	X[AC](within 28 days)		XACDI	X(Imaging does not need to be repeated if done in prior 2 months)ACDI		X ACDI
EKG[B]	X					

Survival and Disease status				X	X	X

It will not be considered a deviation if a cycle or pre-cycle assessment must be adjusted to accommodate scheduling or holidays. Adjustment must be documented with reason to BrUOG

[A]- CT Scan or MRI for disease assessment should be performed within 28 days of study entry. Report required. MRI/PET may substitute. Chest Xray can substitute for chest CT.

[B]- EKG within 8 weeks of study entry. Report required.

[C]- An MRI or PET scan may substitute for disease assessment.

[D]- For patients removed from protocol treatment due to toxicity (or another reason), without progression, follow-up will include disease free and overall survival approximately every 4 months. For CT scans, patients should be evaluated every 4 months for year 1 then every 6 months for year 2 then annually or at MD discretion ending when the patient progresses. CT scans may be done outside of the window as per MD discretion, however it is suggested that CT scans be done as per schedule noted above.. For patients who come off study for progression, overall survival is to be reported every 4 months. Follow-up will be for 5 years. After completion of FOLFOX-A, it should be reported to BrUOG whether patients receive radiation and/or surgical resection after FOLFOX-A. The radiation note (on completion of radiation treatment) and the pathology report should be sent to BrUOG. Pot op scan to be sent as well. The date of progression and time of death to be reported to BrUOG.

[E] post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, documented status required.

[F] It is appropriate to use labs from screening for cycle 1 day 1, if labs are within 14 days (pregnancy must be within 7 days as noted above for applicable patients). A physical exam within 7 days prior to cycle 1 day 1 may be utilized. It is appropriate to use PS, toxicity assessment, weight and vitals for cycle 1 day 1 if they are within the 14 days. Pre-cycle assessments for all subsequent cycles can be within 3 days prior to day 1 of treatment (see **above).

[G] Adverse event evaluation, inclusive of SAE evaluation, and Performance status assessment will be done 30 days (+1 week) post last dose of drug. SAEs occurring outside this 30 day window must be reported if the event is considered to be possibly related to the drug. If a patient begins a new treatment prior to the 30 day assessment, AE evaluation will be stopped unless the patient experiences an event that is thought to be possibly related to the study treatment. Site to submit the final completed full AE log once assessment done.

[H] Physical to be done in coordination with 30 day toxicity assessment (+ 1 week allowed). Physical post 30 day assessments not required per study.

[I] CT scans (or disease assessment by MRI or PET) to be completed approximately every 3 months (post cycle 5 and pre cycle 10). Scans may be done early secondary to MD discretion or to rule out progression of disease. Sites to document reason to BrUOG. It is not required to have pelvic imaging, however, if a pelvic scan is completed at any time point (baseline, during or after the study with follow-up) please forward this to BrUOG. If chest imaging is not done at any time point post baseline it will not be considered a deviation. It is at the discretion of the MD to order chest imaging post baseline, but if chest imaging is completed it must be submitted to BrUOG. Chest x-ray acceptable for use through-out study. Abdominal imaging is required. All scans completed from time of registration through progression of disease required to be sent to BrUOG. Confirmatory scans for response are not required.

Off study/ Follow-up: If follow-up time points, including imaging is done outside of study window it will be a minor deviation, site to document reason.

7.0 RESPONSE ASSESSMENT:

Measurement of Response

Response will be evaluated in this study using the international criteria proposed in the Revised Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 [*Eur J Cancer*. 2009;45:228-247.] See http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf? further details.

Measurable disease: 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).

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis).

Response Criteria: Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions; Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of 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

Confirmatory scans for response are not required as part of this protocol, but if done, the scans are required to be sent to BrUOG.

8.0 PATIENT REGISTRATION

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

Brown University Oncology Research Group,

Brown University
Box G-R 001
Providence, RI 02912
Fax: 401-863-3820
Phone: 401-863-3000
Email: BrUOG@brown.edu,

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form. Sites are to be sure that elements to support all inclusion and exclusion criteria are submitted and that all assessments from the schedule of evaluations (section 6) are submitted for registration.

9.0 PHARMACEUTICAL INFORMATION OF CHEMOTHERAPEUTICS

9.1 Fluorouracil

See package insert for comprehensive information.

9.1.1 Formulation

Each 10 ml ampule contains 500 mg of the drug (50 mg/ml), adjusted to a pH of approximately 9 with sodium hydroxide.

5-Fluorouracil is a fluorinated pyrimidine differing from the normal RNA substrate, uracil, by a fluorinated number 5 carbon. The chemical has a pH of 8.1, and the commercially available solution is buffered with NaOH to obtain an alkaline solution with a pH of around 9.0. The drug is both light sensitive and will precipitate at low temperatures or, occasionally, after a prolonged period at room temperature. Melting range of the solid is 280-284° C. At 25°C the solubility is 1.2 mg/ml in chloroform. The sodium content is 8.24 mg/ml and molecular weight 130.08.

9.1.2 Mechanism of Action

The metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this fashion, 5-FU interferes with the synthesis of DNA. This creates a thymine deficiency that provides unbalanced growth and cell death. Prolonged administration of 5-FU continuous infusion may favor 5-FU incorporation into RNA.

9.1.3 Pharmacokinetics

5-FU is rapidly absorbed by the tissues. Studies with radioactively labeled 5-FU administered i.v., have indicated passage of the drug through the blood-brain barrier. Intravenous administration gives a half-time of 5-7.5 minutes at a 15 mg/kg dose. Following the i.v. administration of a single 15 mg/kg dose of radioactively labeled drug, levels of 28 mcg/ml, 2-8 mcg/ml, and 0.72 mcg/ml in plasma were observed at 10 minutes, 2 hours, and 24 hours, respectively. The drug is largely catabolized in the liver and excreted in the form of nontoxic metabolites. Eighty percent of the drug is excreted as CO_2 from the lungs, and approximately 15% is excreted intact in the urine in 6 hours. Of this, 90% is excreted in the first hour.

9.1.4 Administration

5-FU will be administered as a continuous IV infusion over 46 hours every 2 weeks.

9.1.5 Known Side Effects and Toxicities

Mild nausea and vomiting, stomatitis, anorexia, diarrhea, alopecia, hand/foot syndrome, myelosuppression, cerebellar ataxia, skin, and cardiac toxicity have been observed. The most common toxicities with continuous infusion 5-FU are mucositis and hand/foot syndrome.

9.1.6 Storage and Stability

5-FU is stored at room temperature. 5-FU is light sensitive and forms precipitates at low temperatures.

9.1.7 Supply

Commercially available.

9.2Oxaliplatin

Refer to the package insert for additional information.

9.2.1 *Other Names*

Eloxatin, trans-l-diamino cyclohexane oxaliplatin, cis-[oxalato(trans-l-1,2-diamino cyclohexane)platinum(II)]/-OHP, Eloxatine , Dacplat, SR96669.

9.2.2 *Classification*

Alkylating agent; cytotoxic

9.2.3 *Mode of Action*

The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intra strand cross-linking, therefore inhibiting DNA replication and transcription.

9.2.4 *Availability*

Freeze-dried powder for IV infusion in vials containing 50 mg or 100 mg of oxaliplatin. The powder is a white to off-white cake or powder contained in clear glass vials, sealed with an elastomeric stopper and aluminum seal with a flip-off cover. The excipient is lactose monohydrate, 450 mg and 900 mg respectively.

9.2.5 *Preparation*

Reconstitute with 10 mL for 50 mg and 20 mL for 100 mg product sterile water or 5% dextrose to provide an initial concentration of 5 mg/mL. Subsequent dilution with 250-500 mL 5% Dextrose.

9.2.6 *Incompatibilities*

Do not mix or administer with saline or other chloride containing solutions. Oxaliplatin is unstable in the presence of chloride. Oxaliplatin may be administered simultaneously with leucovorin by the same infusion line, provided that they are reconstituted in D5W. Do not mix with alkaline solutions. Oxaliplatin is unstable under alkaline conditions. Do not use components containing aluminum for the preparation of oxaliplatin administration. There is a risk of drug degradation when in contact with aluminum.

9.2.7 *Administration*

The diluted solution of oxaliplatin in 250-500 ml 5% dextrose is administered IV by an infusion pump over 2 hours.

9.2.8 *Adverse Events*

- Allergy/Immunology: Allergic/Hypersensitivity reactions (including drug fever);
- Auditory: Middle ear/hearing (ototoxicity, mild), inner ear/hearing (mild hearing loss);
- Blood/Bone Marrow: decreased hemoglobin, hemolysis (e.g. immune hemolytic anemia, drug-related hemolysis), decreased leukocytes, decreased platelets, neutropenia;
- Cardiovascular (Arrhythmia): Sinus tachycardia, supraventricular arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmias (PVCs/ bigeminy/trigeminy/ventricular tachycardia);
- Cardiovascular (General): Edema, hypertension, phlebitis (superficial), thrombosis/embolism (including pulmonary embolism);
- Coagulation: DIC (Disseminated intravascular coagulation);
- Constitutional Symptoms: Fever (in the absence of neutropenia), weight loss, fatigue (lethargy, malaise, asthenia);
- Dermatology/Skin: Erythema or skin eruptions, alopecia, injection site reaction, rash/desquamation;
- Endocrine: Hot flashes/flushes;
- Gastrointestinal: Anorexia, constipation, dehydration, dysphagia, diarrhea, esophagitis, odynophagia (painful swallowing), gastrointestinal reflux, enteritis, ascites (NOS), intestinal obstruction, stomatitis/pharyngitis (oral/pharyngeal mucositis), taste disturbance (dysgeusia), nausea, vomiting, colitis, ileus (or neuroconstipation), typhilitis;
- Hepatic: Increased alkaline phosphatase, increased bilirubin, increased GGT (gamma-glutamyl-transpeptidase), hepatic enlargement, increased AST (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase). Veno-occlusive disease of the liver has been reported with the administration of the combination of 5-FU and oxaliplatin.
- Hemorrhage: CNS hemorrhage/bleeding, hemoptysis, hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, melena/GI bleeding, rectal bleeding/hematochezia, other (hemorrhage NOS);
- Infection/Febrile Neutropenia: Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented fever (ANC < 1.0 x 10e9/L, fever > 38.5°C) infection (documented clinically or micro-biologically with grade 3 or 4 neutropenia (ANC < 1.0 x 10e9/L), infection without neutropenia;
- Metabolic/Laboratory: Acidosis (metabolic or respiratory) hyperuricemia, hypokalemia, hypophosphatemia, hyponatremia, hypocalcemia, hypomagnesemia, hyponatremia;
- Musculoskeletal: Involuntary muscle contractions;
- Neurology: Ataxia (incoordination, including abnormal gait) insomnia, mood alteration (depression, anxiety) neuropathy cranial (ptosis), vertigo, neuropathy sensory (including acute laryngeo-pharyngeal dysesthesias, L'Hermitte's sign, paresthesia);
- Ocular/Visual: Conjunctivitis, vision abnormalities (including blindness, optic neuritis, papilledema, hemianopsia, visual field defect, transient blindness;
- Pain: abdominal pain or cramping, arthralgia (joint pain), bone pain, chest pain (non-cardiac and non-pleuritic), headache (including migraine), myalgia (muscle pain including cramps and leg cramps);

- Pulmonary: Pulmonary fibrosis, cough, dyspnea (shortness of breath), hiccoughs (hiccups, singultus), pneumonitis/pulmonary infiltrates (including eosinophilic pneumonia, interstitial pneumonitis, and interstitial lung disease), laryngospasm;
- Renal/Genitourinary: Increased creatinine, renal failure, urinary retention

9.2.9 *Storage and Stability*

Oxaliplatin vials are stored at room temperature between 20° and 25°C. Reconstituted solution in sterile water or 5% dextrose may be stored and will remain stable for 24 hours at 2°-8°C (36°-46°F).

9.2.10 *Supply*

Commercially available.

9.3 Abraxane ®

Availability

ABRAXANE ® will be supplied by Celgene Corporation. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Sites must fax a completed Drug Request Form to Celgene Corporation for drug ordering. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, please complete and fax or email the Drug Request Form as well as the Drug Accountability Log to Celgene Corporation as per instructions on the drug order form.

Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative. Please cc bruog@brown.edu on all email confirmations of receipt of drug.

Storage and Stability

Storage: Store the vials in original cartons at 20º C to 25º C (68º F to 77ºF). Retain in the original package to protect from bright light.

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

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE ® 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 prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 4 hours.

Study Medication Administration

ABRAXANE ® is injected into a vein [intravenous (I.V.) infusion] over approximately 30 minutes. The use of an in-line filter is not recommended.

Reconstitution and use of ABRAXANE ®

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10% by using the formula provided in the study manual. If this is not done it will be considered a minor deviation. Weight gain secondary to edema does not require dose re-calculation.

2. Calculate the total dose (in mg) to be administered by:
   - **Total Dose (mg) = BSA x (study dose mg/m2)**

3. Calculate the total number of vials required by:

   $$\textbf{Total Number of Vials} = \frac{\textbf{Total Dose (mg)}}{\textbf{100 (mg/vial)}}$$

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

4. Using sterile technique, prepare the vials for reconstitution.

5. Swab the rubber stoppers with alcohol.

6. Aseptically, reconstitute each ABRAXANE ® vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.

   - **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 solution 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 (five) 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. Rapid agitation or shaking will result in foaming.

   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

   - Each ml of reconstituted product will contain 5 mg of paclitaxel.

7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:
   - **Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)**
8. The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.
9. Once the exact volume of reconstituted ABRAXANE ® has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted ABRAXANE ® suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.

Administer the calculated dosing volume of reconstituted ABRAXANE ® suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

11. Drug Distribution and Destruction

a. Supplier
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Industry Contact: Norma Powers
Director, Medical Operations
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Mobile: 267-337-2720
Fax: 908-673-2779
Email: npowers@celgene.com

b. Drug Distribution

ABRAXANE ® ® will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE ® ® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.

For re-supply of drug, please complete and fax or email the Drug Request Form as per instructions on form.

Following ABRAXANE® administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with ABRAXANE® (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with ABRAXANE® compared with solvent-based paclitaxel, when the total exposure is comparable. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

It is required that each site use the provided drug order form and that all instructions on the form be followed. Please be sure to cc bruog@brown.edu on all drug orders. For any questions pertaining to the drug, drug shipment or regarding expirations or temperature excursions, please be sure bruog@brown.edu is included on the email.

c. Drug Return and Destruction

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo or log and the site's drug destruction SOP/policy should be sent to BrUOG who will make this available to Celgene. A copy of the drug destruction memo or log should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be sent to BrUOG. At study termination, the site must obtain confirmation from BrUOG before destroying drug.

d. Special Handling Instructions

nab-Paclitaxel is a cytotoxic anticancer 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 *nab*-paclitaxel, events may include tingling, burning and redness. If *nab*-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

e. Drug labeling

Celgene implemented a new NON IMiD IND Exempt drug supply process in February 2017, which was communicated to participating pharmacies in March 2017.

This change in process means that commercial supply of Abraxane is being provided to participating sites on BrUOG 318, by Celgene via shipment from a vendor. Even though commercial drug is being provided, the Abraxane drug is being supplied for this trial as per the study contract and must be segregated, tracked and used specifically for the BrUOG 318 trial. The drug will be shipped and received with no kit # and no reference to the drug being for investigational purposes for this trial. The only reference will be on the invoice sent with the main shipment box, on which pharmacy will see reference to the Celgene study tracking number **AX-CL-PANC-PI-005777. The invoice is requirement to be saved along with the drug order form in the pharmacy BrUOG 318 study binder.**

It is required that pharmacy label the boxes and vials of Abraxane with a label noting "for investigational use BrUOG 318."

9.4 Leucovorin

Leucovorin is a chemically reduced derivative of folic acid, and is useful as an antidote to drugs that act as folic acid antagonists. It is indicated to enhance the activity of 5-fluorouracil. Leucovorin calcium for injection is commercially available and is supplied in sterile, single-use 350 mg vials.

9.4.1 Supply

Leucovorin is commercially available.

9.4.2 Formulation and Storage

Each 350mg vial of leucovorin calcium for injection should be reconstituted according to the manufacturer's instructions. This solution yields a concentration of 20 mg of leucovorin per milliliter and must be used immediately. If leucovorin calcium for injection is reconstituted with bacteriostatic water for injection, the resulting solution must be used within 7 days. Leucovorin calcium vials for injection must be stored at 25°C and protected from light.

9.4.3 Schedule

In the FOLFOX-A regimen leucovorin is administered in 250-500 cc D5W over 2 hours on day 1 of each treatment cycle. Cycles are repeated every 14 days.

9.5 Weight Change:

Doses of chemotherapeutic agents do not need to be recalculated if weight change is less than 10% of total body weight. If this is not done it will be considered a minor deviation. Weight gain secondary to edema does not require dose re-calculation.

10.0 AGENT ACCOUNTABILITY

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from manufacturer using a Drug Accountability Record Form.

10.1 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted.

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

10.2 Study Drug Disposition

See section 9.3, # 11 c for more details.

11.0 ADVERSE DRUG REACTION (ADR) REPORTING

BrUOG considers the SAE reporting period to begin when the subject signs the study specific informed consent.

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Abraxane ® whether or not considered related to Abraxane ®. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

11.1 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious adverse event (SAE)
An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- is life-threatening
- inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

Unexpected adverse event
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

11.2 Monitoring of Adverse Events and Period of Observation
Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

11.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS
Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4.03. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences,

whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

11.3.1 Pregnancies

Pregnancies occurring while the subject is on study drug or within 4 weeks after the subject's last dose of study drug are considered expedited reportable events. If the subject is on study drug, the study drug is to be discontinued immediately. The pregnancy must be reported to the Brown University Oncology Research Group, by the site, immediately (within 24 hours), via the site completed Celgene pregnancy reporting Form **and** a 3500A MedWatch form (site to submit to BrUOG), and BrUOG will in turn report to Celgene immediately (within 1 working day and once in receipt of the site submitted SAE forms). 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 4 weeks (30 days) of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, email, or other appropriate method (to be done by BrUOG), using the Celgene pregnancy report form and the Medwatch3500A form (Celgene pregnancy reporting form and MedWatch 3500A-to be completed by site).

The Investigator will follow the subject until completion of the pregnancy, and must notify Celgene (by informing BrUOG) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to BrUOG who will then report to Celgene by facsimile or email within 1 working day of being made aware of the event via the sites formal submission of the SAE pregnancy forms).

Any suspected fetal exposure to Abraxane ® must be reported to BrUOG immediately who will then report to Celgene within 1 working day of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects to be related to the in utero exposure to the study drug should also be reported. In the case of a live "normal" birth, Celgene should be advised as soon as the information is available.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the 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.

11.3.2: Serious Adverse Event Reporting Procedures

All pregnancies or suspected pregnancies, including suspected fetal exposure or neonatal deaths must be reported to the Brown University Oncology Research Group immediately. BrUOG will report all pregnancies to Celgene within 1 working day, and once being made aware of the event once in receipt of the Celgene Pregnancy Reporting Form/Follow up Pregnancy Reporting Form **and** the Medwatch 3500A,

which is submitted to BrUOG from the site. All other SAEs are to be reported via phone or email to BrUOG within 24 hours of being made aware of the event and the site has 5 business days (from being made aware of the event) to send the written report to BrUOG, who will then report the SAE to Celgene product safety within 1 working day of being in receipt of the Medwatch report submitted to BrUOG from the site. Initial SAE information and all amendments or additions must be recorded on an SAE Form and faxed or emailed to Celgene. Sites are required to report any pregnancy, suspected fetal exposure or neonatal deaths via the Celgene pregnancy reporting form and a 3500A Medwatch form immediately. Both forms need to have the following labeled on both forms:

- **AX-CL-PANC-PI-005777**
    - **BrUOG 318**

Celgene Drug Safety Contact Information: (to be reported to by BrUOG)
Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue
Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

The principal investigator has the obligation to report all serious adverse events to the Brown University Oncology Research Group's (BrUOG) office who in return will report to the FDA, Celgene, and all sites participating in the trial. All SAE reports will be forwarded to Celgene Product Safety by BrUOG. All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form). Sites must alert BrUOG to SAEs within 24 hours of being made aware of the event via phone or email, and will have 5 business days (from when site was made aware of the event) to submit formal notification via the 3500A. BrUOG will then alert Celgene within 1 business day of being in receipt of the Medwatch report. BrUOG will submit the SAE memo, and Medwatch 3500A to the FDA within 7 days.

11.3.3 Expedited Reporting by Investigator to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to ABRAXANE® 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. All events must be reported, by FAX or email, to the Brown University Oncology Research Group who must inform Celgene in writing using the site provided MEDWATCH 3500A form, of any SAE within 1 business day of BrUOG being in receipt of the completed MedWatch 3500A form. The written report must be completed and it will then be supplied by BrUOG to Celgene by facsimile or email within 1 business day of BrUOG being in receipt of the formal SAE submission. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. 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 (such as discharge from hospital) is required. The Celgene tracking number (**AX-CL-PANC-PI-005777**) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission or email confirmation of the SAE

report to Celgene should be attached to the SAE and retained with the study records at BrUOG. (Celgene does NOT send a confirmation so BrUOG will have to use documentation from their fax that it was sent)

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported to BrUOG within 5 business days of being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of FOXLFOX-A, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first.

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Celgene study drug (or therapy) is suspected.
For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

11.3.4 Overdose (to be reported as important medical event)

Overdose, as defined for this protocol, refers to ABRAXANE® dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of ABRAXANE® assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

11.4 Reporting requirements and procedures depend upon:

1. Whether investigational agents are suspected of causing toxicity regardless of causality;
2. Whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer's literature (Expected toxicity); and
3. The severity of grade of the toxicity.

11.5 Assessing Causality:
Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used:

Yes: if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

11.6 Types of Report: Guidelines for sites to report:
Telephone report: For SAE's (initial and follow-up) contact BrUOG Central Office (401) 863-3000 (or via email), immediately upon learning of the event (within 24 hours). Alert BrUOG with 24 hour notice before submitting a SAE report.

Written report: Send the copy of the Medwatch 3500A form (and Celgene pregnancy reporting form for pregnancies if applicable) within 5 business days of being made aware of the event to the BrUOG Central Office by email, scan or Fax:

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: BrUOG@bown.edu

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 business days(from when site was made aware of the event) or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, **deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event. SAEs post 30 days since last dose of drug that are thought to be possibly related to study treatment must be reported to BrUOG within the 5 business day time frame noted above.**

MedWatch 3500A Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**
- **Action taken with Abraxane as a result of the SAE and expectedness**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to **each investigational** product and suspect medication
- Site to be clear to outline which events are being reports as serious
- Must be typed
- ****It is required that sites put the following numbers on the Medwatch form for tracking:**
    - **AX-CL-PANC-PI-005777**
    - **BrUOG 318**

- Document patient status on study (i.e cycle being held, patient coming off secondary to SAE, patient off study etc)

A final report to document resolution of the SAE (such as discharge from hospital) is required.
Follow-up information:

- When submitting a follow-up SAE report submit a new Medwatch3500A and briefly summarize initially reported information, clearly documenting what is being newly reported with the follow-up report (i.e. new attribution to previously reported event, new event, discharge etc).
- A follow-up report is required to report discharge from hospital
- All elements noted under MedWatch 3500A reporting guidelines apply to follow-up reports

Summarize new information including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number (BrUOG 318, AX-CL-PANC-PI-005777), suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted. (The subject identifiers are important so that the new information is added to the correct initial report).

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

11.7 BrUOG Responsibility Regarding Reporting:
The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 7 calendar days after initial receipt of the information. BrUOG will alert Celgene to an SAE within 1 business day of being in receipt of site submitted documentation. SAEs will be reported as an amendment to the IND (if applicable) within 15 days of sponsor notification. They will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA(which will be sent to the Medwatch fax line for IND exemption or to the division fax if there is an IND). A copy of the form will be kept by the BrUOG Central Office.

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND)

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

All SAEs that are serious and reasonably or probably related to the use of Abraxane ® will be faxed to: Celgene

11.8 Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

a. Expedited IND Safety Reports:
BrUOG will fax reports to the FDA for IND Safety Reports: 1 (800) FDA – 0178, unless per the IND status BrUOG is to submit the SAEs to the Division Fax instead.

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to Celgene, as well as any pregnancy occurring in association with use of a Celgene Product to:

BrUOG will send to: Celgene via Email: drugsafety@celgene.com

b. IND Annual Reports, for IND study only
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.
Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

11.9 Adverse event updates/IND safety reports
Celgene shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

1. **Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.**
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
3. The physician feels it is in the best interest of the patient to stop the treatment.
4. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
5. Non protocol chemotherapy or immunotherapy is administered during the study
6. Noncompliance with protocol or treatment—major violation
7. Pregnancies or Suspected Pregnancies(including positive pregnancy test)
8. Patient is lost to follow-up
9. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
10. Death

In this event notify:

Brown University Oncology Research Group (BrUOG) Central Office,
Phone: (401) 863-3000
Fax: (401) 860-3820

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol**

13.0 FOLLOW-UP

All Subjects that discontinue treatment early for any reason as well as patients who complete therapy will be followed for survival (up to 5 years). At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days post the last dose of study drug. In addition off study evaluations will be done when treatment is discontinued -Section 6.0.

14.0 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Howard Safran, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is supported by Celgene (the makers of Abraxane ®).

14.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

14.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be provided to Brown University Oncology Research Group, and Celgene. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Celgene of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, and Celgene. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.3 Protocol amendments or changes in study conduct:
Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be created the Brown University Oncology Research Group, Celgene and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, and Celgene.

- Examples of amendments requiring such approval
- Increases in drug dose or duration of exposure of subjects
- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures
- Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group and Celgene in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group and Celgene must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

- Changes in the staff used to monitor trials (Celgene considers a change in Principal Investigator or the addition of sub-site(s) to be substantial and requires Celgene approval prior to implementation)

15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION
15.1 Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

15.2 Patient Confidentiality: In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Celgene or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's

confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.3 Protocol Compliance: The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Celgene and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Celgene and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

15.4 On-site Audits: Regulatory authorities, the IEC/IRB and/or Celgene clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

15.5 Drug Accountability: Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Celgene for disposal of the drug (if applicable and if approved by Celgene) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing Abraxane ® will be treated and disposed of as hazardous waste in accordance with governing regulations.

15.6 Premature Closure of the Study: This study may be prematurely terminated, if in the opinion of the investigator or Celgene, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Celgene by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to Celgene.

15.7 Record Retention:
The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principle Investigator (Howard Safran, M.D.) and Brown University Oncology Research Group will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Celgene will notify the Principal Investigator if an application is filed.

16.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

17.0 STATISTICS

Sample Size and Statistical Design:

The primary goal is to evaluate the activity of FOLFOX-A for the treatment of locally advanced pancreatic cancer. Activity will be defined as a complete or partial response. We hypothesize that FOLFOX-A would achieve a response rate of at least 40%. A response rate of $\leq$20% would not be considered worthy of future

evaluation. Specifically, the hypothesis that will be tested is:

$$H_{0:}\ p \leq p_0 \text{ versus } H_1: p \geq p_1$$

(where the true response probability is denoted as p, an uninteresting level of probability is denoted as p_0 and the desirable target level as p_1):

A Simon's optimal two-stage design will be used in this study. The first 24 evaluable patients will be assessed for response in the first stage. The trial will be terminated early for futility if 5 or fewer responses are observed in these patients, and it will be concluded that the true response rate is unlikely to be > 40%. If at least 6 responses are observed, accrual will continue in the second stage, until a total of 60 evaluable patients are enrolled. If 18 or more of the 60 have a response, it will be concluded that the treatment regimen has sufficient activity to warrant further investigation.

The characteristics of this study design are as follows: The probability of Type I error (one sided alpha) is 0.04 and power of 93% with this design.

Response criteria are defined as follows: A complete or partial response will be defined according to the RECIST criteria.

Overall survival and time to progression will be determined by the Kaplan Meier method (from the time of study enrollment).
Total Accrual: 60 evaluable treated patients

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APPENDIX A

Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information

BrUOG P318: FOLFOX-A For Locally Advanced Pancreatic Cancer: A Phase II Brown University Oncology Research Group Trial

You are being asked to take part in a research study. All research studies at <INSERT HOSPITAL NAME> follow the rules of the state of <INSERT STATE>, the United States government and <INSERT HOSPITAL NAME>. Before you decide whether to be in the study, you and the researcher will engage in the "informed consent" process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form in front of the person who explained the study to you. This form summarizes the information you discussed. You will be given a copy of this form to keep.

Nature and Purpose of the Study

Your doctors are participating in this research study with the Principal Investigator, Dr. Howard Safran, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

You are being asked to take part in this study because you have recently been diagnosed with locally advanced pancreatic cancer. This means that your cancer has not spread to other organs in your body but it either can't be removed by surgery since your cancer is around major blood vessels in your abdomen. A standard treatment for your cancer is called FOLFIRINOX using FDA approved chemotherapy drugs: fluorouracil, leucovorin, oxaliplatin and irinotecan). In this study you will receive the chemotherapy treatment FOLFOX-A (fluorouracil, leucovorin, oxaliplatin and Abraxane ®), removing irinotecan and using Abraxane ® instead. Even though Abraxane is FDA approved for the treatment of advanced (metastatic) pancreatic cancer, the combination of Abraxane with the other 3 drugs is considered investigational. Your doctors are studying the activity and side effects of FOLFOX-A in locally advanced pancreatic cancer.

This study is supported by Celgene Corporation, the maker of Abraxane ®.

How Many People will take part in the Study?

We expect to enroll approximately 60 subjects into this study. The study is sponsored by the Principal Investigator, Dr. Howard Safran, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

Explanation of Procedures

What will happen if I take part in this research study?

If you take part in this study, you will have exams, tests and procedures to show that you can be in the study, and you choose to take part, then you will need the following tests and procedures, while on the study. They are part of regular cancer care.

Screening:

- Medical history and Demographics
- Physical examination, inclusive of weight, vitals, performance status, toxicity assessment
- Blood tests (requiring approximately 2 tablespoons of blood)
- CT scan (or MRI/PET scan) of the abdomen and chest
- EKG (a test to check your heart function) prior to starting treatment
- Pregnancy Test-Women of child bearing potential must have a negative serum or urine pregnancy test within 7 days prior to starting treatment

During treatment:

- Physical examination approximately every 2 weeks, inclusive of toxicity assessment, performance status, weight and vitals
- Blood tests (requiring approximately 2 tablespoons of blood) every 2 weeks
- CT scan (or MRI/PET scan) of the abdomen and chest approximately every 10 weeks (3 months).

FOLFOX-A is administered intravenously (IV) every 2 weeks (one treatment cycle is equal to 2 weeks). These drugs are given to you through a device called a port-a-cath. A port-a-cath is a standard intravenous device used for chemotherapy that is implanted beneath the skin below your collarbone. A surgeon or radiologist will place the port-a-cath. You will sign a separate surgical consent for placement of the port-a-cath.

When you receive FOLFOX-A treatment, you will first be given Abraxane ® over 30 minutes. The oxaliplatin is then administered over 2 hours. Leucovorin is either administered at the same time as or after the oxaliplatin and also takes about 2 hours. The fluorouracil is then given using a small outpatient chemotherapy pump over the next 46 hours, which is usually started in the chemotherapy clinic and continued at home. Hospitalization is usually not required for the

administration of these drugs. After completion of FOLFOX-A, a nurse will come to your home or you will return to the clinic to have the chemotherapy pump disconnected. After completion of the 48-hour treatment of FOLFOX-A, your doctors may recommend that you receive the standard drug Neulasta, which is given as a shot beneath the skin to help reduce the risk that your white blood cells will become too low after FOLFOX-A and to reduce your risk of infection. During the FOLFOX-A treatments you will have blood tests prior to each treatment, which is standard for patients receiving this type of chemotherapy. If your blood counts are too low, if other blood tests are abnormal, or if you have side effects of the treatment that have not improved in time for your next scheduled treatment, your treatment may be delayed. After approximately 5 treatments (10 weeks), you will have another CT scan of your abdomen to see if your cancer is shrinking; if the cancer is growing or has spread to other organs the treatment will be stopped and you will be taken off of this study.

You will receive FOLFOX-A for 10 treatments (20 weeks or approximately 5 months) as long as your cancer does not grow or spread during the treatments and you do not have such severe side effects from FOLFOX-A that the treatments have to be stopped early. After completion of FOLFOX-A, your doctors will discuss with you whether you will receive radiation treatments to the pancreas or whether they think it would be better to attempt to do surgery to remove your cancer.

Off study/study completion:

- Physical examination at the time of study completion inclusive of toxicity assessment, performance status, weight and vitals and then approximately 30 days later, a physical exam inclusive of toxicity assessment, performance status, and weight
- Blood tests (requiring approximately 2 tablespoons of blood) at study completion
- CT scan (or MRI/PET scan) of the abdomen and chest at study completion, if not done in the prior 2 months

Follow-up:

If you finish the 10 treatments or come off study for reasons other than progression of your disease, you will continue to be followed by a CT scan (or MRI/PET scan) of the abdomen and chest approximately every 4 months for a year, then every 6 months for another year, then once a year. These scans will stop if your cancer progresses.

All patients (whether you complete the treatment or not) will be followed approximately every 4 months for up to 5 years for survival.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include *the drug* Abraxane ®. This drug will be will be provided by Celgene Corporation at no charge and will not be billed to you or your health insurance company.
Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are study doctor visits, the administration of the study drug Abraxane ®, blood tests, pregnancy tests, other chemotherapy drugs and their administration, drugs used to reduce side effects from chemotherapy, CT scans and EKGs. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact your site

Principal Investigator, <INSERT CONTACT NAME> at <INSERT PHONE NUMBER>.

Discomforts and Risks

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or can cause death. In some cases, side effects can be serious, long-lasting, or may never go away.

Taking part in this study may lead to time away from work.

FOLFOX (Fluorouracil, oxaliplatin and leucovorin)

LIKELY (> 20%):

- Lack of enough red blood cells (anemia which may make you short of breath, weak, fatigued, or tired)
- Reduced white blood cells which can cause infection
- Reduced platelets which can cause bleeding
- Numb feeling in the hands and feet, with tingling and burning
- Muscle cramping
- Cold temperatures causing cramps, muscle spasm and numbness. Avoid drinking iced beverages since this can cause temporary spasms of the throat.
- Diarrhea, which could lead to dehydration
- Nausea or vomiting
- Fatigue or tiredness
- Abnormal liver function as detected by blood tests
- Temporary hair thinning or loss
- Darkening of the skin. This happens most often in the palms of the hands or along the vein where 5-FU is given. This is not harmful, but it could be permanent.
- Sores in the mouth and/or throat
- Photosensitivity (exposure to sunlight can cause skin to be sensitive to sunburn). You should use a sunscreen.
- Dizziness
- Changes in fingernails
- Loss of appetite
- Taste changes
- Headache
- Swelling and redness of the eye and eyelids
- Dry or watery eyes
- Constipation
- Dry mouth
- Heartburn
- Excess passing of gas
- Irritation of the stomach
- Allergic reaction
- Dehydration

LESS LIKELY (1-10%):

- Abnormal blood clotting and/or bleeding
- Destruction of red blood cells
- Abnormal heart rhythm
- Hearing loss
- Inflammation in the ear
- Temporary vision problems caused by the cold

- Drooping eyelid
- Swelling around the nerve responsible for sight
- Difficulty swallowing
- Blockage of the intestines with severe constipation
- Inflammation of the pancreas that can cause belly pain and may be serious
- Chills
- Fever
- Difficulty walking
- Chest pain not heart-related
- Abnormal kidney function as seen on a blood test: creatinine
- Abnormal liver function as seen on a blood test: alkaline phosphatase, bilirubin, GGT
- Increased or decreased blood sugar level
- Decreased levels of a protein called albumin
- Abnormal blood chemistries that could lead to abnormal heart, kidney, or nerve function: blood acid, uric acid, calcium, potassium, magnesium, sodium, phosphate
- Pain including joint, back, bone, and muscle
- Difficulty or limitation in ability to open mouth
- Sleepiness
- Speech problems
- Abnormal or involuntary movements
- Anxiety
- Confusion
- Depression
- Difficulty sleeping or falling asleep
- Blood in the urine
- Need to urinate often
- Difficulty emptying the bladder
- Stuffy or runny nose, sneezing
- Cough, wheezing
- Hiccups
- Inflammation of the lungs
- Scarring of the lungs that can cause shortness of breath and interfere with breathing
- Problem of the sinuses
- Voice change
- Dry skin
- Excess sweating
- Itching
- Skin rash or hives
- Sudden reddening of the face and/or neck
- Hot flashes
- High or low blood pressure
- Swelling and redness of the skin on the palms of the hands and soles of the feet that can be serious
- Heart problems (chest pain, heart attack)

RARE (<1%) BUT SERIOUS:

- Formation of blood clots in small blood vessels around the body that leads to a low platelet (a type of blood cell that helps to clot blood) count
- Gas in the intestinal (bowel) wall
- Sudden or traumatic injury to the kidney
- Severe potentially life-threatening damage to the lungs which can lead to difficulty breathing
- Severe diarrhea that may be life threatening
- Accumulation of fluid around the heart
- Death of tissue somewhere in the digestive tract
- Stroke or mini-stroke (TIA)
- A malfunction of the nerves within the head and neck
- Weakness or paralysis caused by damage to nerves
- Convulsion or seizure

Abraxane ®

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

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

Very Common (a 10% or more chance that this will happen):

- Lowered white blood cell count, including lymphocytes and neutrophils, that may lead to infection with or without fever
- Lowered platelets which may lead to an increase in bruising or bleeding.
- Lowered red blood cells which may cause anemia, tiredness, weakness or shortness of breath.
- Nausea or vomiting.
- Diarrhea.
- Hair loss from your head, face and body.
- Loss of appetite
- Pain, swelling or sores on the inside of the mouth or in the throat (stomatitis, mucositis)

- Neuropathy. A disorder of the nerves that can cause tingling, like pins and needles, in your hands and feet, with weakness, or decreased sensation or movement.
- Feeling tired or weak (fatigue)
- Constipation
- pain (including muscle, joints, bone, back, and chest pain)
- swelling caused by fluid held in the tissues, especially of the ankles, feet or fingers
- fever
- cough
- rash, possibly red, bumpy or generalized
- shortness of breath
- Abdominal and stomach pain
- dizziness
- Headache
- chills
- change in taste
- weight loss
- difficulty sleeping
- depression
- itchiness
- changes in nails, including discoloration or separation from nailbed
- abnormal liver and chemistry function test results
- dehydration (loss of water and minerals in the body)
- nose bleed
- Decreased potassium levels in the blood, which may cause fatigue, muscle weakness or cramps and/or an irregular heartbeat.

Common (between a 1% to less than 10% chance that this will happen):

- bone marrow depression which is a severe reduction of red or white blood cells and platelets (at nearly the same time) which can cause weakness, bruising, or make infections more likely
- A very severe infection of the blood which may include a decrease in blood pressure (sepsis)
- thickening, inflammation or scarring in the lungs which may cause breathlessness, cough
- Trouble swallowing
- Heartburn, indigestion, upset stomach
- abnormal chemistry or electrolyte blood test results
- abnormal kidney function test results
- acute kidney failure
- blood in urine
- inflammation or an irritation of the lung passages
- inflammation of the bowel causing abdominal pain or diarrhea (colitis)

- infections, including pneumonia or urinary tract, respiratory (lung), nail, oral (mouth), yeast, hair follicle, gallbladder (which may be bacterial, fungal or viral)
- Blockage of the intestine
- Lack of muscle coordination and muscle weakness, which may include difficulty with balance and walking
- Anxiety
- Nasal congestion
- Pain in mouth or throat
- Dry mouth, nose, throat, skin
- coughing up blood or bloody sputum
- fluid in the chest cavity
- blood clot in the lungs or in a deep vein
- hand-foot syndrome, involving reddening, swelling, numbness and peeling of palms and soles of feet
- red or flushed or dry skin
- Low or high blood pressure.
- Vision changes, including watery eyes and blurry vision
- Faster or slower heartbeat, congestive heart failure, palpitations (rapid or fluttering heart)
- infusion site reactions (described as discomfort, bleeding or bruising/swelling at the needle site, and in some instances infection or leaking of fluid outside of blood vessel)
- localized swelling due to lymph build-up
- A decrease in the heart's ability to pump blood to all parts of the body and possibly heart failure

Uncommon **(between a 0.1 to less than 1% chance that this will happen):**

- stopping of the heart
- Syndrome involving abnormal blood clotting, with decreased platelets, bruising and possibly leading to clot (including tiny red or purple spots under the skin) (Thrombotic purpura)
- edema/swelling and cyst formation of the macular area of the retina
- irritation and redness of the thin membrane covering the eye
- inflammation of the cornea
- feeling unwell
- sleepiness
- allergic reaction (may include skin inflammation, rash, trouble breathing; trouble speaking; fever, and/or diarrhea), sometimes fatal
- Potentially life threatening allergic reaction of the skin and oral mucous membranes (may include lesions in the mouth, itching and blistering skin) usually caused by an infection.
- a loss of nerve function in the muscles of the face
- too much fluid in the body
- scaly or peeling skin
- hives

Additional side effects observed during post-marketing surveillance, not otherwise noted above include:

- lack of movement in the vocal cords with possible voice changes
- skin sensitivity to sunlight
- potentially life threatening allergic reaction affecting the skin and digestive tract usually caused by drug (s) or an infection, and which may include skin rash with skin blistering

skin or tissue damage from prior radiation therapy can become damaged again, when a person receives chemotherapy after having had radiation therapy. This is referred to as radiation recall and may involve redness, peeling, pain, and swelling. Skin changes have been noted to range from mild redness to tissue death. Radiation recall may also occur in the lungs and other internal organs.

Elderly:

In subjects ≥ 65 years old with a history of metastatic breast cancer who pervioulsy received *nab*-paclitaxel alone (monotherapy), a higher rate of nose bleed, diarrhea, dehydration (loss of water and minerals in the body), feeling tired or weak and swelling caused by fluid held in the tissues, especially of the ankles, feet or fingers has been reported.

The following events are also possible side effects that are being noted as they have been observed by the Principal Investigator of the study:

- Liver Failure
- Hearing loss.
- Pain and bruising at injection sites.
- Heart damage.
- Kidney and liver damage.
- Irregular heartbeat.
- Bone, muscle and joint pains and cramps in legs or back
- Allergic reactions of skin rash
- Mood changes
- Respiratory Failure

Neulasta or Neupogen (drugs that you may get to prevent your white blood cell count from dropping too low for too long due to the chemotherapy drugs; your doctor will tell you if you should receive one of these drugs, which can either be started with the first cycle of FOLFOX-A or after any number of cycles if your white blood cell counts are too low)

Common (likely to occur in more than 20% of patients):

- Pain in muscles, joints, lower back or pelvis
- Itching
- Pain arms or legs
- Fever
- Headache

- Shortness of breath
- Skin rash
- Redness, swelling or pain at injection site

Rare, but Serious (unlikely to occur in more than 1% of patients):

- Chest pain
- Rapid or Irregular Heartbeat
- Wheezing

Risk of Secondary Cancers or Leukemia: The chemotherapy drugs oxaliplatin, fluorouracil or Abraxane ® may increase the risk of other cancers or leukemia (a blood cancer).

Reproductive Risks

Chemotherapy may decrease the sperm count. This is usually temporary but is infrequently permanent, which would result in sterility. Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study. Ask your study doctor for more information regarding preventing pregnancy during the study treatments. You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

Females: Abraxane ® (paclitaxel albumin) can cause harm to an unborn child if given to a pregnant woman. You cannot take part in this study if you are pregnant or breast-feeding. Because of the possible risks to an unborn child, if you are a female who can become pregnant, you will be asked to take a pregnancy test within 7 days prior to starting study drug treatment.

If you decide to take part in this study, you must agree to use medical doctor-approved contraception throughout the study, and for 3 months after your last dose of study drug. If you become pregnant during the study you must tell the study doctor right away. If this happens, your participation in this study will be discontinued (stopped). If you become pregnant within 3 months after taking your last dose of study drug you must tell the study doctor right away. The study doctor will follow you and your pregnancy to birth.

Males: If you have a partner of childbearing age, you must agree to use a medical doctor-approved form of contraception throughout the study, and should avoid fathering a child for 6 months after your last dose of study drug. If your partner becomes pregnant during the study or within 6 months after you took your last dose of study drug, you must tell the study doctor right away.

By signing this document you are acknowledging that you understand and agree to the information presented in this Reproductive Risk section.

Antiemetics (anti-nausea medications): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

When you receive chemotherapy by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

In order to monitor the side effects, and as part of standard of care, your physician will examine you frequently and obtain laboratory tests (blood tests, chest x-rays, or CT scans as needed) to determine the effects of your treatment and alter the drug dosages if necessary.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits

Taking part in this study may or may not make your health better. While doctors hope that FOLFOX-A will be active against pancreatic cancer and the side effects are not too severe, this is not yet known. We do know that the information from this study will help doctors learn more about these drugs as a treatment for cancer. This information could help future cancer patients.

Alternative Therapies

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

- Receiving radiation therapy alone
- Receiving radiation therapy with the chemotherapy drug capecitabine.
- You should discuss with your doctor whether there is the possibility of surgery at this time without first receiving chemotherapy or radiation.
- Getting treatment or care for your cancer without being in a study such as receiving the chemotherapy drug gemcitabine or combinations of chemotherapy such as FOLFOX or FOLFIRINOX
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

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

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the standard of care health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

If you make the decision to withdraw from this study (stop taking study medication) for any reason, tell your doctor immediately. You will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. Howard Safran, the sponsor of the study, nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care

under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact <ENTER CONTACT INFORMATION IRB>, in the <ENTER NAME OF IRB>, at <ENTER CONTACT INFORMATION>.

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of<INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor, PI Howard Safran, MD, BrUOG, The Brown University Oncology Research Group and their representatives and Celgene Corporation (Financial study supporter);
- Doctors, nurses, laboratories and others who provide services to you in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME>to release your health information without your permission. For example, <ENTER STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

You will not be allowed to see or copy the information described in this form as long as the research study is open. You may see and copy the information when the study is completed.

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

For more detail about your privacy rights see the <INSERT HOSPITAL NAME>Joint Privacy Notice which has or will be given to you.

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the* <INSERT HOSPITAL NAME> *Privacy Notice*

This informed consent document expires on _____.

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____
Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____
Signature of witness (required if consent is presented orally or at the request of the IRB) Date

_____ _____
Signature of Translator Date

_____ _____ _____
Signature of researcher or designate Date and Time when signed

* If signed by agent other than study volunteer, please explain below.

_____

_____

APPENDIX B: Checklist

FOLFOX-A For Locally Advanced Pancreatic Cancer:
A Phase II Brown University Oncology Research Group Trial

Inclusion Criteria

_____(y/n) Pathologically or cytological confirmed pancreatic ductal adenocarcinoma. Patients with pathology or cytology showing carcinoma of pancreas or adenosquamous of the pancreas are also eligible.
_____(y/n) Locally advanced pancreatic cancer pancreatic cancer as defined in eligibility. Required to document in writing to BrUOG which criterion patient meets by treating physician.
_____(y/n) Measurable disease by RECIST 1.1
_____(y/n) Voluntary, signed written informed consent, Date signed_____

_____(y/n) Age ≥18

_____(y/n) Must be willing to consent to use effective contraception 28 days prior to treatment, while on treatment and for at least 3 months afterwards (men at to use contraception for 6 months afterwards).

_____(y/n) CT scan of chest/abdomen prior to registration (PET or MRI can substitute)

_____(y/n) EKG within 8 weeks study entry

_____(y/n) No prior chemotherapy for pancreatic cancer

_____(y/n) Absolute neutrophil count ≥ 1,500/ul, Date_____

_____(y/n) Platelet ≥ 100,000/uL, Date_____ *must be transfusion independent- see inclusion*

_____(y/n) Hemoglobin > 9 Date :_____ transfusional support allowed (must document)

_____(y/n) Total bilirubin ≤1. 5 x ULN, Date_____

_____(y/n) AST≤ 2.5x ULN and ALT ≤ 2.5x ULN Institution ULN_____, Date_____

_____(y/n) Alkaline phosphatase ≤ 2.5xULN, ULN_____, Date_____
*see inclusion for details

_____(y/n) Creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 ml/minute, Date_____

_____(y/n) ECOG 0-1

Exclusion Criteria:

_____(y/n) Distant metastases.

_____(y/n) neuropathy from any cause.

_____(y/n) prior invasive malignancy within the prior two years. However, patients with an early stage malignancy that is not expected to require treatment in the next 2 years (such as early stage, resected breast cancer or asymptomatic prostate cancer) are eligible.

_____(y/n) Prior hypersensitivity to Oxaliplatin or Abraxane ® that in the investigators opinion would put the patient at risk if re-exposed

_____(y/n) Patients with serious medical risk factors involving any of the major organ systems such that the investigator considers it unsafe for the patient to receive FOLFOX-A

_____(y/n) Patients with unstable biliary stents or plastic stents

_____(y/n) uncontrolled diabetes

_____(y/n) Patients with active infection or fever (no fever for 48 hrs) (patients on antibiotics for infection or patients getting over a cold or seasonal virus are not excluded), or known historical or active infection with HIV, hepatitis B, or hepatitis C.

_____(y/n) Patients with active sepsis or pneumonitis.

_____(y/n) Patients with a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies that in the investigator's opinion would put the patient at an increased risk.

_____(y/n) Patients on concurrent anticancer therapy.

_____(y/n) major surgery within 3 weeks of study treatment start date. See eligibility for more details

_____(y/n) Pregnant or breastfeeding. Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to beginning of treatment. Post-menopausal women (surgical menopause or lack of menses $\geq$24 months) do not need to have a pregnancy test, please document status.

Signed informed consent: The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form Enclosed __Not Enclosed _____ Not Applicable __

2) Heme/Onc initial note Enclosed __Not Enclosed _____ Not Applicable __

3) Pathology Report(s) Enclosed __Not Enclosed _____ Not Applicable __

4) MRI/CT Report(s) Enclosed __Not Enclosed _____ Not Applicable __

5) Lab Source Document Enclosed __Not Enclosed _____ Not Applicable __

6) ICF signature page

7) Other documents, please list_____

IRB approval date of protocol: _____

Hospital where patient will be treated with Oncologist: _____

Date patient will begin treatment: _____ Primary Physician: _____

Your signature: _____

APPENDIX C

NCI CTC Version 4.0

Toxicity will be scored using NCI CTC Version 4 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4 can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4

APPENDIX D

ECOG PATIENT PERFORMANCE STATUS

STATUS	KARNOFSKY	ZUBROD-ECOG-WHO	Description
No complaints	100	0	Normal activity
Able to carry on normal activities	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed >50% of the day, but not bedridden
Disabled, requires special care and assistance	40		

Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization Necessary. Active support treatment necessary	20		
Moribund	10		
Dead	0		

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536

APPENDIX E

CASE REPORT FORMS

Attached separately are the BrUOG Case Report Forms