

FOLFOX-A For Metastatic
Pancreatic Cancer:
A Phase II Brown University Oncology Research Group Trial
Howard Safran, MD
Medical Director, Brown University Oncology Group
Kevin Charpentier, MD
Rimini Breakstone, MD
Rhode Island Hospital Comprehensive Cancer Center
Anthony Thomas, MD
Memorial Hospital

Sonia Seng, MD
Southcoast Center for Cancer Care

In recognition of the Eastman family
Coordinating Center
Brown University Oncology Research Group
233 Richmond Street Box G-R001
Providence, Rhode Island 02903
Phone: (401) 863-3000
Fax: (401) 863-3820
Email: BrUOG@brown.edu

CONFIDENTIAL

The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless law or regulations require such disclosure. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Celgene tracking number: AX-CL-PANC-PI-003263

Initial protocol 12/20/13
Amendment # 1 6/24/14
Amendment # 2 9/10/14
Amendment #3 1/13/15
Amendment #4 3/19/15
Amendment #5 8/11/15
Amendment #5V2 10/6/15
Amendment #6 12/15/15
Amendment # 7 3/23/16
Amendment # 8 7/5/16
Amendment #9 12/4/16
Amendment # 10 2/3/2017 with IB 19
Amendment # 11 5/22/17
Amendment # 12 8/21/17
Amendment # 13 12/26/18

TABLE OF CONTENTS

<u>Section</u>	<u>Page</u>
1.0 OBJECTIVES	3
2.0 BACKGROUND	3
3.0 PATIENT ELIGIBILITY	5
4.0 TREATMENT	7
5.0 TOXICITIES, ASSESSMENT, AND DOSE MODIFICATIONS	7
6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR	11
7.0 RESPONSE ASSESSMENT	13
8.0 PATIENT REGISTRATION	14
9.0 PHARMACEUTICAL INFORMATION	14
10.0 AGENT ACCOUNTABILITY	21
11.0 ADVERSE DRUG REACTION REPORTING	22
12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY	29
13.0 FOLLOW UP	29
14.0 REGULATORY CONSIDERATIONS	29
15.0 DATA MONITORING/QUALITY ASSURANCE/ RECORD RETENTION	31
16.0 DATA SAFETY AND MONITORING BOARDS	32
17.0 STATISTICAL CONSIDERATIONS	33
18.0 REFERENCES	34

APPENDIX SECTION:

APPENDIX A INFORMED CONSENT

APPENDIX B ELIGIBILITY CHECKLIST

APPENDIX C COMMON TOXICITY CRITERIA

APPENDIX D ECOG PERFORMANCE STATUS

APPENDIX E CASE REPORT FORMS

1.0 OBJECTIVES

1.1 Primary Objective

1.1.1. To evaluate the survival for patients with metastatic pancreatic cancer with first-line treatment with FOLFOX-A as compared to historical controls of gemcitabine alone.

1.2 Secondary Objectives

1.2.1 To assess the toxicities associated with FOLFOX-A for metastatic pancreatic cancer

1.2.2 To evaluate the response of patients with metastatic pancreatic cancer who receive the FOLFOX-A regimen

2.0 BACKGROUND

Advanced pancreatic cancer:

Pancreatic cancer is the fourth-leading cause of cancer-related death in the United States.¹ Single agent gemcitabine has been the most commonly utilized treatment for advanced pancreatic cancer improving survival and quality of life as compared to single agent fluorouracil.² The median survival for patients with metastatic pancreatic cancer treated with gemcitabine is approximately 6.5 months.³⁻⁵

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).⁶ 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. FOLFIRINOX has significant toxicity. 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.

Irinotecan is not an effective agent in pancreatic cancer: The contribution of irinotecan in FOLFIRINOX is unclear. Single agent irinotecan is without significant activity in pancreatic cancer.⁷ Furthermore, the combination of irinotecan and gemcitabine does not improve survival as compared to gemcitabine alone.⁸ 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. 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.⁹ A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane.¹⁰ 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.¹⁰ Pancreatic cancer cells and surrounding stroma are known to overexpress SPARC (secreted protein acid rich in cysteine), which is associated with poor clinical outcomes.¹¹ The albumin-bound nanoparticle form of paclitaxel increases tumor accumulation of paclitaxel through binding of albumin to SPARC.^{11,12}

Abraxane® + Gemcitabine in pancreatic cancer: The regimen of Abraxane®, 125mg/m², and gemcitabine, 1gm/m², 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.^{11,12} 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.¹³

	<i>Abraxane®</i> + 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 FOLFIRINOX-Abraxane®(FOLFIRINOX-A): Irinotecan is responsible for much of the toxicity of FOLFIRINOX but may not contribute significantly to the regimen’s activity. 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® in patients with metastatic pancreatic cancer – this new regimen is called FOLFIRINOX-A. All patients received oxaliplatin, 85 mg/m², leucovorin 400 mg/m² and 5-FU 2400 mg/m² IVI 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

All patients received 1 gram of magnesium sulfate and 1 gram of calcium gluconate before and after oxaliplatin. Neulasta was required with the first 2 cycles of FOLFOX-A then became optional. The protocol received an IND exemption and is listed via clinicaltrials.gov NCT01744353.

All 3 dose-levels have been evaluated and the maximum tolerated dose has been determined in patients with metastatic pancreatic cancer. One of six patients at dose-level 1 had grade 3 nausea. At dose-level 2, one of six patients had urosepsis with an absolute neutrophil count of 900 cell/mm³. Noteworthy was that on dose-level 2 an 81 year-old and a 76 year-old patient have been on treatment without significant toxicity. (In contrast, FOLFIRINOX is not recommended for patients > 75 years of age).

At dose-level 2, one of six patients had urosepsis with an absolute neutrophil count of 900 cell/mm³. Noteworthy was that on dose-level 2 an 81 year-old and a 76 year-old patient have been on treatment without significant toxicity. (In contrast, FOLFIRINOX is not recommended for patients > 75 years of age). The MTD of Abraxane ® is 150mg/m² every 2 weeks with FOLFOX. Cumulative peripheral neuropathy, similar to other FOLFOX regimens, is the most significant toxicity generally occurring after ≥ 10 cycles of treatment. Eight of 9 patients (88%) who received 10 or more cycles of FOLFOX-A had grade 2 or greater neuropathy including 2 of 9 (22%) with grade 3 neuropathy, None of the patients receiving less than 10 cycles of FOLFOX-A developed grade 2 neuropathy. FOLFOX-A has substantial activity and may represent a promising regimen in pancreatic cancer. Based on the initial activity and toxicity profile from the phase I study, FOLFOX-A appears to be a promising regimen for patients with advanced pancreatic cancer. To further evaluate efficacy and toxicity, a phase II study will be initiated. To reduce the potential for neurotoxicity, this protocol will include dose reductions of oxaliplatin for grade 2 neurotoxicity.

Current Proposal - A Phase II Study of FOLFOX-A: Based on the initial activity and toxicity profile from the phase I study, FOLFOX-A appears to be a promising regimen for patients with advanced pancreatic cancer. To further evaluate efficacy and toxicity, a phase II study will be initiated.

3.0 PATIENT ELIGIBILITY

3.1 Conditions for Patient Eligibility

1. Pathologically or cytological confirmed pancreatic ductal adenocarcinoma. Patients with pathology or cytology showing carcinoma of pancreas or adenosquamous of the pancreas are also eligible.
2. Measurable disease not required at baseline. Patient's without measurable disease may be enrolled if there is known evidence of metastatic disease without measurable lesions as per imaging or per treating MD. For example a patient with peritoneal disease detected at exploratory surgery which is not seen on imaging is eligible.
3. Metastatic advanced disease.
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.

Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18

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 \geq 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 \geq 12 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 during treatment and for three months after completing treatment (men are to use contraception for six months). Documentation of this being discussed required.
11. Required Initial Laboratory Values:
 - Neutrophils \geq 1,500/mm³
 - Platelet count \geq 100,000/mm³
 - Creatinine \leq 1.5 mg/dL -or- creatinine clearance \geq 60 mL/min
 - Total bilirubin $<$ 1.5 x ULN
 - AST (SGOT) & ALT (SGPT) \leq 2.5 x ULN (for patients with liver metastases, AST&ALT \leq 5xULN)
 - Alkaline phosphatase \leq 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 \leq 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 known brain metastases
- 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 (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.

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 (example: clinic, patient or MD schedules etc). Any Adjustment must be documented on applicable CRFs with reason to BrUOG

Abraxane ®: 150mg/m² IV over 30 minutes, day 1 (administered first) every 14 days.

Oxaliplatin: 85mg/m², IV over 2 hours, day 1 every 14 days

Leucovorin: 400mg/m², IV over 2 hours, day 1 every 14 days

5-FU infusion: 1200mg/m²/day, as a continuous IV infusion over 2 days, day 1 and day 2 (for a total dose of 2400mg/m² 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 with metastatic disease can receive up to 12 cycles of FOLFOX-A as part of this study as long as their cancer does not progress. After 12 cycles of FOLFOX-A, additional treatment/management will be as per institutional standards of care. Patients will not receive more than 12 cycles of FOLFOX-A on this study.

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 4.0 (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 $\geq 100 \times 10^9/L$ (100,000/mm³)

Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18

- Granulocytes (ANC) $\geq 1.5 \times 10^9/L$ (1500/mm³)
- Recovery from other treatment related, non-hematologic toxicities to \leq Grade 2, this does not include alopecia.

If the patient does not meet these criteria delay day 1 until recovery. 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/mm³)
- ANC < 1000/mm³ with fever (temp > 101) or infection
- Platelets < 25,000/mm³
- Platelets < 50,000/mm³ 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 12 cycles 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 ≤ 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 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, oxaliplatin should be permanently decreased to oxaliplatin dose level - 2 (54mg/m²). Abraxane® and 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 ≤ 1 , however, Abraxane®, 5-FU and leucovorin may be administered.
- 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.

- For patients developing grade 2 neuropathy, it is the investigators discretion to stop FOLFOX-A after 10 cycles instead of continuing to 12 cycles. Reason for patient discontinuing treatment 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 or less. When treatment is resumed oxaliplatin and Abraxane[®] dose should be permanently decreased to 68mg/m² and 120mg/m² respectively. 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 or less. When treatment is resumed oxaliplatin and Abraxane[®] dose should be permanently decreased to 54mg/m² and 96mg/m² respectively.
- For patients developing a third episode of grade 3 neuropathy they should be removed from study treatment.
- Patients developing grade 3 neuropathy should not receive more than 10 cycles of FOLFOX-A. Reason for patient discontinuing treatment must be documented.
- 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: For patients experiencing grade 4 neuropathy, patients must come off study treatment.

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.

For example if a patient experiences grade 2 neuropathy, per section 5.3.1, Abraxane, Leucovorin and 5_FU are to be administered, but only when neuropathy is \leq grade 1 can Oxaliplatin be reinstated. Oxaliplatin will be reduced by 1 dose level. However if they then 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.

For patients who experience neuropathy grade 3, per section 5.3.2, FOLFOX-A will be held and when neuropathy is \leq grade 1, Abraxane[®] and Oxaliplatin will 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. However, the risk has been higher for the combination of *Abraxane*® with gemcitabine. Pneumonitis has been reported at a rate of 4% with the use of *Abraxane*® in combination with gemcitabine. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with *Abraxane*® and gemcitabine 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.

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 Friday can be used for treatment Monday as this is within 3 days*

Parameter	Pre-study (to be sent to BrUOG prior to registration)	Within 3 days prior to each Day 1 of Each Cycle (Every 2 weeks) ^F	After completion of FOLFOX A (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 ^I	
Weight	X	X	X	X ^I	
Vital signs	X	X	X		
Toxicity Assessment	X	X	X	X ^H	
Performance Status	X	X	X	X ^H	

CBC, diff, platelet count	X (within 14 days)	X			
Na, K, BUN, Cr	X (within 14 days)	X			
AST, ALT, Bili	X (within 14 days)	X			
Mg, Calcium, Alk phos	X(within 14 days)	X ^G			
Serum Pregnancy ^E	X (within 7 days of drug)				
CA19-9	X(within 14 days)	X ^G	X		
CT scan of Chest/abd ^{AcDj} RECIST for assessment see section 7	X ^{AC} (within 28 days)	X ^{ACDJ}	X(CT does not need to be repeated if done in prior 2 months)ACDJ		XACDJ
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, without progression, follow-up will include CT, disease free and overall survival every 3 months. CT scans may be done outside of the 3 month window as per MD discretion, however it is suggested that CT scans be done q 3 months. Once the patient progresses, CTs are no longer needed. For patients who come off study for progression, overall survival is to be reported every 3months. Follow-up will be for 5 years.

^E post-menopausal women (surgical menopause or lack of menses ≥ 12 months) do not need to have a pregnancy test, document status

^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 to be within 3 days prior to day 1 of treatment.

^G CA19.9 and Mg, Ca, Alk Phos, to be drawn approximately every 3 months (every 6 cycles)

^H 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 this study treatment or study drug, regardless if patient begins a new treatment within the 30 day window. If a patient begins a new treatment, AE evaluation will be stopped, but SAEs will be captured for the full 30 days post treatment.

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

^JCT scans (or disease assessment by MRI or PET) to be completed approximately every 3 months (approximately every 6 cycles). 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 patients do not have disease in their chest from baseline chest imaging is not required moving forward and can be done per MD discretion. If done it is required to be sent to BrUOG. Abdominal imaging is 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:

Note: The primary endpoint of this study is survival. Measurable or assessable disease is not required in this study, but for patients who do have measurable disease, measurements must be submitted to BrUOG at baseline and RECIST to be used throughout to assess response. Radiographic response will be recorded when available but is not a primary endpoint.

Patient's without measurable disease at baseline: To be followed for survival. Progression and response can be defined as clinical progression, the appearance of one or more new lesions and tumor burden at baseline to be used for assessment and measurement for objective response by treating MD.

Patient's with measurable disease at baseline:

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

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
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 CO₂ 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 10⁹/L, fever > 38.5°C) infection (documented clinically or micro-biologically with grade 3 or 4 neutropenia (ANC < 1.0 x 10⁹/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 laryngo-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.

Storage and Stability

Storage: Store the vials in original cartons at 20° C to 25° C (68° F to 77°F). 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 20°C to 25°C (68°F to 77°F), 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 2°C to 8°C (36°F to 46°F) 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 25° 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:

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

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.
 11. 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
 12. Following administration of Abraxane, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose, according to local practice

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 to Celgene as per instructions on the form.

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 provided to BrUOG. At study termination, the site must obtain confirmation from BrUOG before destroying drug.

d. 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 292, 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 contract and must be segregated, tracked and used specifically for the BrUOG 292 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-003263**. **The invoice is requirement to be saved along with the drug order form in the pharmacy BrUOG 292 study binder.**
- It is required that pharmacy label the boxes and vials of Abraxane with a label noting “for investigational use BrUOG 292.”

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 doses are not re-calculated it will be deemed 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 4.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 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 4.0. A copy of the CTCAE Version 4.0 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 4.0. 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, 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 Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18

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 in receipt of the submitted SAE forms from the site).

Any suspected fetal exposure to Abraxane® must be reported to BrUOG within 24 hours who will then report to Celgene within 1 working day of being in receipt of the submitted SAE forms from the site. 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 within 24 hours. BrUOG will report all pregnancies to Celgene within 1 working day of being made aware of the event via the submission of the Celgene Pregnancy Reporting Form/Follow up Pregnancy Reporting Form and the Medwatch 3500A, which will be sent to BrUOG from the site. All SAEs are to be reported via phone or email to BrUOG within 24 hours 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 receipt of the SAE forms sent to BrUOG by the site. Initial SAE information and all amendments or additions must be recorded on an SAE Form and faxed 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. Both forms need to have the following labeled on both forms:

- AX-CL-PANC-PI-003263
- BrUOG 292

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 via phone or email, and will have 5 business

days (from being 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 SAE forms sent to BrUOG from the site. BrUOG will submit the SAE memo, and Medwatch 3500A to the FDA within 7 days.

11.3.3 Expedited Reporting by Investigator to Celgene

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 a MEDWATCH 3500A form, of any SAE within 1 business day of being in receipt of the Medwatch form sent to BrUOG from the site. 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 SAE documentation from the site. 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-003263) 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 or email transmission 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 within 5 business days (from 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 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.

This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

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 an 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 C_{max} 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.

11.4 Reporting requirements and procedures depend upon:

1. Whether investigational agents are suspected of causing toxicity;
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: For sites:

Telephone report: For SAE's 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 (from 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@brown.edu

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 business days (from 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 within 24 hours of the investigator being made aware of the event.

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**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication (sites to document what event is related to as well as relationship to Abraxane)
- Site must be clear about what events are being reported as serious
- Must be typed
- ****It is required that you put the following numbers on the Medwatch form for tracking:**
 - AX-CL-PANC-PI-003263
 - BrUOG 292
- 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:

Additional Info may be added to a previously submitted report by any of the following methods.

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarize new information and fax it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, 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 from the site. BrUOG will alert Celgene to an SAE within 1 business day of being made aware of the event via 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 or email 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 or emailed 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 or emailed 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 CFR 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

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” as defined above are present. The Brown University Oncology Research Group is responsible for reporting adverse events to Celgene as described above.

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 ®).

Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18

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 reviewed and approved by 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.

Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

- 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)
- Minor changes in the packaging or labeling of study drug.

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.

Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18

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 Principle 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

Null Hypothesis:

Median survival with experimental FOLFOX-A in metastatic pancreatic cancer is less than or equal to that with standard gemcitabine.

Alternate Hypothesis:

Median survival with experimental FOLFOX-A in advanced pancreatic cancer is *increased by 3 months* with standard gemcitabine.

This study is a phase II non-randomized clinical trial that would compare survival of patients receiving FOLFOX-A regimen in this trial to that of historical controls who received gemcitabine. The median survival of patients receiving gemcitabine alone is approximately 6.5 months. We would assume that our study would show that median survival by FOLFOX-A is increased by 3 months with FOLFOX-A, i.e. to about 9.5 months.

We calculated a sample size of about 50 patients with an accrual period of 24 months (about 2 patients/month) with a 6 month additional follow up time after recruitment. This would provide a power (1-beta) of 75% to reject the null hypothesis with a type I error probability (alpha) of 0.2.

Patients treated at the phase II dose level from the phase I study with metastatic pancreatic cancer may be included in the analysis of the phase II study.

18.0 REFERENCES

1. American Cancer Society: Cancer facts and figures 2010. Atlanta, GA, American Cancer Society, 2010, p 65
2. Burris HA 3rd, Moore JJ, Anderson J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 2403-2413, 1997
3. Hidalgo M: Pancreatic cancer. *N Engl J Med* 362:1605-1617, 2010
4. Moore MJ, Goldstein D, Hamm J, et al: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 25:1960-1966, 2007
5. Heinemann V, Boeck S, Hinke A, et al: Metaanalysis of randomized trials: Evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 8:82, 2008
6. Conroy, T, Desseigne F, Yehou M, et al. Folfirinox versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364:1817-1825, 2011
7. Wagener DJ, Verdonk HE, Dirix LY, et al. Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. *Ann Oncol* 1995; 6:129-132
8. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 22:3776-3783, 2004.
9. Ibrahim NK, Samuels B, Page R, et al. Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. *J Clin Oncol* 23:6019-6026, 2005
10. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 23:7794-7803 2005.
11. Von Hoff DD, Ramanathan RK, Borad MJ, et al. SPARC correlation with response to gemcitabine (G) plus nan-paclitaxel (Abraxane ® ®) in patients with advanced metastatic pancreatic cancer: A phase I/II study. *J Clin Oncol* 27:15s, 2009 (suppl;abstr 4525).
12. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus Abraxane ® ® aclitaxel is an active regimen in patients with advanced pancreatic cancer: A phase I/II trial. *J Clin Oncol* 29:4549-4554, 2011. Von Hoff DD, Ervin T, Arena, FP, et al Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine *N Engl J Med* 2013; 369:1691-1703

APPENDIX A

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

FOLFOX-A For Metastatic 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> hospitals 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 advanced (metastatic) pancreatic cancer. This means that your cancer has spread from your pancreas to other parts of your body and cannot be removed by surgery. 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 pancreatic cancer, the combination of Abraxane with the other 3 drugs is being investigated. Your doctors are studying the activity and side effects of FOLFOX-A in advanced (metastatic) pancreatic cancer.

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

How Many People will take part in the Study?

Approximately 50 patients will participate

Explanation of Procedures

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

If the exams, tests and procedures 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. Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18

- Medical history prior to starting treatment.
- Physical examination prior to starting treatment and then every 2 weeks
- Blood tests (requiring approximately 2 tablespoons of blood) prior to starting treatment and then every 2 weeks
- CT scan (or MRI/PET scan) of the abdomen and chest prior to starting treatment and then approximately every 12 weeks (3 months).
- 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

FOLFOX-A is administered intravenously (IV) every 2 weeks (one treatment cycle is equal to 2 weeks). These drugs are given into a special intravenous (into your vein) 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 the 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. This is standard-of-care.

When you receive FOLFOX-A treatment, you will first be given Abraxane ® over 30 minutes. The oxaliplatin is then administered over 2 hours. The leucovorin can either be administered after the oxaliplatin or at the same time and takes about 2 hours. The fluorouracil is then given using a small outpatient chemotherapy pump which will last over 46 hours. 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.

How long will I be in the study?

You will receive FOLFOX-A for up to six months (12 treatments) or as long as your cancer does not grow or spread and you do not have severe side effects from FOLFOX-A. After completion of FOLFOX-A, you will be followed 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

Abraxane ® will be provided by Celgene Corporation at no charge. All of the other medications, as well as the services you will receive during this research study are considered to be “routine clinical services” that you would have received even if you were not participating in the research study. These include all study doctor visits, the administration of the study drug Abraxane ®, blood tests, pregnancy tests, other chemotherapy drugs, drugs used to reduce side effects from chemotherapy, CT scans and EKGs. Therefore, all of the services listed in this paragraph will be billed to your health insurance company, and 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 or your insurance does not cover these services, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact the site Principal Investigator, <insert name> MD at <insert phone number >.

Discomforts and Risks

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.

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 may never go away. In some cases, side effects can be serious, long-lasting, or can cause death.

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® nab-paclitaxel

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

The following is a list of the most medically significant or most common side effects reported in completed studies considered to be related to *nab*-paclitaxel albumin. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/therapy and some may never go away. The study doctor may alter the dosage regimen of *nab*-paclitaxel (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):

- anemia (a decrease in the number of red blood cells (which may make you feel weak or tired) or cause shortness of breath.
- low number of white blood cells with or without fever (that may make it easier get infections) a decrease in the number platelets, the cells that help your blood to clot (which may lead to unusual bleeding or bruising under the skin)
- Nausea .
- Vomiting
- Diarrhea.
- stomach pain
- Hair loss from your head, face and body.
- decreased appetite
- Pain, swelling or sores on the inside of the mouth or in the throat
- Neuropathy. A disorder of the nerves that can cause tingling or numbness, with weakness, or decreased sensation or movement
- Feeling tired or weak
- Constipation
- pain (including muscle, joints, bone 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 pain
- dizziness
- Headache
- Chills
- change in taste
- weight loss
- difficulty sleeping
- depression
- itchiness
- changes in nails, including discoloration or separation from nailbed
- abnormal liver 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 heart beat

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
- indigestion or 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 infection of the lung, mouth, gallbladder, urinary tract, nail, or hair follicle, (which may be bacterial, fungal or viral)
- Blockage of the intestine
- Lack of muscle coordination, which may include difficulty with balance and walking
- muscle weakness
- Anxiety
- Nasal congestion
- mouth or throat pain
- Dry mouth, nose, throat
- 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 skin
- dry skin
- Low blood pressure
- high blood pressure
- watery eyes
- changes in vision or blurry vision

- Faster heartbeat or slower heartbeat, congestive heart failure, palpitations (rapid or fluttering heart)
- A decrease in the heart's ability to pump blood to all parts of the body and possibly heart failure.
- infusion site reactions (described as discomfort, bleeding or bruising/swelling at the needle site, and in some instances infection or leaking of IV fluid outside of blood vessel into the surrounding tissue)
- localized swelling due to build-up of lymph

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.

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

Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18

- 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

Elderly:

In subjects ≥ 65 years old with a history of metastatic breast cancer who previously 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.

Neulasta or Neupogen

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® (*nab-paclitaxel*) 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 should avoid becoming pregnant while receiving study medication. You must commit to complete abstinence from heterosexual contact, or agree to use medical doctor-approved contraception throughout the study without interruption; while receiving study medication or for a longer period if required by local regulations. If you become pregnant while receiving study medication or within 3 months after taking your last dose of study medication, you must tell the study doctor right away. If this happens, study medication will be discontinued. The study doctor will follow you and your pregnancy to completion.

Males:

If you have a partner of childbearing potential, you should avoid fathering a child while receiving study medication and for 6 months after the last dose of study medication. You must agree to complete abstinence from heterosexual contact or use a condom during sexual contact with a female of child bearing potential while receiving study medication and within 6 months after last dose of study medication. If your partner becomes pregnant while you are receiving study medication or within 6 months after you took your last dose of study medication, 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 the Reproductive Risk section above.

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?

- 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.

If you decide to withdraw from this study (stop taking study medication) for any reason, 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.

If you decide to quit the study please tell your site Principal Investigator, <Insert Name>, MD at <Insert phone number.>

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 <insert Hospital name> Office of Research Administration, at <insert phone number>

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, BrUOG, The Brown University Oncology Research Group 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, <insert 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 effect 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.

If after you have signed this form you have any questions relating to your rights, please contact <insert name> in the Office of Research Administration, XXXXXXXX.

For more detail about your privacy rights see the <insert Hospital name> Joint Privacy Notice which has or will be given to you.

Research authorization for use and disclosure of information.

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.

Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, 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. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to <insert contact information>

If after you have signed this form you have any questions relating to your rights, please contact <Insert name and contact.>

Uses and releases covered by this authorization (permission)

Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

- Every research site for this study, including this hospital, and including each site's research staff and medical staff
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol
- The following research sponsors or supporters and the people and companies that they use to oversee, administer, or conduct the research: BrUOG, the group coordinating the study, and Celgene Corporation (study supporter)
- 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
- The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study
- Principal Investigator and other Investigators
- Study Coordinator
- Additional members of the Research Team
- The Patient Advocate or Research Volunteer Protector: _____

- Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
- Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)
- Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee
- The members and staff of the hospitals affiliated Privacy Board (if such a board is used)
- Others: _____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

- The entire research record and any medical records held by the hospital may be used and released.
- The following information: _____

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY 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*

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

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

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

I ASSURE THAT I HAVE FULLY EXPLAINED TO THE ABOVE STUDY VOLUNTEER/ AUTHORIZED REPRESENTATIVE, THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH STUDY.

Signature of researcher or designate Date and Time when signed
* If signed by agent other than study volunteer, please explain below.

Documentation that a copy of this Informed Consent was given to the research participant is a Federal requirement. Prior to making a copy of the signed and dated Informed Consent please check appropriate box(es) as applicable to indicate copy provided to:

- Study Volunteer Medical Record Researcher Other (Specify)

APPENDIX B: Checklist

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

Inclusion Criteria

_____ (y/n) Metastatic pancreatic cancer: 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) Measurable disease not required at baseline. Patient's without measurable disease may be enrolled if there is known evidence of metastatic disease without measurable lesions as per imaging or per treating MD. For example a patient with peritoneal disease detected at exploratory surgery which is not seen on imaging is eligible.

∴
*Please document:

Patient has measurable disease (be sure measurements are provided on imaging CRF for RECIST tracking): _____ (y/n) (confirmation is per CRF and source imaging form)

Patient does not have measurable disease _____ (y/n) ** required confirmation by MD. Please also submit source scan and imaging CRF to document site(s) of disease. _____

_____ (y/n) Voluntary, signed written informed consent, Date signed _____

_____ (y/n) Age ≥ 18

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

_____ (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 $\geq 1,500/\text{ul}$, Date _____

_____ (y/n) Platelet $\geq 100,000/\text{uL}$, Date _____

_____ (y/n) Total bilirubin $< 1.5 \times \text{ULN}$, Date _____

_____ (y/n) AST $\leq 2.5 \times \text{ULN}$ and ALT $< 2.5 \times \text{ULN}$ Institution ($\leq 5 \times \text{ULN}$ if pt has liver mets) ULN _____, Date _____

_____ (y/n) Alkaline phosphatase $\leq 2.5 \times \text{ULN}$, ULN _____, Date _____

See inclusion for more details

_____ (y/n) Creatinine $\leq 1.5 \text{ mg/dl}$ or creatinine clearance $\geq 60 \text{ ml/minute}$, Date _____

_____ (y/n) ECOG 0-1

Exclusion Criteria:

_____ (y/n) peripheral neuropathy from any cause

_____ (y/n) 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.

_____ (y/n) Patients with known brain metastases

_____ (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) No uncontrolled diabetes

_____ (y/n) Patients with active infection or fever (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 12 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 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 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 4.0

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

Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18 56

Submitted to FDA 4-8-14, 5/16/14, 5/19/14, 5/20/14, 5/29/14, 6/4/14, Amendment # 1 6/24/14, Amendment # 2 9/10/14, Amendment # 3, 1/13/15, Amendment # 4 3/19/15, Amendment #5 8/11/15 HS approved, Amendment #5V2 10/6/15 Celgene approved, Amendment #6 12/8/15 HS approved, 12/15/15 celgene approved, Amendment # 7 3/23/16, Amendment # 8 7/5/16, Celgene approved 8/8/16, Amendment # 9 12/4/16, Amendment # 10 2/3/17 with IB 19, Amendment # 11 5/22/17, HS approved 5/24/17, Amendment # 12 8/21/17, Amendment # 13 12/26/18