

Adjuvant FOLFOX-A For Resected 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

Sponsored in part by the Eastman, Browning and Davis families

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

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1.0 OBJECTIVES

1.1 Primary Objective

1.1.1. To evaluate the feasibility of adjuvant FOLFOX-A for patients with resected pancreatic cancer

1.2 Secondary Objective

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

2.0 BACKGROUND

Adjuvant treatment of pancreatic cancer: Pancreatic cancer is the fourth most common cause of cancer death in the United States. Only those patients who have undergone resection have the potential to be cured. However, despite potentially curative resection, the 5-year survival rate is <25%.¹⁻³ The benefit of adjuvant radiation is unclear. The Gastrointestinal Tumor Study Group (GITSG) performed a small, randomized trial that demonstrated an improvement in survival for patients receiving adjuvant radiation with fluorouracil.⁴ However a statistically significant benefit was not detected with radiation in the EORTC and ESPAC trials.^{5,6}

A multinational German trial (the CONKO-1 trial) randomly assigned 368 patients with resected pancreatic cancer to gemcitabine or no additional therapy. There was a significant improvement in median and 3-year survival advantage in the gemcitabine group (median 22.8 versus 20.2 months, $p = 0.005$, five-year survival 21 versus 9 percent).^{7,8} However, even with gemcitabine, the majority of patients will relapse and die of systemic disease. Substantially more effective chemotherapy regimens are needed to increase the number of patients who can be cured.

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 ($P < 0.001$).⁹ Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group. The objective response rate was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group. Grade 3/4 toxicities increased with FOLFIRINOX including neutropenia (18.7% versus 45.7%), febrile neutropenia (0.6% versus 5.4%), diarrhea (1.2% versus 12.7%) and neuropathy (0% to 9%), respectively. It is possible that FOLFIRINOX may improve survival as compared to gemcitabine in the adjuvant pancreatic cancer setting and this is being investigated by the consortium in France. However, toxicity associated with FOLFIRINOX can be prohibitive, especially for patients recovering from major pancreatic cancer surgery.

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.¹⁰ Furthermore, the combination of irinotecan and gemcitabine does not improve survival as compared to gemcitabine alone.¹¹ 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.¹² A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane.¹³ 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.¹³ Pancreatic cancer cells and surrounding stroma are known to overexpress SPARC (secreted protein acid rich in cysteine), which is associated with poor clinical outcomes.¹³ The albumin-bound nanoparticle form of paclitaxel increases tumor accumulation of paclitaxel through binding of albumin to SPARC.^{13,14}

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.¹⁴ 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.¹⁵

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

Table 1: Abraxane + gemcitabine is superior to gemcitabine alone

Phase I Study of FOLFOX-Abraxane (FOLFOX-A): Irinotecan is responsible for much of the toxicity of FOLFIRINOX but may 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 – this new regimen is called FOLFOX-A.

All patients received oxaliplatin, 85 mg/m², leucovorin 400 mg/m² and 5-FU 2400 mg/m² IV over 46 hours with Abraxane. Cycles were repeated every 14 days. Three dose-levels of Abraxane were evaluated:

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

All 3 dose-levels have been evaluated and the maximum tolerated dose has been determined. Fifteen patients were entered: Dose level 1 (n=6), dose level 2 (N=6), dose level 3 (N=3). The median age was 64 (35-81). Ten patients had metastatic and 5 had locally advanced disease. 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). The MTD of nab-P 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. 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 adjuvant FOLFOX-A: Our preliminary data suggests that FOLFOX-A may have equal or superior activity as compared to FOLFIRINOX and appears to be better tolerated. Therefore, FOLFOX-A may be a better regimen in the adjuvant setting for patients with resected pancreatic cancer. This protocol will obtain preliminary data on safety and disease-free and overall survival following administration of FOLFOX-A for patients with resected pancreatic cancer.

3.0 PATIENT ELIGIBILITY

3.1 Conditions for patient eligibility

3.1.1. Histologic proof of primary pancreas invasive adenocarcinoma or adenosquamous cancer, managed with a potentially curative resection (i.e., removal of all gross tumor). Patients with invasive adenocarcinoma that also contains a component of intraductal papillary mucinous neoplasm (IPMN) are eligible.

3.1.2. Interval between definitive tumor-related surgery and registration 21-70 days (21-70 days out from surgery).

3.1.3. Any stage, completely resected patients (to document stage, T, N, M), and with no metastatic disease.

3.1.4. Post resection serum CA19-9 ≤ 180 units/mL within 14 days of registration on study.

3.1.5. Preexisting neuropathy ≤ grade 1 (per CTCAE).

3.1.6. ECOG performance status 0 or 1.

3.1.7. Age ≥ 18

3.1.8. 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 ≥ 12 months) do not need to have a pregnancy test, please document status.

3.1.9. Women of childbearing potential and sexually active males must use an effective contraception method during treatment and for three months after completing treatment. Documentation in writing is required to confirm patient understanding of this requirement.

3.1.10. Required Initial Laboratory Values:

- Neutrophils $\geq 1,500/\text{mm}^3$
- Platelet count $\geq 100,000/\text{mm}^3$
- Creatinine $\leq 1.5 \text{ mg/dL}$ -or- creatinine clearance $\geq 60 \text{ mL/min}$
- Total bilirubin $\leq 1.5 \times \text{ULN}$
- AST (SGOT) & ALT (SGPT) $\leq 2.5 \times \text{ULN}$
- Alkaline phosphatases $\leq 2.5 \times \text{ULN}$

3.1.11. Abdominal CT scan with contrast and chest CT/x-ray (CT of chest preferred) within 6 weeks of registration on study. Patients can have PET/MRI of the chest/abdomen instead. For patients with a documented contrast allergy CT scan of abdomen is not required as long as treating physician has confirmed disease assessment of response is suitable without contrast.

3.2 Exclusion criteria

3.2.1 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

3.2.2 Prior hypersensitivity to Oxaliplatin or Abraxane that in the investigators opinion would put the patient at risk if re-exposed

3.2.3 Patients with islet cell (neuroendocrine) tumors, cystadenomas, cystadenocarcinomas, carcinoid tumors, duodenal carcinomas, distal bile duct, and ampullary carcinomas.

3.2.4 Prior systemic chemotherapy for pancreas cancer; note that prior chemotherapy for a different cancer is allowable. Patients must not have received chemotherapy for a year prior to registering on study

3.2.5 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. This must be documented.

4.0 TREATMENT

4.1 Schema:

FOLFOX-A: 1 cycle = 14 days. Patients may receive up to 12 cycles of FOLFOX-A.

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

FOLFOX-A

Abraxane: $150\text{mg}/\text{m}^2$ IV over 30 minutes, day 1 (administered first) every 14 days.

Oxaliplatin: $85\text{mg}/\text{m}^2$, IV over 2 hours, day 1 every 14 days

Leucovorin: $400\text{mg}/\text{m}^2$, IV over 2 hours, day 1 every 14 days

5-FU infusion: $1200\text{mg}/\text{m}^2/\text{day}$, as a continuous IV infusion over 2 days, day 1 and day 2 (for a total dose of $2400\text{mg}/\text{m}^2$ over 46 hours.)

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- It is at the discretion of the treating investigator that Neulasta, 6 mg sq x 1 be given every cycle post treatment
- Antiemetics will be administered as per standard institutional policy.

(Adjuvant radiation therapy with concurrent fluoropyrimidine may be administered post patient coming off FOLFOX-A according to standard institutional policy)

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).

Dose modification table: for neuropathy reductions see section 5.3

	Starting Dose for all patients	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	768mg/m ²

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

****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****

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 $\geq 10\%$.

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

- Platelets $\geq 75 \times 10^9/L$ (75,000/mm³)
- Granulocytes $\geq 1.0 \times 10^9/L$ (1000/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 4 weeks from the scheduled treatment day due to treatment related toxicity will be removed from protocol treatment (see section 5.3 for allowed holds for neuropathy). Treating investigators may hold treatment for clinical reasons to alleviate toxicities as long as the toxicities with grades and delay are documented and submitted to BrUOG.

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

- Grade 4 neutropenia (ANC < 500/mm³)
- ANC < 1000/mm³ with fever 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 or 4 electrolyte abnormalities do not require a dose modification the electrolyte disorder can be corrected to grade 2 or less within 72 hours. This must be documented and submitted to BrUOG.
- Delay of treatment for > 2 weeks due to toxicity**If the 2 week delay is secondary to neuropathy see section 5.3 for dose reductions for neuropathy**

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:

- Oxaliplatin should be permanently decreased to Oxaliplatin dose level -1 (68mg/m²) for patients who develop grade 2 neuropathy. Patients may continue on treatment with grade 2 neuropathy at this 20% reduced dose of oxaliplatin. Abraxane, 5-FU and Leucovorin doses are not reduced for grade 2 neuropathy.
- 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:

- For patients developing grade 3 neuropathy, FOLFOX-A should be held until neuropathy improves to grade 2 or less. When treatment is resumed oxaliplatin and abraxane doses should be permanently decreased to dose level -1, 68mg/m² and 120mg/m² respectively.
- Patients developing grade 3 or worse neuropathy investigators should not receive more than 10 cycles of FOLFOX-A.
- For patients developing a second episode of grade 3 neuropathy, FOLFOX-A should be held until neuropathy improves to grade 2 or less. When treatment is resumed oxaliplatin and Abraxane[®] dose should be permanently decreased to dose level -2, 54mg/m² and 196mg/m² respectively.
- Investigators may hold FOLFOX-A treatment for up to six weeks secondary to patient's experiencing grade 3 neuropathy, however treatment holds of greater than 6 weeks require the patient to come off study. Hold for neuropathy must be documented on treatment and AE forms.

5.3.3 For patient experiencing grade 4 neuropathy, they will be removed from study

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 Oxaliplatin will be reduced by 20%. 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 (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 as per section 5.2.

For patients who experience neuropathy grade 3, per section 5.3.2, FOLFOX-A will be held and when neuropathy is \leq grade 2, Abraxane and Oxaliplatin will be reduced by 20% (or 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 grade 4 hypersensitivity reactions from oxaliplatin or Abraxane must be removed from protocol treatment. Patients with grade 3 hypersensitivity reactions may be re-challenged with the use of additional pre-medications to prevent allergic reactions based on institutional standard practice.

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 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, oxaliplatin should be discontinued until further investigation excludes interstitial pulmonary fibrosis. If interstitial pulmonary fibrosis is confirmed, 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.

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5.6 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*

Parameter	Pre-study	Within 3 days prior to Day 1 of Each Cycle (Every 2 weeks) ^F	End of Treatment (+ 1 week window provided after EOT date)	30 days post last dose of drug + 7 days	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				
Demographics	X				
History ^G	X				
Physical examination	X	X	X	X ^I	
Weight	X	X			
Vital signs	X	X			
Toxicity Assessment ^K	X	X	X	X ^H	
Performance Status	X	X	X		
CBC, diff, platelet count	X (within 14 days)	X	X		
Na, K, BUN, Cr	X (within 14 days)	X	X		
AST, ALT, Tbili, Alk Phos	X (within 14 days)	X	X		
Serum Pregnancy ^E	X (within 7 days of drug)				
CA19-9	X(within 14 days)		X		
CT scan of Chest/abd ACDJ	X ^{AC} (within 6 weeks)	X ^{ACDJ}	X (CT does not need to be repeated if done in prior 2 months)ACDJ		X ^{ACDJ}
EKG ^B	X				
Survival and Disease status				X	X ^D

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/PET for disease assessment to be performed within 6 weeks of study entry. Report required. Chest Xray can substitute CT/MRI of chest for baseline. CT abdomen to be done with contrast, unless there is a documented contrast allergy, which is required to be submitted to BrUOG.

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

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

D- For patients who come off study after 12 cycles or who are removed from protocol treatment due to toxicity (or another reason), without progression, Follow-up until disease progression will include CT, disease free and overall survival every 6 months (a month window is allotted for scheduling). For patients who come off study for progression, overall survival is to be reported every 6 months (a month window is provided). Follow-up will be for 5 years.

E post-menopausal women (surgical menopause or lack of menses \geq 12 months) do not need to have a pregnancy test, document status. If HCG is not drawn, sites are asked to document menopausal status on lab form.

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). It is appropriate to use weight, vital signs, performance status and toxicity assessment for cycle 1 day 1 if they are done within 14 days. A physical exam within 7 days prior to cycle 1 day 1 may be utilized. Pre-cycle assessments for all subsequent cycles can be within 3 days prior to day 1 of treatment.

G Physician note required to be sent

H Adverse event evaluation, inclusive of SAE evaluation, will be done 30 days post last dose of drug (+1 week window). SAEs occurring outside this 30 day window must be reported if the event is considered to be possibly related to the drug, even if patient begins a new treatment. If a patient begins a new treatment, AE evaluation will be stopped unless the patient experiences an event that is thought to be possibly related to the study treatment. It is required to inform BrUOG of patient beginning a new 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.

J CT 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 chest imaging is not done at any time point post baseline it will not be considered a deviation. It is at the discretion of the MD to order chest imaging post baseline, but if chest imaging is completed it must be submitted to BrUOG. Abdominal imaging is required. Imaging post progression not required.

K Patients who sign a consent or who sign a consent and are registered, but do not receive drug do not need to be assessed for AEs post coming off study.

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 ASSESSMENT OF DISEASE PROGRESSION:

The development of any site of disease will be defined as disease recurrence.

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, 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.

9.2 Oxaliplatin

Refer to the package insert for additional information.

9.2.1 Other Names

Eloxatin, trans-1-diamino cyclohexane oxaliplatin, cis-[oxalato(trans-1-1,2-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

9.3.1 Availability

Abraxane is commercially available. Each single-use 50 ml vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products. Unreconstituted Abraxane should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its carton. Reconstituted Abraxane should be used immediately. If not used immediately, the vial of reconstituted Abraxane must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

9.3.2 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.

9.3.3 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.

9.3.4 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 8 hours.

Study Medication Administration

ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line liter 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.

9.3.5: Supply

Commercially available. A drug accountability log is required

9.4 Leucovorin

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

9.4.1 Supply

Leucovorin is commercially available.

9.4.2 Formulation and Storage

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

9.4.3 Schedule

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

9.5 Weight Change:

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

does not require dose re-calculation.

10.0 AGENT ACCOUNTABILITY

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

10.1 Treatment Compliance

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

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

10.2 Study Drug Disposition

All study vials should be destroyed in accordance with the institution's standard operating procedure for the destruction of a cytotoxic agent.

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
- a life-threatening adverse drug experience
- 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. Question 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.

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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.

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.

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 treatment the treatment is to be discontinued immediately. The pregnancy must be reported by the Brown University Oncology Research Group within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify BrUOG of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE. 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 by facsimile within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to Abraxane must be reported to BrUOG within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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

11.3.2 Serious Adverse Event Reporting Procedures

A notification is required, prior to the submission for all SAEs and pregnancy reports or fetal exposures to the Brown University Oncology Research Group. Initial SAE information and all amendments or additions must be recorded on a MedWatch 3500A SAE form and be faxed or emailed to BrUOG within 5 days of being made aware of the event (unless event is a pregnancy or fetal exposure which requires more expedited reporting). See section 11.5 for more information

BrUOG fax: 401-863-3820 Email: BrUOG@brown.edu

The treating 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, and all sites participating in the trial.

Expedited Reporting by Investigator to BrUOG

Serious adverse events (SAE) are defined above. All events must be reported, by FAX or email to the Brown University Oncology Research Group. 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 is required.

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 or as soon as the investigator is 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.

11.4 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.

11.5 Types of Report:

Telephone report: For SAE's contact BrUOG Central Office at (401) 863-3000 within 24 hours upon learning of the event and submit a notification to BrUOG within 24 hours prior to submitting the SAE as well (see reporting requirements for pregnancy and fetal exposure above as report itself requiring within 24 hours, therefore notification required more expeditiously).

Written report: Send the copy of the complete and signed (by treating MD or PI) Medwatch 3500A within 5 business days of being made aware of the event (unless it is a pregnancy-see pregnancy reporting section) to the BrUOG Central Office by email, scan or Fax:

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

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. Site must document relationship to FOLFOX and to Abraxane.
- SAEs must be typed
- Document BrUOG 295
- Document action taken with treatment and study based on SAE (i.e. was treatment held, discontinued, if patient coming off study etc).

Follow-up information:

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

Summarizing new information, 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).

11.6 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 the sponsors initial receipt of the information. A copy of the form will be kept by the BrUOG Central Office.

**Medwatch
5901B Ammendale Road
Beltsville, MD 20705**

Fax: 1-800-FDA-0178 (1-800-332-0178)

11.7 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:

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a. Expedited IND Safety Reports:

7 Day calendar Telephone or Fax Report:

The Sponsor-Investigator is required to notify the FDA of any event that is serious, unlisted/unexpected and assessed by the investigator to be possibly related to the use of study drug(s). An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA as soon as possible but no later than 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the MedWatch fax number.

Sites are required to submit MedWatch3500A reports no later than 5 business days after being informed of an event.

BrUOG will fax reports to the FDA for IND Safety Reports: 1 (800) FDA - 0178

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

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:

Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.

1. 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.
2. The physician feels it is in the best interest of the patient to stop the treatment.
3. 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
4. Non protocol chemotherapy or immunotherapy is administered during the study
5. Noncompliance with protocol or treatment—major violation
6. Suspected Pregnancy
7. Patient is lost to follow-up
8. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
9. 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.

IND 12/4/13, 12/11/13 to LOCR, 1/23/14 post IRB, Amendment #1 2/1/14, Amendment #2 3/28/14, Amendment # 3 5/22/14, Amendment #4 6/19/2014, Amendment # 5 9/10/14, Amendment # 6 11/21/14, Amendment # 7 2/13/15, Amendment # 8 10/5/15HS approval, Amendment # 9 11/16/15, Amendment #10 3/16/16, Amendment # 11 3/1/17, Amendment # 12 5/25/17, Amendment #13 8/21/17, Amendment 14 2/20/18, Amendment #15 6-26-18, Amendment # 16 11/20/18

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for five years 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 five 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.

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. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC 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. 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:

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- 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, 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. 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 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 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
- 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. 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 BrUOG 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 BrUOG 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 BrUOG 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 BrUOG clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

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

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

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 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. Amgen will notify the Principal Investigator if an application is filed.

16.0 DATA SAFETY AND MONITORING BOARDS

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

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

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

17.0 STATISTICS

17.1: Feasibility of Adjuvant FOLFOX-A

The primary goal will be to determine the feasibility of administration of adjuvant FOLFOX-A in patients who have undergone resection of pancreatic cancer. Successful administration of FOLFOX-A will be defined as the ability to receive ≥ 8 cycles of FOLFOX-A. To address the feasibility of administering FOLFOX-A, the $\leq 65\%$ rate of receipt of ≥ 8 cycles of FOLFOX-A will be considered unacceptable. According to Fleming's single-stage design, the study will have 90% power to reject the null hypothesis

(that the treatment delivery rate is $\leq 65\%$) if at least 30 out of planned 38 subjects will receive ≥ 8 cycles of FOLFOX-A.

17.2 Assessment of disease-free and overall survival

Disease-free and overall survival will be assessed from the day of study entry.

18.0 REFERENCES

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15. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: A phase I/II trial. *J Clin Oncol* 29:4549-4554, 2011.

APPENDIX A

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

Adjuvant FOLFOX-A For Resected 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 carried out at <INSERT HOSPITAL> are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPITAL>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement that states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. 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 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.

You are being asked to take part in this study because you recently had surgery to remove your pancreatic cancer. All the cancer has been removed but there is a high risk that your cancer will come back. The current standard of care for resected pancreatic cancer is Gemcitabine. Your doctors are studying the chemotherapy drug treatment FOLFOX-A (fluorouracil, oxaliplatin, leucovorin and Abraxane) to see if it can safely be given to patients with pancreatic cancer after pancreatic surgery. Your doctors will also evaluate the risk of recurrence (your tumor growing back) of pancreatic cancer after completion of FOLFOX-A chemotherapy.

How Many People will take part in the Study?

Approximately 38 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, while on the study. They are part of regular cancer care.

- Medical history prior to starting treatment.

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- Physical examination prior to starting treatment then every 2 weeks
- Blood tests prior to starting treatment then every 2 weeks
- CT scan, PET scan, or MRI of the chest and abdomen prior to starting treatment, approximately every 3 months while on treatment, then approximately every 6 months during follow-up if your disease has not spread or grown.
- EKG 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 (in your vein) device called a port-a-cath. A port-a-cath is a standard 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 the 46 hour infusion of fluorouracil, a nurse will come to your home or you will return to the clinic to have the chemotherapy pump disconnected. After completion of the FOLFOX-A treatment you may receive the standard drug called Neulasta, which is a shot given beneath the skin to help reduce the risk that your white blood cells will become too low 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 approximately every 6 months for up to 5 years to evaluate for pancreatic cancer recurrence. If you are taken off study for disease progression, you will also be followed approximately every 6 months for five years.

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

All 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, blood tests, chemotherapy drugs and the administration of the 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, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance 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 Principal Investigator, <INSERT NAME AND CONTACT>

Discomforts and Risks

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

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or may never go away. There also is a small risk of 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

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 or give you medicines to help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

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

- Lowered white blood cell count, with or without fever, that may lead to infection.
- Lowered platelets which may lead to an increase in bruising or bleeding.
- Lowered red blood cells which may cause anemia, tiredness, or shortness of breath.
- Nausea or vomiting.

- Headache.
- Diarrhea.
- Hair loss from your head, face and body.
- Loss of appetite
- Pain, swelling or sores in mouth or throat
- Tingling, like pins and needles, in your hands and feet, with weakness or decreased sensation or movement
- stomach pain
- 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
- 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 irregular heart beat

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

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

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

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

- hives

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

- lack of movement in the vocal cords with possible voice changes
- skin sensitivity to sunlight
- potentially life threatening allergic reaction affecting the skin and digestive tract usually cause 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:

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

Reproductive Risks

Chemotherapy may decrease sperm count. This is usually temporary but can be permanent, which would result in sterility (not being able to father a baby).

Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study.

If you are a woman of childbearing potential or sexually active male, you must practice an effective method of birth control while receiving study treatment and for at least 3 months after completing or discontinuing study treatment. 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.

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

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

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

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

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

In order to monitor the side effects, 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.

Risk of CT imaging: CT imaging uses x-rays. The radiation dose associated with this procedure is estimated to be a small fraction of the annual permissible dose to an x-ray technologist. There is no significant risk from this amount of radiation.

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

While doctors hope that FOLFOX-A will help lower the risk that your pancreatic cancer will come back 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 FOLFIRINOX or gemcitabine and Abraxane.
- Receiving radiation treatments.
- Taking part in another study
- Getting no treatment
- Being followed closely by CT scans and not receiving treatment.

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

Refusal/Withdrawal

You decide whether or not you want to be in the study. Participation is voluntary. If you decide now to participate, you can change your mind later and quit the study. If you decide not to participate, or if you quit the study, it will not affect the health care services that you normally receive. If the researcher or your doctor feels it is in your best interest, they may choose to take you out of the study at any time before you complete the study.

As soon as it becomes available, the researcher will give you new information about the study that may or may not affect your decision to stay in the research study.

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.

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> 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 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> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL> policy. However, <INSERT HOSPITAL> 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 NAME AND CONTACT FOR IRB>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL> 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>) 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 and Principal Investigator Dr. Howard Safran, the central coordinating office and sponsor representative: The Brown University Oncology Research Group and their affiliates.
- 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> 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 affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL> 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.

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 AND CONTACT FOR IRB>

For more detail about your privacy rights see the <INSERT HOSPITAL> 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 Howard Safran, MD c/o the Medical Oncology Clinical Research Office at Rhode Island Hospital, 593 Eddy Street, APC Building Rm. 131, Providence, RI 02903.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT NAME AND CONTACT IN IRB>

Uses and releases covered by this authorization (permission)

IND 12/4/13, 12/11/13 to LOCR, 1/23/14 post IRB, Amendment #1 2/1/14, Amendment #2 3/28/14, Amendment # 3 5/22/14, Amendment #4 6/19/2014, Amendment # 5 9/10/14, Amendment # 6 11/21/14, Amendment # 7 2/13/15, Amendment # 8 10/5/15HS approval, Amendment # 9 11/16/15, Amendment #10 3/16/16, Amendment # 11 3/1/17, Amendment # 12 5/25/17, Amendment #13 8/21/17, Amendment 14 2/20/18, Amendment #15 6-26-18, Amendment # 16 11/20/18

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 and the people and companies that they use to oversee, administer, or conduct the research:

Sponsor and Principal Investigator Dr. Howard Safran, the central coordinating office and sponsor representative: The Brown University Oncology Research Group and their affiliates.

- 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> 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

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

Inclusion Criteria

_____ (y/n) Resected pancreatic adenocarcinoma or adenosquamous carcinoma. Patients with invasive adenocarcinoma that also contains a component of intraductal papillary mucinous neoplasm (IPMN) are eligible.

_____ (y/n) Interval between definitive tumor-related surgery and registration between 21-70 days.

_____ (y/n) Any stage, completely resected patients (to document stage, T, N, M), and with no metastatic disease.

_____ (y/n) Post resection serum CA19-9 \leq 180 units/mL within 14 days of registration on study.

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

_____ (y/n) Age \geq 18

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

_____ (y/n) Abdominal CT scan with contrast and chest CT/x-ray (CT of chest preferred) within 6 weeks of registration on study. Patients can have PET/MRI of the chest/abdomen instead. See 3.1.11 for contrast allergy information

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

_____ (y/n) Absolute neutrophil count \geq 1,500/ul, Date _____

_____ (y/n) Platelet \geq 100,000/uL, Date _____

_____ (y/n) Total bilirubin \leq 1.5 x ULN, Date _____

_____ (y/n) Alkaline Phos \leq 2.5xULN, date _____

_____ (y/n) AST \leq 2.5x ULN and ALT \leq 2.5x ULN Institution ULN _____, Date _____

_____ (y/n) Peripheral neuropathy must be \leq Grade 1

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

_____ (y/n) ECOG 0-1

_____ (y/n) 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).

Exclusion Criteria:

_____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 Prior hypersensitivity to Oxaliplatin or Abraxane that in the investigators opinion would put the patient at risk if re-exposed

_____y/n Patients with islet cell (neuroendocrine) tumors, cystadenomas, cystadenocarcinomas, carcinoid tumors, duodenal carcinomas, distal bile duct, and ampullary carcinomas.

_____y/n Prior systemic chemotherapy for pancreas cancer; note that prior chemotherapy for a different cancer is allowable. Patients must not have received chemotherapy for a year prior to registering on study.

_____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. This must be documented.

_____ (y/n) Pregnant or breastfeeding.

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 documentation

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