PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Distributed for IRB Review Only 10/1/13
Activated 1/6/14

SWOG

A PHASE IB/II RANDOMIZED STUDY OF MODIFIED FOLFIRINOX + PEGYLATED RECOMBINANT HUMAN HYALURONIDASE (PEGPH20) VERSUS MODIFIED FOLFIRINOX ALONE IN PATIENTS WITH GOOD PERFORMANCE STATUS METASTATIC PANCREATIC ADENOCARCINOMA

NCT #01959139

STUDY CHAIRS:

Ramesh K. Ramanathan, M.D. (Medical Oncology)
Mayo Clinic, Arizona
Division of Hematology/Oncology
13400 E. Shea Boulevard
Scottsdale, AZ 85259
Phone: 480/301-8000
FAX: 480/301-4675
E-mail: ramanathan.ramesh@mayo.edu

Sunil Hingorani (Translational Medicine)
Fred Hutchinson Cancer Research Center
1959 NE Pacific St.
Seattle, WA 98195
Phone: 206/667-6921
FAX: 206/598-6611
E-mail: srh@fhcrc.org

Philip Philip, M.D. (Medical Oncology)
Karmanos Cancer Institute
Hematology/Oncology
4100 John R. 4HWCRC
Detroit, MI 48201
Phone: 313/576-8746
FAX: 313/576-8729
E-mail: philipp@karmanos.org

AGENTS:

IND-Exempt Agents:
Enoxaparin (Lovenox©) (NSC-728167)
Filgrastim (r-mehHuG-CSF) (Neupogen®) (NSC-614629)
5-Fluorouracil (5-FU, Adrucil ®) (NSC-19893)
Irinotecan (CPT-11) (NSC-616348)
Leucovorin (NSC-3590)
Oxaliplatin (Eloxatin ®) (NSC-266046)
Pegfilgrastim (Neulasta™) (NSC-725961)

SWOG-Held IND Agents:
Pegylated Recombinant Human Hyaluronidase (PEGPH20) (NSC-772519) (IND-118849)

BIOSTATISTICIANS:

Shannon McDonough, M.S.
Katherine A. Guthrie, Ph.D.
SWOG Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-C102
PO Box 19024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: smcdonou@fhcrc.org
E-mail: kguthrie@fhcrc.org

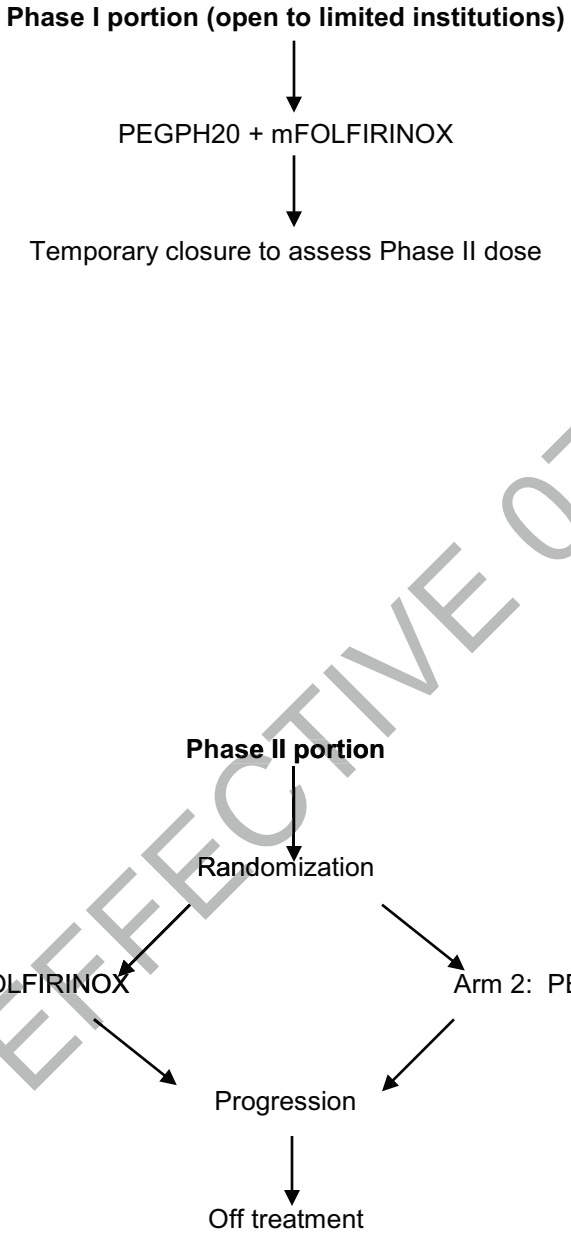
PARTICIPANTS

Phase I
SWOG:
AZ017/University of Arizona
CA011/University of Southern California
CA043/City of Hope
CO070/University of Colorado
CT018/Yale University
MI020/Wayne State University
WA020/University of Washington

PHASE II
SWOG/SWOG

TABLE OF CONTENTS

SCHEMA



***** Patients will be enrolled into either the Phase I portion or the Phase II portion, not both.

1.0 OBJECTIVES

1.1 Primary Phase I Objective

a. The primary objective of the Phase I portion will be to assess the safety of mFOLFIRINOX in combination with PEGPH20 and select the optimal dose of PEGPH20 for the Phase II portion in patients with metastatic pancreatic adenocarcinoma.

1.2 Primary Phase II Objective

a. To assess the overall survival of patients with metastatic pancreatic adenocarcinoma treated with mFOLFIRINOX + PEGPH20 compared to those treated with mFOLFIRINOX alone.

1.3 Secondary Objectives

a. To assess progression free survival (PFS) in patients receiving mFOLFIRINOX with PEGPH20 and patients receiving mFOLFIRINOX alone in this patient population.

b. To assess objective tumor response (confirmed and unconfirmed, complete and partial) in patients with measurable disease treated with mFOLFIRINOX with PEGPH20 and patients receiving mFOLFIRINOX alone in this patient population.

c. To determine the frequency, severity, and tolerability of adverse events of mFOLFIRINOX with PEGPH20.

1.4 Translational Objectives

a. To explore the correlation of maximum decrease in CA 19-9 levels and time to maximum decrease in CA 19-9 levels with overall survival, progression-free survival and response.

b. To explore the correlation of plasma hyaluronan (HA) and tumor expression of HA with overall survival, progression-free survival and response.

2.0 BACKGROUND

Overview

The outcome of patients with metastatic pancreatic cancer (PC) remains very poor. Until recently, gemcitabine was the only agent with reproducible activity and resulting in a median survival of only 5-6 months. *(*1,2,3*)* Despite attempts to improve the outcome by adding a second agent to gemcitabine, no worthwhile progress has been made thus far. One single Phase III study of gemcitabine with erlotinib had a statistically better overall survival for the combination arm, but this was of no meaningful clinical benefit. *(4,5)* There are grounds for optimism as two new regimens (gemcitabine/nab-paclitaxel and FOLFIRINOX) have emerged as front line options. The gemcitabine/nab-paclitaxel regimen was evaluated in a Phase III study and findings were presented recently. In this study, 861 patients were randomized to either gemcitabine alone or to the combination of gemcitabine and nab-paclitaxel. The overall survival was 8.5 vs 6.7 months (P = 0.000015); in favor of the combination arm. *(6)* The other regimen which is now commonly used is FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) which has shown significant improvement in survival of patients with favorable performance status compared to gemcitabine alone and has become a new standard for patients with advanced PC. *(7)* Significant advances have been made in understanding the biology and molecular pathology of pancreatic cancer. The dense stromal reaction that is characteristic of this disease has emerged as a critical factor limiting cytotoxic drug delivery, development of drug resistance, and promoting invasion and

metastases. Preclinical studies have shown that effective targeting of cancer cells may be achieved by degrading and depleting the surrounding stromal structures of PC by agents such as hyaluronidase. The studies described below support the rationale for this proposal.

FOLFIRINOX

The PRODIGE study of FOLFIRINOX showed improvement in median survival of patients with metastatic pancreas cancer of over 4 months when compared to gemcitabine alone in patients with favorable performance status and good liver function. *(8)* This Phase III study randomized 342 patients with no prior cytotoxic chemotherapy to single agent gemcitabine or to FOLFIRINOX. With a median follow-up time of 26.6 months, the primary endpoint of median OS was significantly improved for patients receiving FOLFIRINOX (11.1 vs. 6.8 months for gemcitabine; $P < .0001$) and PFS was 6.4 vs. 3.3 months, respectively ($P < .0001$). Compared with gemcitabine, Grade 3-4 adverse events were significantly greater with FOLFIRINOX: these included neutropenia (46% vs. 19%); febrile neutropenia (5.4% vs. 0.6%); vomiting (14.5% vs. 4.7%); fatigue (23% vs. 14.2%); and diarrhea (12.7% vs. 1.2%). Hematopoietic growth factor support was required for > 40% of patients. Prior abdominal radiation was not allowed and study was confined to good PS (0-1) patients. FOLFIRINOX, especially in its modified form, has now become a standard and its use by community oncologists in USA is steadily increasing, with reports of acceptable safety and efficacy in carefully selected patients. *(9)*

Pancreatic tumor microenvironment

Pancreatic cancer is known to be very hypovascular with an extensive desmoplastic reaction consisting of a variety of stromal cells such as pancreatic stellate cells, activated fibroblasts and inflammatory cells that are embedded in a dense extracellular matrix. This matrix consists mainly of collagens and glycosaminoglycans and has been shown to impede drug delivery to the tumor cells. *(10)* Understanding the biology of stroma and developing effective treatment strategies were only possible with breakthroughs in genetically engineered mouse pancreatic tumor models. These models mirror human pancreatic cancer progression, are Kras mutated and have an intense fibroblastic reaction that is indistinguishable from that of human PC. Two landmark studies have been recently reported using these mouse models showing the importance of targeting hyaluronan (HA), a non-sulphated glycosaminoglycan that forms the bulk of the extracellular matrix in PC.

In the first study from Dr. Hingorani's Lab at the Fred Hutchinson Cancer Research Center, Seattle a number of important findings were made *(11)*:

(a) The stroma surrounding the pancreatic tumor generated very high interstitial fluid pressures (IFPs), exceeding those previously measured for other solid tumors, and induced vascular collapse, while presenting substantial barriers to perfusion, diffusion, and delivery of therapeutic agents.
(b) HA was identified as the primary matrix determinant of these barriers and systemic administration of an enzymatic agent that ablated stromal HA from autochthonous murine PC normalized the IFP and re-expanded the tumor microvasculature.
(c) In combination with gemcitabine, the treatment permanently remodeled the tumor microenvironment and consistently achieved objective tumor responses, resulting in a near doubling of overall survival of treated mice.
(d) Reduction in the number of metastases was also seen in mice treated with both gemcitabine and PEGPH20 compared with those treated with gemcitabine alone.

These findings of significantly improved survival in Kras-mutated genetically engineered mice treated with PEGPH20 and gemcitabine were also confirmed by the investigators in Cambridge from the Dr. Tuveson's Lab. Despite some differences in the experimental methodology the findings validated the hypothesis and conclusions of the previous study. *(12)*

Extensive preclinical data now exist for targeting HA in pancreatic cancer and demonstrating that PEGPH20 can effectively deplete stroma and increase delivery of agents into the tumor cells. Depletion of the stroma may also influence the biology of the disease by removing cells and growth factors responsible for the maintenance and progression of PC. *(13)*

In the past chemotherapy regimens have been tested empirically in advanced PC; in this case, Hingorani et al has demonstrated increased survival in a highly faithful genetically engineered mouse model which mimics the clinical syndrome and histopathological features of advanced human PC. There is also substantial patient experience with respect to safety of PEGPH20. The recommended Phase II dose of PEGPH20 has been identified and no additive adverse events with chemotherapy have been noted thus far. mFOLFIRINOX is now a standard regimen for advanced PC and the combination with PEGPH20 can be expected to substantially improve the overall survival of patients with advanced pancreatic cancer given the superiority of FOLFIRINOX to kill cancer cells when compared to gemcitabine. Given the patterns of toxicity with FOLFIRINOX and the common and standard practices in the USA the mFOLFIRINOX regimen will be used by omitting the bolus 5FU.

Recombinant pegylated human hyaluronidase (PEGPH20)
Recombinant human hyaluronidase is commercially available and widely used to enhance subcutaneous dispersion and absorption of various agents. Pegylation of this compound (PEGPH20) enhances its circulatory half-life and prolongs systemic exposure to this enzyme. In preclinical studies, PEGPH20 removes HA from tumors, reduces tumor IFP, inhibits tumor growth, and enhanced effects of chemotherapy in mouse models of cancer. *(14,15,16,17)* A Phase I study with PEGPH20 was conducted in patients with advanced solid tumors. PEGPH20 was administered as IV infusion, once or twice weekly for 4 weeks, then once weekly. The dose levels tested were 0.5, 1.6, 3, and 5 ug/kg by 5 min infusion. At this time 18 patients have been treated. PEGPH20 was generally well tolerated at doses up to 3.0 ug/kg. The dose limiting toxicities were muscle spasms and myalgia at the 5 ug/kg dose level and muscle spasms at the 3 ug/kg dose level. The incidence of myalgias and arthralgias is reduced by administration of steroids (i.e. dexamethasone 8 mg bid on PEGPH20 dosing days). The most common AEs related to PEGPH20 were muscle spasm (74%), arthralgia (37%), and myalgia (21%). There was no hematological toxicity reported. Extensive PK/PD assessment have been performed with serial tumor biopsies, PET and DCE-MRI imaging. Preliminary analyses indicate target inhibition (ablation) as revealed by dose-dependent increases in circulating HA plasma concentrations, enhanced tumor perfusion (DCE-MRI), and reduced tumor metabolic activity (FDG-PET) in treated patients. *(18)*

An international, multicenter Phase IB/II study is currently underway with the combination PEGPH20 and gemcitabine in advanced PC (Sunil Hingorani, MD, Global PI). At this time, the recommended Phase II dose of the combination is gemcitabine 1000 mg/m^2 with PEGPH20 at the dose of 3.0 ug/kg given twice a week for the first cycle and then weekly for subsequent cycles, every 4 weeks.

CA 19-9
In the Phase I/II study that evaluated nab-paclitaxel and gemcitabine for MPC, CA19-9 was measured every 4 weeks. *(19)* Rapid decreases in CA19-9 levels were observed with the median time to maximum decrease of 89 days. The median maximum percentage change in CA19-9 level was 91%. CA19-9 level decrease correlated strongly with efficacy parameters. Patients with 50% or larger decrease versus less than 50% decrease in CA19-9 levels had a 62% vs 33% ORR (P=0.105), 8.0 vs 3.6 month median PFS (P=0.001) and 13.6 vs 6.5 month median OS (P=0.004), respectively. FOLFIRINOX is a highly active regimen and similar decreases in CA19-9 are expected and will be formally evaluated in this study.

Study Rationale
Until very recently, the uniformly accepted standard of care for pancreatic ductal adenocarcinoma (PDA) was single agent gemcitabine, which provided modest object response rates (7-10%) and similarly modest improvements in both median and one-year survival. *(20,21)* Recently, two regimens have suggested that different outcomes may be possible. In a Phase II study, patients with Stage IV disease received a combination of with gemcitabine plus nab-paclitaxel, an albumin-coated nanoparticle, resulting in a median survival of 8.5 months compared to 6.7 months with gemcitabine monotherapy. *(22)* More recently, a Phase III trial of the multi-drug regimen, FOLFIRINOX, conferred a median survival of 11.1 months compared with 6.8 months

for single agent gemcitabine (p<0.0001). *(23)* Interestingly, these two regimens share one notable feature: sustained exposure of the tumor to circulating drug concentrations which can help overcome the pronounced interstitial fluid pressures that oppose drug penetration (see below). Below is a proposed strategy to overcome these barriers and extend the efficacy observed with FOLFIRINOX.

An emerging concept in pancreas cancer pathophysiology is the extent to which the associated robust desmoplastic reaction erects physical barriers to systemic therapies. These barriers limit the ability to achieve therapeutic drug concentrations and serve as primary and underappreciated mechanisms of drug resistance. Detailed analyses of the tumor microenvironment in PDA are revealing an unusually complex cellular and extracellular matrix composition that includes stromal fibroblasts; various classes of immunosuppressive cells; and a dense network of glycosaminoglycans (GAG), proteoglycans, and proteins that collectively conspire to create a drug-free and immune privileged sanctuary for the disease. *(24)* One especially abundant GAG, hyaluronan or hyaluronic acid (HA), is the primary determinant of inordinately high interstitial fluid pressure (IFP) that rival mean arterial pressure and cause widespread vascular collapse. *(25)* HA is a large linear polymer composed of alternating units of N-acetyl glucosamine and glucuronic acid units with viscoelastic properties that contribute to the architecture and malleability of tissues, particularly during dynamic process such as embryogenesis and oncogenesis. *(26,27)* The viscoelastic properties of HA underlie its role in clinical and cosmetic applications. In PDA, HA functions as a hydrogel, trapping and retaining water, which both serves to elevate IFP and further retards drug perfusion by inhibiting convection. *(28,29,30)* Dr. Hingorani's lab has recently defined a strategy in the Murine Clinical Trials Program (MCTP) to overcome these prohibitive IFPs in PDA and restore both diffusive and convective components of drug delivery. *(31)* Systemic administration of a chemically modified form of recombinant hyaluronidase (PEGPH20) normalizes IFP and mobilizes intratumoral fluid permitting chemotherapies to freely penetrate the tumor bed. Phase I studies with single agent PEGPH20 have already established that it is well-tolerated and appears to have similar effects on tissue perfusion as observed in the genetically engineered mouse model studies. *(32)* A Phase IB/II trial is currently underway for which Dr. Hingorani serves as the Global PI.

The Phase II dose of PEGPH20 3.0 ug/kg given twice a week during dosing weeks x 4 weeks and then once a week during dosing weeks has been identified and no additive adverse events with chemotherapy have been noted thus far. mFOLFIRINOX (modified or dose-reduced FOLFIRINOX) is now a standard regimen for advanced PDA and this study hypothesizes that the combination with PEGPH20 will substantially improve overall survival. PEGPH20 in this study will follow the same schedule as evaluated in the Phase I study (twice a week x 4 weeks and then once a week). This schedule is also similar to ongoing sponsor studies of PEGPH20 in combination with gemcitabine and nab-paclitaxel. During the course of testing this hypothesis correlative studies will be performed to determine: 1) if intratumoral HA content can serve as a useful prognostic marker; and 2) whether circulating levels of HA metabolites during the course of treatment can serve to demonstrate target degradation and whether this can also predict survival benefit.

Thromboembolic Events in Cancer

Patients with pancreatic cancer are at high risk of developing venous thromboembolic events (VTE) compared to other cancers. *(33)* The incidence rate is between 5-36% in retrospective studies and between 19-67% in autopsy cases series. *(18)* In a meta-analysis of 38 papers in cancer patients, pancreas cancer had approximately 102 VTE in 1000 person-years, as compared to brain (116/1000 PY), lung (52/1000 PY), and hematologic cancer (35/1000 PY) (Horsted 2012). The high incidence of VTE is though secondary to alternations in coagulation included fibrin, plasminogen, and thrombin. Patient characteristics that increase risk of VTEs are hospitalization/sedentary status, surgery, venous access/catheterization, weight extremes, anemia, medications (erythropoietin-stimulating agents, chemotherapy, and megestrol), and other co-morbidities (e.g., heart, liver, and kidney disease; diabetes). *(34)*

A Phase II study sponsored by Halozyme Inc (HALO-109-202: A Phase 2, Randomized, Multicenter Study of PEGPH20 (PEGylated Recombinant Human Hyaluronidase) Combined with nab-Paclitaxel Plus Gemcitabine Compared With nab-Paclitaxel Plus Gemcitabine in Subjects With Stage IV Previously Untreated Pancreatic Cancer) was placed on clinical hold by the FDA due to imbalance of thromboembolic (TE) events in subjects receiving PEGPH20. As of 4/1/2014, 146 subjects were randomized to the study. As a result of discussions held by Halozyme with the FDA, risk mitigation strategies have been implemented and approved by the FDA on 6/5/14. As of time of study hold, **S1313** had accrued 2 patients, both had received PEGPH20 with FOLFIRINOX. No TE events were reported in **S1313**. As a safety precaution, **S1313** has instituted additional exclusion criteria as per Revision #2.

An ongoing analysis of patients treated in the randomized Phase II part of this trial showed that patients treated with FOLFIRINOX and PEGPH20 had an imbalance of TE events, primarily VTE events. Due to this elevated risk, patients on the investigational arm will be required to start low molecular weight heparin prophylaxis prior to beginning study treatment as per Revision #7.

SWOG's Phase I Experience

At dose level 1 (PEGPH20 dose of 3 mcg/kg on Day 1 and Day 3 or 4), there were 5 patients entered with 2 DLTs consisting myalgias in one patient and fatigue/mucositis in the other patient. Due to the occurrence of 2 dose limiting toxicities (DLT), further accrual to this dose level was halted and accrual to the next lower level occurred. A total of 7 patients were accrued to dose level 2 (PEGPH20 dose of 3 mcg/kg on Day 1 only). One patient was not considered evaluable and in the 6 patients evaluable for toxicity determination there was one DLT of fatigue, AST/ALT elevation, dehydration and sepsis. Dose level 2 was considered suitable for further expansion. The Phase II dose was established as mFOLFIRINOX + PEGPH20 3 mcg/kg on Day 1.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	4	3	7
Not Hispanic or Latino	78	87	165
Total Ethnic	82	90	172
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	2	2	4
Black or African American	7	7	14
Native Hawaiian or other Pacific Islander	1	1	2
White	71	79	150
Racial Category: Total of all Subjects	82	90	172

3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, filgrastim, fluorouracil, irinotecan, leucovorin, oxaliplatin, and pegfilgrastim are commercially available; therefore, Investigator Brochures are not applicable to this/these drug(s). Information about commercial drugs is publicly available in the Physician's Desk Reference (PDR), prescribing information and other resources.

For this study, PEGPH20 is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Enoxaparin (Lovenox©) (NSC-728167)

a. PHARMACOLOGY

Mechanism of Action: Enoxaparin exerts its antithrombotic activity by binding to and accelerating the activity of antithrombin III (AT III). By activating antithrombin, coagulation factor Xa and factor IIa (thrombin) are inhibited. Ultimately, thrombin inhibition prevents the formation of fibrin clots.

b. PHARMACOKINETICS

Absorption: subcutaneous administration has a bioavailability of 100% with the agent reaching a Tmax in 3-5 hours.

Distribution: enoxaparin has a volume of distribution of 4.3L. The agent has a low binding affinity to endothelial cells and does not cross the placenta to any great extent.

Metabolism: hepatic metabolism involves desulfanation and depolymerization.

Elimination: 40% renal through dose independent mechanisms. Total body clearance of drug is 15L with an elimination half-life of 7 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of enoxaparin

Adverse effects reported in > 20% of subjects treated with enoxaparin: none
Adverse effects reported in 4-20% of subjects include: anemia, hematoma, hemorrhage, LFT elevation, fever.
Adverse effects reported in ≤ 3% of subjects include: Diarrhea, nausea, thrombocytopenia, atrial fibrillation, heart failure, intracranial hemorrhage, pneumonia.

2. Pregnancy and Lactation: Enoxaparin is classified as FDA pregnancy risk category B. Teratogenic effects have not been demonstrated in animals. No well controlled studies exist in pregnant women. Several

reports have described the use of enoxaparin during pregnancy without fetal or maternal complications. There have been reports of congenital anomalies including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect, when women received enoxaparin during pregnancy. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population. There have been post-marketing reports of fetal death when pregnant women received enoxaparin. Causality for these cases has not been determined. Pregnant women receiving anticoagulants, including enoxaparin, are at increased risk for bleeding. According to the manufacturer, it is unknown if enoxaparin is excreted into breast milk. The manufacturer recommends caution when using enoxaparin in women who are breast-feeding. However, because of the relatively high molecular weight of enoxaparin, excretion is expected to be minimal. Also, because of inactivation by the GI tract on oral ingestion, any potential risk to a nursing infant posed by enoxaparin should be negligible.

3. Drug Interactions:

As enoxaparin elimination is primarily renal minimal CYP interactions are found. Agents that increase the risk of hemorrhage should be discontinued prior to initiation of enoxaparin. Due to potential drug interactions, a complete patient medication list, including enoxaparin should be screened prior to initiation of and during treatment with enoxaparin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Enoxaparin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive Filgrastim (r-metHuG-CSF) (Neupogen®) (NSC-614629)

3.2 Filgrastim (r-metHuG-CSF) (Neupogen®) (NSC-614629)

a. PHARMACOLOGY

Mechanism of Action: Filgrastim stimulates the production, maturation, and activation of neutrophils; filgrastim activates neutrophils to increase both their migration and cytotoxicity.

b. PHARMACOKINETICS

1. Absorption: First-order pharmacokinetic modeling with maximum serum concentration reached within 2 to 8 hours after subcutaneous injection

2. Distribution: Average Vd 150 mL/kg

3. Metabolism: Unknown

4. Elimination: Renal and neutrophil receptor-mediated, elimination half-life is approximately 3.5 hours

c. ADVERSE EFFECTS

1. Possible Side Effects of Filgrastim: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

   Most frequent adverse reactions reported are skeletal pain (> 20%).

2. Pregnancy and Lactation: Category C, filgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies have demonstrated adverse effects and fetal loss. Filgrastim has been shown to cross the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Excretion in breast milk unknown/use caution.

3. Drug Interactions: Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

   Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

   Filgrastim should not be administered on the same day with anticancer chemotherapeutic agent(s) with leukocyte suppressive properties.

   Filgrastim is contraindicated in patients with hypersensitivity to *E.coli*-derived proteins, filgrastim, or any component of the product

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

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

e. PREPARATION, STORAGE & STABILITY

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

f. HOW SUPPLIED

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

3.3 Fluorouracil (5-FU, Adrucil ®) (NSC-19893)

a. PHARMACOLOGY

Mechanism of Action: Fluorouracil is a pyrimidine analog antimetabolite that interferes with DNA and RNA synthesis. After activation, the active metabolite F-UMP is incorporated into RNA to replace uracil and inhibit cell growth. The active metabolite, F-dUMP, inhibits thymidylate synthetase and depletes thymidine triphosphate.

b. PHARMACOKINETICS

1. Absorption: Rapid intravenous injection of fluorouracil results in high early levels of drug achieved both in plasma and bone marrow with a rapid fall afterwards. Prolonged infusions of fluorouracil show constant levels of the drug in plasma and significantly less in bone marrow.

2. Distribution: Fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver, third space fluids and other tissues. Fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

3. Metabolism: Fluorouracil is primarily metabolized in the liver via dihydropyrimidine dehydrogenase (DPD) to the active metabolites 5-fluoroxyuridine monophosphate (F-UMP) and 5-5-fluoro-2'-deoxyuridine-5'-O-monophosphate (F-dUMP).

4. Elimination: The mean elimination half-life of fluorouracil from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. Small amounts of fluorouracil are excreted unchanged in the urine.

c. Adverse EFFECTS

Adverse Events with Possible Relationship to Fluorouracil		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Agranulocytosis	
	Anemia	
	Leukopenia	
	Pancytopenia	
	Thrombocytopenia	
CARDIAC DISORDERS		
		Angina
		Arrhythmia
		Coronary arteriosclerosis
CARDIAC DISORDERS (contd.)		
		Heart failure
		Myocardial infarction
		Myocardial ischemia
		Vasospasm
		Ventricular ectopy
EYE DISORDERS		
	Lacrimation	
	Lacrimal duct stenosis	
	Photophobia	
	Visual changes	
GASTROINTESTINAL DISORDERS		
Anorexia	Bleeding	Acute mesenteric ischemia
Diarrhea	Nausea	Ulceration
Esophagopharyngitis	Vomiting	

Adverse Events with Possible Relationship to Fluorouracil		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤ 3%)**
Stomatitis		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Generalized allergic reactions	Anaphylaxis
NERVOUS SYSTEM DISORDERS		
Headache	Acute cerebellar syndrome	Stroke
	Confusion	
	Disorientation	
	Euphoria	
	Nystagumus	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Epistaxis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia	Vein pigmentation	Stevens-Johnson syndrome
Dermatitis		Toxic epidermal necrolysis
Dry skin		
Fissuring		
Hand-foot syndrome		
Maculopapular rash		
Nail changes		
Photosensitivity		
Pruritis		
VASCULAR DISORDERS		
	Thrombophlebitis	

1. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.
2. Pregnancy and Lactation: Pregnancy Category D. Excretion in human breast milk is unknown and the manufacturer recommends against breastfeeding while receiving fluorouracil.
3. Drug Interactions: Fluorouracil is a strong inhibitor of CYP2CP. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including fluorouracil, should be screened prior to initiation of and during treatment with fluorouracil. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

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

e. PREPARATION, STORAGE & STABILITY

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

f. HOW SUPPLIED

Fluorouracil is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.4 Irinotecan (Camptosar ®) (NSC-616348)

a. PHARMACOLOGY

Mechanism of Action: Irinotecan and its metabolite SN-38 inhibit topoisomerase I. Topoisomerase I relieves torsional strain in the DNA helix during replication and RNA transcription by inducing single-strand breaks. By binding with the topoisomerase I—DNA complex, irinotecan or SN-38 prevents the religation of the single-strand breaks. Irreversible DNA damage occurs when a DNA replication fork encounters the irinotecan or SN-38/topoisomerase I complexes resulting in double-strand DNA breaks. Camptothecins are highly S-phase specific in their activity due the requirement of DNA synthesis.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: Protein binding of irinotecan is 30-70%, whereas SN-38 shows a higher protein binding of 95%. Both irinotecan and SN-38 are primarily bound to albumin. Volume of distribution of irinotecan is approximately 110-234 L/m^2.

3. Metabolism: Irinotecan is metabolized primarily in the liver by carboxylesterase to SN-38, and via hepatic cytochrome P450 (CYP) 3A4 to aminopentane carboxylic acid (APC). SN-38 is conjugated to form a glucuronide metabolite by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1). Genetic polymorphisms exist in the enzyme UGT1A1, leading to different levels of exposure and toxicity among patients. In addition, both irinotecan and SN-38 undergo plasma hydrolysis between their active (lactone) and inactive forms (carboxylate). Finally, a small amount of irinotecan is metabolized by the intestinal wall.

4. Elimination: Approximately 10-25% of irinotecan is recovered unchanged in urine whereas only small amounts of SN-38 have been found. Clearance is approximately 13.5 L/hr/m^2. In addition, irinotecan has approximately 25% biliary excretion.

c. ADVERSE EFFECTS

Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Irinotecan		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
Leukopenia		
Neutropenia		
Thrombocytopenia		
CARDIAC DISORDERS		

Adverse Events with Possible Relationship to Irinotecan		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
	Hypotension	
GASTROINTESTINAL DISORDERS		
Abdominal pain	Dyspepsia	
Constipation	Flatulence	
Diarrhea	Stomatitis	
Mucositis		
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Asthenia	Hypersensitivity reaction	
Cholinergic syndrome		
Fever		
Pain		
INFECTIONS AND INFESTATIONS		
Infection		
INVESTIGATIONS		
	Abnormal bilirubin	
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
Weight loss		
NERVOUS SYSTEM DISORDERS		
Dizziness	Confusion	
	Headache	
	Insomnia	
	Somnolence	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	Pneumonia	
Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia	Cutaneous signs	
	Exfoliative dermatitis	
	Hand and foot syndrome	
	Rash	
VASCULAR DISORDERS		
	Edema	
	Hemorrhage	
	Thromboembolic events	

Adverse events occurring in < 1%, postmarketing, and/or case reports: myocardial ischemia, symptomatic pancreatitis, Hyponatremia, transient dysarthria

1. Pregnancy and Lactation: Pregnancy Category D. It is not known whether irinotecan or its derivatives are excreted in human milk.

2. Drug Interactions: Irinotecan and its active metabolite SN-38 may be substrates for CYP3A4, CYP2B6, OATP1B1/SCLO1B1, P-glycoprotein/ABCB1 and UGT1A1. Inducers or inhibitors may affect

serum concentrations of irinotecan. Due to potential drug interactions, a complete patient medication list, including irinotecan, should be screened prior to initiation of and during treatment with irinotecan. Refer to the current FDA-approved package insert. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

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

e. PREPARATION, STORAGE & STABILITY

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

f. HOW SUPPLIED

Irinotecan is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.5 Leucovorin (NSC-3590)

a. PHARMACOLOGY

Mechanism of Action: During normal processes, thymidylate synthetase forms a noncovalent ternary complex with deoxyuridylate (dUMP) and the reduced folate cofactor of leucovorin 5-methyl-tetrahydrofolate (5MTHF). The reduced folate facilitates the association and disassociation of the complex and the formation of thymidylate (dTMP) and dihydrofolate. Fluorouracil inhibits thymidylate synthetase through the covalent binding of 5-fluorodeoxyuridine monophosphate (FdUMP) and 5MTHF. The binding of FdUMP is dependent upon the intracellular concentration of 5MTHF. Since l-leucovorin is metabolized to 5MTHF, it increases and stabilizes the binding of FdUMP to thymidylate synthetase, thus increasing the cytotoxic effects of fluorouracil.

b. PHARMACOKINETICS

1. Absorption: Studies have produced bioavailabilities of 97%, 75% and 37% for doses of 25 mg, 50mg and 100mg respectively.

2. Distribution: Leucovorin is rapidly converted to 5-methyl-tetrahydrofolate (5MTHF) and widely distributed to tissues including the CNS. The time to peak concentration for oral, folate isomers and 5MTHF is 2 hours, 10 minutes and 1 hour respectively.

3. Metabolism: Leucovorin is metabolized by intestinal mucosa and hepatically to the active form 5MTHF.

4. Elimination: Leucovorin is primarily excreted unchanged in the urine and minimally in the feces. Leucovorin has a half-life elimination of approximately 4 to 8 hours.

c. ADVERSE EFFECTS

Adverse Events with Possible Relationship to Leucovorin		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Thrombocytosis	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
		Allergic reactions
		Anaphylactoid reactions
METABOLISM AND NUTRITION DISORDERS		
	Hypocalcemia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Wheezing	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash	
	Pruritis	
	Erythema	
	Urticaria	

1. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

2. Pregnancy and Lactation: Pregnancy Category C. Excretion in human breast milk is unknown.

3. Drug Interactions: Leucovorin may interact with antimetabolites, antifolates and anticonvulsants. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including leucovorin, should be screened prior to initiation of and during treatment with leucovorin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

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

e. PREPARATION, STORAGE & STABILITY

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

f. HOW SUPPLIED

Leucovorin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.6 Oxaliplatin (Eloxatin®) (NSC-266046)

a. PHARMACOLOGY

Mechanism of Action: Oxaliplatin is a non-cell cycle specific, alkylating antineoplastic agent that inhibits DNA synthesis through the formation of crosslinks between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription.

b. PHARMACOKINETICS

1. Absorption: N/A

2. Distribution: At the end of a 2-hour infusion, approximately 15% of the administered oxaliplatin is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of oxaliplatin is irreversible and greater than 90%. The main binding proteins are albumin and gamma-globulins. No oxaliplatin accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks.

3. Metabolism: Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism *in vitro*. Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples from patients, including several cytotoxic species and a number of noncytotoxic, conjugated species.

4. Elimination: The major route of oxaliplatin elimination is renal excretion. At five days after a single 2-hour infusion, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Oxaliplatin was cleared from plasma at a rate (10 – 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultrafilterable oxaliplatin. The renal clearance of ultrafilterable oxaliplatin is significantly correlated with GFR.

c. ADVERSE EFFECTS

Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Oxaliplatin		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	Disseminated intravascular coagulation	Thrombotic thrombocytopenic purpura
	Febrile neutropenia	
	Hemolysis	
CARDIAC DISORDERS		
	Atrial fibrillation	
	Atrial flutter	
	Paroxysmal atrial tachycardia	

Adverse Events with Possible Relationship to Oxaliplatin		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
	Sinus bradycardia	
	Sinus tachycardia	
	Supraventricular tachycardia	
	Ventricular arrhythmia	
	Ventricular fibrillation	
	Ventricular tachycardia	
EAR AND LABYRINTH DISORDERS		
	Hearing impaired	
	Middle ear inflammation	
EYE DISORDERS		
	Conjunctivitis	
	Dry eye	
	Eye disorders - Other (amaurosis fugax)	
	Eye disorders - Other (cold-induced transient visual abnormalities)	
	Eyelid function disorder	
	Papilledema	
GASTROINTESTINAL DISORDERS		
Diarrhea	Abdominal pain	Gastrointestinal disorders – Other (pneumatosis intestinalis)
Nausea	Ascites	
Vomiting	Colitis	
	Constipation	
	Dry mouth	
	Dyspepsia	
	Dysphagia	
	Enterocolitis	
GASTROINTESTINAL DISORDERS (contd.)		
	Esophagitis	
	Flatulence	
	Gastritis	
	Gastrointestinal hemorrhage	
	Gastrointestinal necrosis	
	Gastrointestinal ulcer	
	Ileus	
	Mucositis oral	
	Pancreatitis	
	Small intestinal obstruction	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	Chills	
	Edema face	
	Edema limbs	
	Fever	
	Gait disturbance	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS (contd.)		
	General disorders and	

Adverse Events with Possible Relationship to Oxaliplatin		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
	administration site conditions - Other (Hepato-renal syndrome)	
	Injection site reaction	
	Non-cardiac chest pain	
HEPATOBILIARY DISORDERS		
	Hepatic failure	Cholecystitis
	Hepatobiliary disorders - Other(hepatic enlargement)	
	Hepatobiliary disorders - Other (veno-occlusive liver disease)	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
INFECTIONS AND INFESTATIONS		
	Infection	
INVESTIGATIONS		
Alanine aminotransferase increased	Activated partial thromboplastin time prolonged	
Aspartate aminotransferase increased	Alkaline phosphatase increased	
Platelet count decreased	Blood bilirubin increased	
	Creatinine increased	
	GGT increased	
	INR increased	
	Lymphocyte count decreased	
	Neutrophil count decreased	
	Weight gain	
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Acidosis	
	Anorexia	
	Dehydration	
	Hyperglycemia	
	Hyperuricemia	
	Hypoalbuminemia	
	Hypocalcemia	
	Hypoglycemia	
	Hypokalemia	
	Hypomagnesemia	
	Hyponatremia	
	Hypophosphatemia	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Myalgia	
	Trismus	
NERVOUS SYSTEM DISORDERS		

Adverse Events with Possible Relationship to Oxaliplatin		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
Peripheral sensory neuropathy	Ataxia	
	Depressed level of consciousness	
	Dizziness	
	Dysgeusia	
	Dysphasia	
	Extrapyramidal disorder	
NERVOUS SYSTEM DISORDERS (contd.)		
	Headache	
	Intracranial hemorrhage	
	Ischemia cerebrovascular	
	Nerve disorder	
	Nervous system disorders - Other (multiple cranial nerve palsies)	
	Peripheral motor neuropathy	
	Seizure	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Confusion	
	Depression	
	Insomnia	
RENAL AND URINARY DISORDERS		
	Hematuria	Acute kidney injury
	Renal hemorrhage	
	Urinary frequency	
	Urinary retention	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
	Hematosalpinx	
	Ovarian hemorrhage	
	Prostatic hemorrhage	
	Spermatic cord hemorrhage	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS (cont.)		
	Testicular hemorrhage	
	Uterine hemorrhage	
	Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Allergic rhinitis	Adult respiratory distress syndrome
	Bronchopulmonary hemorrhage	
	Bronchospasm	
	Cough	
	Dyspnea	
	Hiccups	
	Pneumonitis	
	Pulmonary fibrosis	
	Sinus disorder	
	Voice alteration	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	Palmar-plantar erythrodysesthesia

Adverse Events with Possible Relationship to Oxaliplatin		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
		syndrome
	Dry skin	
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
	Urticaria	
VASCULAR DISORDERS		
	Flushing	
	Hot flashes	
	Hypertension	
	Hypotension	
	Phlebitis	
	Thromboembolic event	
	Vascular disorders - Other (hemorrhage with thrombocytopenia)	

1. Pregnancy and Lactation: Pregnancy Category D. It is not known whether oxaliplatin or its derivatives are excreted in human milk.

2. Drug Interactions: No specific cytochrome P-450-based drug interaction studies have been conducted. Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied. Refer to the current FDA-approved package insert. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

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

e. PREPARATION, STORAGE & STABILITY

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

f. HOW SUPPLIED

Oxaliplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.7 Pegfilgrastim (Neulasta™) (NSC-725951)

a. PHARMACOLOGY

Mechanism of Action: Similar to filgrastim, pegfilgrastim is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end-cell functional activation. Studies on cellular proliferation, receptor binding, and

neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action.

b. PHARMACOKINETICS

Absorption: Similar to filgrastim, first-order pharmacokinetic modeling is expected with maximum serum concentration reached within 2 to 8 hours after subcutaneous injection

1. Distribution: Similar to filgrastim, volume of distribution of averaged at 150 mL/kg

2. Metabolism: Unknown

3. Elimination: Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared with filgrastim. The half-life of pegfilgrastim ranges from 15 to 80 hours after subcutaneous injection.

c. ADVERSE EFFECTS

1. Possible Side Effects of Pegfilgrastim: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Most frequent adverse reactions are skeletal pain (< 20%).

2. Pregnancy and Lactation: Category C, pegfilgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies have demonstrated adverse effects and fetal loss. Pegfilgrastim has been shown to cross the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Excretion in breast milk unknown/use caution.

3. Drug Interactions: Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs such as lithium may potentiate the release of neutrophils; ensure that patients receiving lithium and pegfilgrastim have more frequent monitoring of neutrophil counts.

   Pegfilgrastim should not be administered on the same day with anticancer chemotherapeutic agent(s) with leukocyte suppressive properties.

   Pegfilgrastim is contraindicated in patients with hypersensitivity to *E.coli*-derived proteins, filgrastim, or any component of the product

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

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

e. PREPARATION, STORAGE & STABILITY

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

f. HOW SUPPLIED

3.8 Pegylated Recombinant Human Hyaluronidase (PEGPH20) (NSC-772519) (IND-118849)

a. PHARMACOLOGY

Mechanism of Action: Hyaluronic acid (HA) is a linear, repeating polysaccharide that consists of N-acetylglucosamine and glucuronic acid disaccharide units. PEGylated recombinant human hyaluronidase (PEGPH20) is a PEGylated version of human recombinant PH20 hyaluronidase (rHuPH20). PEGylated rHuPH20 demonstrates a significantly increased half-life relative to the non-PEGylated rHuPH20. *In-vitro* studies showed that HA is re-synthesized within 24 hours suggesting that sustained activity of PEGPH20 is needed. PEGPH20 enzymatically depletes HA (which is the substrate for the enzyme) from the extracellular matrix (ECM) of tumor cells by depolymerizing the substrate. By changing the ECM surroundings, there is an increase in the penetration of drugs such as anti-tumor drugs. Tumors that accumulate HA are more sensitive to PEGPH20 alone or in combination with chemotherapy. Other beneficial mechanisms proposed include remodeling of tumor stroma, decreased tumor interstitial fluid pressure (IFP is correlated with tumors that have high levels of HA), and expansion of blood vessels. In addition, the role in metastasis may include reducing cell adhesion and invasion and decreasing metastatic tumor burden.

b. PHARMACOKINETICS

1. Limited studies have been conducted to directly analyze absorption, distribution, metabolism, and excretion of PEGPH20.

2. Absorption: Dexamethasone, when administered with PEGPH20, was found to not alter the pharmacokinetics of intravenous (IV) PEGPH20 in beagle dogs.

3. Distribution: Most likely has a small volume of distribution in humans. In single dose IV studies in mice and monkeys plasma activity decreased in biphasic manner, and the drug had a fast initial distribution phase.

4. Metabolism: Not available.

5. Elimination: In mice, rHuPH20 has a very short half-life (t½) of 2.3 minutes. The rapid HA re-synthesis (within 24 hrs in *in-vitro* studies) made it essential to create the PEGlyated version which extended the t½ in mice to 10.3 hours. Preliminary pharmacokinetics studies in humans show a slow plasma clearance and a terminal t½ of approximately 2 days. The longer t½ not only sustains the duration of action to degrade HA but also helps prevent re-accumulations of HA. After repeated dosing of PEGPH20, there was no evidence of significant accumulation of the drug in the plasma.grastim is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

c. ADVERSE EFFECTS

1. Human data:

Adverse Events with Possible Relationship to PEGPH20		
Likely (>20%)	**Less Likely (4 – ≤20%)**	**Rare but Serious (≤3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Thrombocytopenia	
CARDIAC DISORDERS		
	Atrial fibrillation	
	Hypotension	
GASTROINTESTINAL DISORDERS		
Abdominal distension	Diarrhea	
Abdominal pain	Dry mouth	
Constipation	Dysgeusia	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Dysphonia	Asthenia	
Fatigue	Contusion	
	Infusion reactions	
	Oropharyngeal pain	
	Pyrexia	
	Weight increase	
INFECTIONS AND INFESTATIONS		
	Cellulitis	
	Urinary tract infection	
INVESTIGATIONS		
	Hyponatremia	
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite		
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS-most common but dose related and controlled with dexamethasone		
Arthralgia	Back pain	
Muscle spasms	Extremity pain	
Myalgia	Muscle atrophy	
	Muscle weakness	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Dyspnea	
	Ear congestion	
	Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Oedema peripheral	Ascites	
VASCULAR DISORDERS		
		Deep vein thrombosis
		Pulmonary embolism

Adverse events occurring in < 1%, postmarketing, and/or case reports: 1 patient died due to a cerebrovascular accident and embolism that may have been related to PEGPH20.

2. Animal Data: Decrease in red blood cells (RBC), decrease in hemoglobin and hematocrit, increase in platelets and fibrinogen, decrease in serum albumin and total protein, transient increase in neutrophil count, small increase in lymphocytes, monocytes and eosinophils (which were dose-related), increase in activated partial thromboplastin time (APTT), increase incidence of cardiomyopathy and musculoskeletal events.

3. 3. Pregnancy and Lactation: The risks of PEGPH20 to an unborn fetus are not known. There have been no animal studies to test for reproductive and developmental toxicity with PEGPH20. It is not known whether PEGPH20 is excreted in breast milk; therefore, women who are breast feeding should not receive PEGPH20.

4. Drug Interactions: No pharmacokinetic drug interaction studies have been conducted with PEGPH20.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan. Dose recalculation based on weight change must be done if the patient experiences 10% or more weight gain or weight loss from the last dosing weight.

2. PEGH20 is administered intravenously as an IV injection over 10 minutes (1 mL/min).

e. PREPARATION, STORAGE & STABILITY

1. PEGPH20 histidine formulation (frozen) preparation:

f. Preparation: PEGPH20 is available as 3.5 mg/mL (3500 mcg/mL) solution in 0.6 mL and 1.2 mL vials. No more than **ONE** vial of PEGPH20 is required per dose. Remove the vial from the freezer and allow to thaw at room temperature for 30-90 minutes. Once thawed, PEGPH20 should be gently inverted 3 times to mix contents. The intact thawed solution is stable in the refrigerator for up to 24 hours. PEGPH20 is dispensed in a final volume of 10 mL and compounded in two separate dilutions.

1. First Dilution (1:10): To a 10 mL empty glass vial add:

a. 0.4 mL of PEGPH20 (1400 mcg) with a 1 mL syringe

b. 3.6 mL of 0.9% sodium chloride with a 5 mL syringe

Mix well by inverting the vial gently one or two times. Label the vial as “Dilution 1” with a concentration of “350 mcg/mL.”

2. Second Dilution: Dosing will be prescribed on a mcg/kg basis. Calculate the dose and volume (based on the above concentration of 350 mcg/mL) of PEGPH20 needed for the patient plus 20% overage.

a. Calculate the **dose volume** to dilute to a total volume of 12 mL:

Dose level (mcg) x patient weight (kg) x 1.2 = _____ mL
350mcg/mL (Dilution 1)

b. Calculate the **diluent** (0.9% Sodium chloride) **volume**:

12 mL – dose volume (from **1**) mL=
_____ mL 0.9% Sodium Chloride

c. Add the diluent volume (0.9% sodium chloride) calculated in **b** to an empty 20mL glass vial.

d. Remove the dose volume calculated in **a** from "Dilution 1" vial and add to the diluent in the 20 mL glass vial.

e. Mix the solution well by inverting the vial slowly 2-3 times. Label the vial as "Final Dilution" with "Patient ID" and "Initials."

f. Withdraw 10 mL of the Final Dilution into a syringe for injection. Label according to institution guidelines.

Example:
Dose level: 3 mcg/kg
Patient weight: 70 kg

Dose volume:
$\frac{3 \text{ (mcg)} \times 70 \text{ (kg)}}{350 \text{ mcg/mL}}$ **x** 1.2 = 0.72 mL

Diluent (0.9% Sodium chloride) volume:

12 mL – 0.72 mL = 11.28 mL

3. PEGPH20 succinic acid (refrigerated) preparation:

a. Preparation: PEGPH20 is available as 0.3 mg/mL (300 mcg/mL) solution in 1.2 mL vials. Remove the vial from the refrigerator and allow the vial to reach room temperature for approximately 30 minutes. Once at room temperature, PEGPH20 should be gently inverted 3 times to mix contents. The vial of PEGPH20 must be used within 5 hours of being placed at room temperature. The intact solution is stable in the refrigerator for up to 24 hours. The diluted PEGPH20 is dispensed in a final volume of 10 mL.

4. A calculated amount of PEGPH20 will be added to an empty glass vial (e.g., 20-30 mL vial) and brought up to a total volume of 12 mLs with normal saline (20% overage).

a. To calculate volume taken from PEGPH20 vial:

$$\frac{\text{Dose level (mcg)} \times \text{patient weight (kg)} \times 1.2}{300 \text{ mcg/ml (concentration of PEGPH20)}}$$

While exact measurements are desirable, rounding to the nearest 0.05 mL is acceptable. However, the actual dose must be captured in the e-CRF and the rounding should be accounted for the final dose.

b. Mix the solution well by inverting the vial slowly 2-3 times. Label vial as final dose with Patient ID and initials.

c. Draw 10 mLs from the dilution vial into a 10 mL syringe for injection into the patient. Label the syringe according to institutional guidelines.

Example:
Dose level: 3 mcg/kg
Patient weight: 70 kg

Dose volume:
$\frac{3 \text{ (mcg)} \times 70 \text{ (kg)}}{300 \text{ mcg/mL}} \times 1.2 = 0.84 \text{ mL}$

Diluent (0.9% Sodium chloride) volume:

12 mL – 0.84 mL = 11.16 mL

1. Stability: The final dilution of PEGPH20 must be used within 24 hours after preparation. Once placed at room temperature, the vial must be used within 5 hours. After reaching room temperature, the vial cannot be re-frozen or re-refrigerated for future use.

2. Compatibility: The infusion line may be flushed with 0.9% sodium chloride before and after the IV injection. Additional compatibility information is not available.

d. Storage: PEGPH20 histidine formulation should be stored at or below -20°C prior to use. PEGPH20 succinic acid formulation should be stored at 2-8°C prior to use.

g. HOW SUPPLIED

1. PEGPH20 IS SUPPLIED IN 2 FORMS:

PEGPH20 formulation	Vial volume	Final concentration
Histidine (frozen)	1.2ml	3.5mg/mL
Succinic acid (refrigerated)	1.2ml	0.3mg/ml

a. The PEGPH20 drug product histidine formulation is supplied as a frozen, sterile, single-use, injectable liquid. PEGPH20 drug product (clinical test article) is an aqueous solution containing 3.5 mg/mL PEGPH20 with 10 mM Histidine, 130 mM NaCl, at a pH of 6.5. Each vial contains 1.2 mL (4.2 mg) or 0.6 mL (2.1 mg) of PEGPH20 drug product. PEGPH20 drug product are packaged in clear, Type I, 2 mL glass vials.

b. The PEGPH20 drug product succinic acid formulation is supplied as a refrigerated, sterile, single-use, injectable liquid. PEGPH20 drug product (clinical test article) is an aqueous solution containing 0.3mg/mL PEGPH20 with 10 mM succinic acid/NaOH, 130 mM NaCl, and 10 mM L-Methionine at a pH of 6.2. Each vial contains 1.2 mL (0.36 mg) of PEGPH20 drug product. PEGPH20 drug product is packaged in clear, Type I, 2 mL glass vials.

2. PEGPH20 is an investigational agent supplied to investigators by Biologics Inc. from Halozyme Inc.

3. Drug ordering and shipping

a. PEGPH20 may be requested by the Principal Investigator (or their authorized designee) by completing and faxing the Biologics Drug Request form for **S1313**. The form should be faxed to the number listed on the order form. Authorized and completed orders will be processed and shipped "same day" of receipt if received before 2:00 pm EST Tuesday through Thursday. Authorized and completed orders received after 2:00 pm EST Tuesday through Thursday and on Friday or Monday will be processed and shipped the next business morning. Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments. Biologics will be closed for the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, Thanksgiving Friday, Christmas Eve, and Christmas Day.

b. Once a patient is registered, the site will fax a completed Drug Request form to Biologics at 919-256-0794. Upon receipt of faxed Drug Request form, Biologics will:

1. Place a call or email to the site confirming the Drug Request form was received, while providing the estimated day and time of arrival of the study drug.

2. Biologics will ship the requested quantity of vials for the patient to complete their cycles of PEGPH20. Approximately 10 days into the first, third, seventh, eleventh, and 15th cycle, Biologics will place a call to the study site to arrange for the next shipment of study drug for the subsequent cycle. If the patient requires dosing

past 16 cycles, the site will be contacted 10 days into each odd numbered cycle (i.e., 17, 19, 21 etc,) to plan for the next shipment. Shipments after cycle 16 will be 2 vials each (enough for 2 cycles).

3. All study drug will be shipped in original manufacturers packaging with a protocol-specific label adhered to the outer packaging. Biologics will place the manufacturer's packaging in a Ziploc bag. Each shipment includes a protocol label on the resealable bag with the following information:

   - The Study Number (i.e., SWOG **S1313**);
   - IND caution statement and/or local regulatory statements
   - Drug identification
   - Lot number and Expiration
   - Dosing instructions (Administer as directed per Protocol)
   - Storage instructions
   - Emergency contact instructions

4. Each shipment is delivered in a pre-conditioned -20°C or colder shipping solution qualified at 72 hours and a TagAlert monitoring system to ensure temperature maintenance during transit. At receipt, each site will review the monitor to confirm temperature stability.

5. Once study drug is received at the clinical trial site, the designated site coordinator validates the contents of package and matches the information provided on packing slip, signs off on the packing slip, and faxes completed form to Biologics to validate shipment has been received and is accurate.

c. All drug orders are shipped via *FedEx for Priority Overnight* delivery for shipments to US sites.

The Biologics distribution team monitors packages throughout duration of transit via Fed Ex website and FedEx One Call Solution (live support). Real-time monitoring enables the Biologics distribution team to mitigate potential delivery delays (e.g. misrouted packages).

In the event a package cannot be delivered within the 24 hour time period (i.e. due to severe weather), Biologics' distribution team works proactively with Fed Ex One-Call, confirming the exact location of the package and providing instruction to Fed-Ex to return the package to Biologics. Upon notification of a delayed shipment, a replacement shipment will be sent to the site, as authorized. Sites are also alerted "same day" to any delays in delivery and provided estimated time for arrival of replacement package. All delivery exceptions will be reported via Accountability Reporting.

d. Drug Handling and Accountability

e. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Questions about drug orders, transfers, returns, or accountability should be addressed to Karl Buer at Biologics, Inc. at 800-693-4906 or kbuer@biologicsinc.com.

f. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

4. Drug return and/or disposition instruction

a. Drug Return: At the conclusion of the study, remaining inventory is documented in the accountability records and unused drug will be destroyed per local institutional guidelines. A drug return/destruction form will be included with each shipment and must be returned to Biologics Inc. once all patients are off study drug and drug has been destroyed.

Sites may use vials on hand for multiple patients enrolled to the study.

b. Disposition: Used vials should be disposed of in accordance with institution policies.

c. Drug expiration: Stability evaluation is ongoing. The supplier will monitor drug stability and provide expiration updates on an ongoing basis.

5. Questions about drug orders, transfers, returns, or accountability should be addressed to Clinical Research Services at Biologics, Inc. at 800-693-4906 or Clinicaltrials@biologicsinc.com.

4.0 STAGING CRITERIA

Staging criteria are not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have newly diagnosed, untreated metastatic histologically or cytologically documented pancreatic adenocarcinoma. Patients must not have known history of brain metastases.

b. Patients must have measurable metastatic disease, as defined in Section 10.1. CT scans or MRIs used to assess measurable disease must have been completed within 28 days prior to registration. CT scans or MRIs used to assess non-measurable disease must have been completed within 42 days prior to registration. CT scans or MRIs must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

c. Patients must not have had any prior treatment with oxaliplatin or irinotecan within 3 years prior to registration. Patients must not have had prior chemotherapy in metastatic setting. Prior abdominal radiation therapy is not allowed.

5.2 Clinical/Laboratory Criteria

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

Patients must be ≥ 18 and ≤ 75 years of age.

c. Patients must have adequate hematologic function as evidenced by all of the following within 14 days prior to registration: ANC ≥ 1,500/mcL; platelets ≥ 100,000/mcL; and hemoglobin ≥ 9 g/dL.

d. Patients must have adequate hepatic function as evidenced by all of the following within 14 days prior to registration: total bilirubin ≤ Institutional Upper Limit of Normal (IULN); AST and ALT both ≤ 2.5 X IULN in the absence of liver metastasis or ≤ 5.0 x IULN with liver metastasis; and serum albumin ≥ 3 g/dL.

e. Patients must have adequate kidney function as evidenced by at least ONE of the following:

- Serum creatinine ≤ ULN within 14 days prior to registration OR
- Calculated creatinine clearance > 50 ml/min. The serum creatinine value used in the calculation must have been obtained within 14 days prior to registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times [0.85 \text{ (if female)}]}{72 \times \text{creatinine (mg/dL)}}$$

f. Patients must have INR ≤ 1.2 within 14 days prior to registration. Patients must not be receiving warfarin for therapeutic use, have history of cerebrovascular accident (CVA), history of transient ischemic attack (TIA) requiring intervention or treatment, pre-existing carotid artery disease requiring intervention or treatment, or current use of megestrol acetate (use within 10 days of registration).

g. Patients must not be receiving chronic treatment (equivalent of prednisone > 10 mg/day) with systemic steroids or other immuno-suppressive agent.

h. Patients must not have liver disease such a cirrhosis, chronic active hepatitis or chronic persistent hepatitis.

i. Patients must not have active bleeding or a pathological condition that is associated with a high risk of bleeding.

j. Patients with a known history of HIV must not be on active treatment for HIV.

k. Patients must have no non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with protocol therapy.

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

m. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

n. Patients must be able to start low-molecular weight heparin, as prophylaxis.

5.3 Specimen Submission Criteria

a. Patients must have tumor (paraffin block or slides) available for submission and be willing to submit tumor and blood samples as described in Section 15.1.

5.4 Regulatory Criteria

a. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

c. Patients planning to enroll in the Phase I portion of this study must first have a slot reserved in advance of the registration. All site staff will use OPEN to create a slot reservation (see Section 13.2 for OPEN slot reservation instructions). NOTE: Phase I is closed to accrual **effective 4/1/15**.

6.0 STRATIFICATION FACTORS

Phase I Portion: Stratification factors are not applicable to this portion.

Phase II Portion: Patients will be stratified according to Zubrod Performance Status: 0 vs. 1.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Ramanathan at 480/301-8000 or Dr. Philip at 313/576-8746. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Treatment Overview

The study will be conducted in two sequential parts. A patient may be enrolled to either the Phase I Portion or the Phase II Portion, but not both.

Phase I Portion – Details are in Section 7.3.

Phase II Portion – Details are in Section 7.4.

7.2 Pre-Medication

Administration of PEGPH20 requires steroid premedication prior to dosing and for a total of 4 days after (i.e. dexamethasone 8 mg bid [PO or IV] on first day of dosing then 4 mg bid the 3 subsequent days) to reduce the incidence of myalgias and arthralgias. For subsequent cycles, 8 mg dexamethasone bid on day of PEGPH20 administration and treating physician may increase or decrease subsequent dexamethasone based on patient symptoms.

PEGPH20 + mFOLFIRINOX can be considered a highly emetogenic regimen. Prophylaxis with a regimen including aprepitant/steroids or as per institutional policy is recommended.

7.3 Phase I

IMPORTANT NOTE: The Phase I portion of this trial is now closed. Rapid reporting of dose limiting toxicities (Section 15.2) is no longer required.

This will be a dose de-escalation clinical trial with two dose levels of PEGPH20. The starting dose level for PEGPH20 is Level 1. No patients will be enrolled in the next dose level until the toxicity is fully assessed after the completion of one cycle in at least 6 patients enrolled at the previous dose level. The maximum tolerated dose (MTD) is defined as the highest dose studied in which the incidence of dose-limiting toxicities (DLT) is ≤ 17%.

a. Treatment

Agent	Dose	Route	Day	Schedule*
PEGPH20	assigned dose ***	IV over 10 min	1, 3 or 4**	24 hours prior to beginning mFOLFIRINOX
Oxaliplatin	85 mg/m^2	IV over 2 hours	2	Prior to irinotecan and leucovorin
Leucovorin****	400 mg/m^2	IV over 2 hours	2	With irinotecan
Irinotecan	180 mg/m^2	IV over 1.5	2	With leucovorin

		hours		
5-FU	2,400 mg/m^2	IV over 46 hours	2-4	Following leucovorin and irinotecan
Pegfilgrastim Or Filgrastim	6 mg 300 or 480 mcg	SQ SQ	4 4-8	Following disconnection of 5-FU Following disconnection of 5-FU daily for 4-5 days

* Note: One cycle = 14 days
** For Dose Level 1 Only: PEGPH20 given on Day 3 or 4 (treating physician's choice) for Cycles 1 and 2 only.
*** See dose de-escalation schema in Section 7.3b. Only one dose level will be open at a time.
**** In the event of a leucovorin shortage, the dosage may be reduced to 20 mg/m^2 or 200 mg/m^2 racemic levoleucovorin may be substituted.

IMPORTANT NOTE: The Phase I portion of this trial is now closed. Rapid reporting of dose limiting toxicities (Section 15.2) is no longer required.

b. PEGPH20 Dose de-escalation schema

Dose Level	PEGPH20 (IV over 10 min)
1	3 mcg/kg on Day 1 and Day 3 or 4
2	3 mcg/kg on Day 1 only
3	1.6 mcg/kg on Day 1 only

c. Dose Determination Rules

1. Dose Limiting Toxicity (DLT) is defined in Section 7.3d

2. Only DLTs occurring during Cycle 1 will be used to guide dosing determination of PEGPH20.

3. Patients will be considered evaluable for DLT if they received PEGPH20 at the assigned dose for Cycle 1, or if they developed a DLT. If for any reason a patient does not develop a DLT but does not receive the full assigned PEGPH20 dose, the patient will be considered not evaluable for DLT and will be replaced.

4. The following dosing scheme will be used for dose determination:

   a. Begin at Dose Level 1 (see Dose De-escalation Scheme above):

   b. Enroll 6 patients and evaluate for toxicity. Enroll additional patients as required until 6 evaluable patients have been enrolled.

   c. If 0 or 1 of the initial 6 patients experiences a DLT during the first cycle, then this dose Level is the MTD.

d. If 2 or more of the initial 6 patients experience a DLT during the first cycle, continue to the next lower dose level and return to "b" immediately above. If the current dose level is Dose Level 3 the study may be permanently closed.

Only one dose level of PEGPH20 will be opened at a time. Adverse events and accrual monitoring are done routinely by the Study Chairs and Study Statisticians. A mandatory conference call for study teams with active patients will take place once a week (see Section 15.2).

d. Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0.

Dose-limiting toxicities (DLT) apply only during Cycle 1 and must be defined as attributable to PEGPH20 and/or mFOLFIRINOX (possible, probable or definite). DLT is defined as any of the following drug-related toxicities occurring in the first cycle (2 week period) of treatment:

1. Any Grade ≥ 3 non-hematologic toxicity (except alopecia and Grade 3 nausea, vomiting and diarrhea responding to medical treatment within 72 hours)

2. Hematologic toxicity

   a. Grade 4 anemia or thrombocytopenia

   b. Grade 4 ANC lasting > 7 days

   c. Grade ≥ 3 febrile neutropenia

3. Laboratory test

   a. Grade ≥ 3 elevation of AST/ALT, total bilirubin, and creatinine. If baseline values are elevated, then increase should be by 2 grades to be called a DLT.

4. Delay in starting the 2nd cycle of mFOLFIRINOX by > 2 weeks due to drug related toxicity.

7.4 Phase II

The study will temporarily close prior to opening the Phase II portion to define the Phase II dose of PEGPH20 and amend the protocol. Patients will be randomly assigned to Arm 1 or Arm 2.

a. Treatment: Arm 1 - mFOLFIRINOX

Patients assigned to Arm 1 will receive the following treatment until meeting one of the criteria in Section 7.5.

Agent	Dose	Route	Day	Schedule*
Oxaliplatin	85 mg/m^2	IV over 2 hours	1	Prior to irinotecan and leucovorin
Leucovorin**	400 mg/m^2	IV over	1	With irinotecan

		2 hours		
Irinotecan	180 mg/m^2	IV over 1.5 hours	1	With leucovorin
5-FU	2,400 mg/m^2	IV over 46 hours	1-3	Following leucovorin and irinotecan
Pegfilgrastim Or	6 mg	SQ	3	Following disconnection of 5-FU
Filgrastim	300 or 480 mcg	SQ	3-7	Following disconnection of 5-FU daily for 4-5 days

* Note: One cycle = 14 days
** In the event of a leucovorin shortage, the dosage may be reduced to 20 mg/m^2 or 200 mg/m^2 racemic levoleucovorin may be substituted.

b. Treatment: Arm 2 – PEGPH20 + mFOLFIRINOX

Patients assigned to Arm 2 will receive the following treatment until meeting one of the criteria of in Section 7.5.

Agent	Dose	Route	Day	Schedule $^{\alpha}$
Enoxaparin $^{\Delta}$ /LMWH	1 mg/kg $^{\beta}$	SQ	1-14	Initial dose prior to PEGPH20 and continued daily
PEGPH20	3 mcg/kg	IV over 10 min	1	24 hours prior to beginning mFOLFIRINOX
Oxaliplatin	85 mg/m^2	IV over 2 hours	2	Prior to irinotecan and leucovorin
Leucovorin***	400 mg/m^2	IV over 2 hours	2	With irinotecan
Irinotecan	180 mg/m^2	IV over 1.5 hours	2	With leucovorin
5-FU	2,400 mg/m^2 46 hours	IV over	2-4	Following leucovorin and irinotecan
Pegfilgrastim Or	6 mg	SQ	4	Following disconnection of 5-FU
Filgrastim	300 or 480 mcg	SQ	4-8	Following disconnection of 5-FU daily for 4-5 days

α Note: One cycle = 14 days
β Round up to closest syringe strength.
Δ Enoxaparin, dalteparin, or other low molecular weight heparin equivalent are acceptable.
*** In the event of a leucovorin shortage, the dosage may be reduced to 20 mg/m^2 or 200 mg/m^2 racemic levoleucovorin may be substituted.

7.5 Criteria for Removal from Protocol Treatment

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

b. Unacceptable toxicity.

c. Treatment delay for any reason > 4 weeks except in a patient without prior history of a thromboembolic event (TE) not receiving low molecular weight heparin at baseline who has a Grade 3 or less venous TE managed with low molecular weight heparin who has been stable for 4 weeks (see Section 8.4c).

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

7.6 Discontinuation of Treatment

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

7.7 Follow-Up Period

All patients will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Wait for the recovery of toxicities to Grade 1 or less to resume the treatment.

b. Prevent the risk of “delayed” nausea/vomiting by aprepitant or similar agent according to institutional guidelines (plus corticosteroids, use with caution in diabetes).

c. In case of cholinergic syndrome, use 0.25 mg of atropine subcutaneous unless contraindicated.

d. Use a total sunscreen cream in case of solar exposure.

e. Explain instructions in cases of diarrhea after irinotecan according to Section 8.3e.

f. The following drugs are not allowed for therapeutic use: warfarin, metronidazole, ornidazole

g. The dose of leucovorin is not modified for toxicity, but is omitted if fluorouracil is omitted.

h. Once a dose is decreased, re-escalation is not permitted.

i. All dose adjustments should be based on the toxicity graded using the CTCAE (Version 4.0) requiring the largest dose reduction.

8.3 Toxicities To Be Monitored

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0. These toxicities should be closely monitored during the first 2 cycles of treatment for every patient.

1. Any Grade ≥ 3 non-hematologic toxicity (except alopecia and Grade 3 nausea, vomiting and diarrhea responding to medical treatment within 72 hours)

2. Hematologic toxicity

   a. Grade 4 anemia or thrombocytopenia

   b. Grade 4 ANC lasting > 7 days

   c. Grade ≥ 3 febrile neutropenia

3. Laboratory test

   a. Grade ≥ 3 elevation of AST/ALT, total bilirubin, and creatinine. If baseline values are elevated, then increase should be by 2 grades.

4. Delay in starting the 2nd cycle of mFOLFIRINOX by > 2 weeks due to drug related toxicity.

8.4 Dose Modifications for mFOLFIRINOX

a. Dose Modifications

Drug	Initial dose	Dose Reduction Level 1	Dose Reduction Level 2
5-FU	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
Oxaliplatin	85 mg/m^2	60 mg/m^2	50 mg/m^2

b. Neutrophil Count Decreased

Hold treatment until recovery to at least Grade 1 for up to two weeks. If patient has not recovered to ≤ Grade 1 in two weeks, discontinue treatment. Follow drug specific modifications below for subsequent cycles.

Toxicity Grade	Modification: 5-FU	Irinotecan	Oxaliplatin
3-4	Maintain dose	1st occurrence: Reduce by 1 dose level	1st occurrence: Maintain dose
		2nd occurrence:	2nd occurrence:

	Maintain at current dose	Reduce by 1 dose level
	3rd occurrence: Discontinue treatment	3rd occurrence: Discontinue treatment

c. Platelet Count Decreased

Hold treatment until recovery to ≤ Grade 1 for up to two weeks. If patient has not recovered to ≤ Grade 1 in two weeks, discontinue treatment. Follow drug specific modifications below for subsequent cycles.

Toxicity Grade	Modification: 5-FU	Irinotecan	Oxaliplatin
3-4	1st occurrence: Reduce by 1 dose level	1st occurrence: Maintain dose	1st occurrence: Reduce by 1 dose level
	2nd occurrence: Reduce by 1 dose level	2nd occurrence: Reduce by 1 dose level	2nd occurrence: Maintain current dose
	3rd occurrence: Discontinue treatment	3rd occurrence: Discontinue treatment	3rd occurrence: Discontinue treatment

d. Non-hematologic toxicities*

All treatment related non-hematological toxicities (with the exception of hair loss) should resolve to Grade 1 prior to starting next cycle of therapy.

Toxicity Grade	Modification: 5-FU, Irinotecan, and Oxaliplatin
3	Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level.
4	Discontinue all protocol treatment

* For all other specific non-hematological toxicities, dose reduction is detailed below.

e. Diarrhea

Patients should be instructed in the use of loperamide (2 mg every 2 hours until diarrhea resolves for 12 hours; 4 mg q 4 hours at night is allowed) as treatment for diarrhea. Hold treatment if diarrhea > Grade 1 (without loperamide) at start of cycle. Patient should not be retreated with irinotecan until diarrhea has resolved to Grade 1, without loperamide, for at least 24 hours.

Toxicity Grade	Modification
2-4	1st occurrence: Reduce irinotecan by 1 dose level 2nd occurrence: Reduce oxaliplatin dose by 1 dose level and 5-FU dose by 1 dose level. 3rd occurrence: Discontinue all protocol treatment

f. Mucositis

Toxicity Grade	Modification	
	Oxaliplatin	5-FU
2	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.
3-4	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at same dose level.	Hold treatment. Check weekly. When resolves to ≤ Grade 1, continue at next lowest dose level.

g. Paresthesia or Peripheral Sensory Neuropathy – Dose modifications for oxaliplatin only

Toxicity Grade	Duration of Toxicity 1 – 7 days	> 7 days	Persistent between cycles
2	No dose modification	No dose modification	Next lowest dose level for oxaliplatin
3	Next lowest dose level for oxaliplatin	Next lowest dose level for oxaliplatin	Discontinue
Peripheral Sensory Neuropathy Grade 4	Discontinue	Discontinue	Discontinue

h. Hand-Foot Skin Reaction

Toxicity Grade	Modification:	5-FU
3-4		Reduce by 1 dose level

8.5 Dose Modifications for PEGPH20

a. Dose modifications

Drug	Initial dose	Dose Reduction Level 1
PEGPH20	3 mcg/kg on Day 1 only	1.6 mcg/kg on Day 1 only

* Only one dose reduction is allowed in Phase II. If 2nd dose reduction is needed, continue with other drugs.

b. Musculoskeletal

Toxicity Grade	Modification
2	Maintain current dose for first episode of Grade 2 musculoskeletal event that resolves to Grade 1 by the beginning of the next cycle (with or without dexamethasone, muscle relaxer, or additional pain medication). If Grade 2 musculoskeletal event is still present at beginning of next cycle reduce PEGPH20 by 1 dose level. For a second episode of Grade 2 requiring any dexamethasone, muscle relaxer, or additional pain medication, that resolves to Grade 1 by the beginning of next cycle reduce PEGPH20 by 1 dose level. If second episode of Grade 2 is still present at the beginning of next cycle then reduce PEGPH20 by 1 dose level or omit if no further dose reduction is possible. PEGPH20 can be dose escalated after Cycle 1 by one level if musculoskeletal event is Grade 1 or less with preceding dose.
3 or 4 that resolve to ≤ Grade 2 within 14 days	Hold treatment. If resolved to ≤ Grade 2 within 14 days, reduce by 1 dose level and resume treatment.
3 or 4 that persists and remains at > Grade 2 after 14 days	Discontinue treatment.

c. Thromboembolic events

Should a patient experience an arterial TE event (i.e. stroke; TIA; MI) or a Grade 4 venous TE event while on study, PEGPH20 treatment must be discontinued permanently. In a patient on low molecular weight heparin (LMWH) at baseline, a second TE event while on study will result in permanent discontinuation of PEGPH20 treatment.

d. Non-musculoskeletal

Toxicity Grade	Modification
3	Hold treatment. Treatment may resume at the same dose level if toxicity is resolved to baseline within 14 days. Dose may be reduced by one dose level at treating investigator's discretion.
4	Hold treatment. Treatment may resume at a reduced dose level if resolved to ≤ Grade 2 or baseline.

8.6 Dose Modifications for Pegfilgrastim or Filgrastim

Pegfilgrastim or filgrastim, including biosimilars, must be utilized per ASCO guidelines (http://jop.ascopubs.org/cgi/content/full/2/4/196) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professional/physician_gls/pdf/myeloid_growth.pdf).

8.7 Dose Modifications Contacts

For treatment or dose modification questions, please contact Dr. Ramanathan at 480/301-8000 or Dr. Philip at 313/576-8746.

8.8 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the SWOG Operations Office, the Study Chair, the NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Study Calendar Phase I

			Cycle 1		Cycle 2		Cycle 3		Cycle 4			
REQUIRED STUDIES	**Pre-study**	**D 1**	**48 hours post initial PEGPH20 dose**	**D 8**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 50 Σ**	**Off Treatment Pre-Progression Follow-Up Ω**	**Post-Progression Follow-Up %**
PHYSICAL Σ												
History and Physical Exam	X~				X		X		X		X	X
Weight and Performance Status	X				X		X		X		X	
Toxicity Notation		X		X	X		X		X		X	
LABORATORY Σ												
CBC, Differential, Platelets	X~				X		X		X			
Total Bilirubin	X~				X		X		X			
Serum Creatinine or Calculated Creatinine Clearance	X~				X		X		X			
AST/ALT	X~				X		X		X			
Alkaline phosphatase	X~				X		X		X			
Sodium, Potassium, Chloride, Glucose, BUN, CO2	X~				X		X		X			
INR	X~											
CA19-9	X~						X					
Serum Albumin	X~											
X-RAYS AND SCANS Σ												
CT/MRI for Disease Assessment	X									X	X	
SPECIMEN SUBMISSION												
Tissue block or slides (Required) α	X											
Blood specimen (Required) α	X		X		X		X					
TREATMENT Σ												
PEGPH20 β		X	X		X		X		X			
Irinotecan		X			X		X		X			
Oxaliplatin		X			X		X		X			
5-FU £		X			X		X		X			
Pegfilgrastim/Filgrastim ¥		X			X		X		X			

Click here for footnotes.

9.2 Study Calendar Phase II

REQUIRED STUDIES	Pre-study	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 Σ	Off Treatment Pre-Progression Follow-Up Ω	Post-Progression Follow-Up %
PHYSICAL Σ	X~							
History and Physical Exam	X		X	X	X	X	X	X
Weight and Performance Status	X		X	X	X	X	X	
Toxicity Notation			X	X	X	X	X	
LABORATORY Σ								
CBC, Differential, Platelets	X~		X	X	X	X		
Total Bilirubin	X~		X	X	X	X		
Serum Creatinine or Calculated Creatinine Clearance	X~		X	X	X	X		
AST/ALT	X~		X	X	X	X		
Alkaline phosphatase	X~		X	X	X	X		
Sodium, Potassium, Chloride, Glucose, CO2	X~		X	X	X	X		
INR	X~							
CA19-9	X~							
Serum Albumin	X~							
X-RAYS AND SCANS Σ								
CT/MRI for Disease Assessment	X					X	X	
SPECIMEN SUBMISSION								
Tissue block or slides (Required) α	X							
Blood specimen (Required) α	X	X§						
TREATMENT Σ								
Enoxaparin Ł		X	X	X	X	X		
PEGPH20 β		X	X	X	X	X		
Irinotecan		X	X	X	X	X		
Oxaliplatin		X	X	X	X	X		
5-FU £		X	X	X	X	X		
Pegfilgrastim/Filgrastim ¥		X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.
NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20upddate.pdf. **Click here for footnotes.**

Footnotes for Phase I and II:

Σ Protocol treatment and parameters will continue at these intervals until progression of disease or until patient has met any of the guidelines in Section 7.5.

Ω After off treatment prior to disease progression, scans for disease assessment and physical assessments (with lab tests performed at the discretion of the treating investigator) should take place every 8 weeks until progression.

% After off treatment following disease progression, physical assessments (with lab tests performed at the discretion of the treating investigator) should take place once every 3 months for three years from the time of registration.

α See Section 15.0 for more information.

β Infusion must be given one day prior to mFOLFIRINOX regimen for patients in Phase I or Phase II Arm 2.

£ Infusion to be given over 46-48 hours. See Section 7.3 and 7.4 for more information.

¥ Growth factor support to be given for Arm 1 on Day 3 (pegfilgrastim) or on Days 3-7 (filgrastim) and for Arm 2 on Day 4 (pegfilgrastim) or on Days 4-8 (filgrastim) per institutional guidelines. See Section 7.3 and Section 7.4.

~ Must be performed within 14 days prior to registration.

Ł For patients in Phase II Arm 2 only, enoxaparin must be given prior to initial dose of PEGPH20 and continued daily while on protocol treatment. See Section 7.4b.

§ Blood to be collected 48 hours post-initial PEGPH20 dose, see Section 15.1.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT MEASURABILITY OF LESIONS

This study will use the RECIST 1.1 guidelines. *(35)*

10.1 Measurability of Lesions

a. Measurable disease

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

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

10.6 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goals

This study will initially be open to limited institutions, with an expected accrual of 6-18 eligible and evaluable patients in the Phase I Portion of the trial. The Phase II Portion of the trial will be open to a larger group of limited institutions. Patients treated on the Phase I portion of the trial will not be included in the Phase II trial. We estimate the median survival of patients with newly diagnosed metastatic pancreatic adenocarcinoma treated with mFOLFIRINOX as 10 months in a cooperative group setting. In a Phase II randomized study, we expect the investigational arm to increase survival by at least 5 months (HR 1.5) to 15 months for results to be considered clinically worthwhile for a subsequent Phase III study. Based on these estimates, we will accrue 138 eligible patients (69 in each arm). The Phase II portion of the study will require approximately 2 years of accrual, 1.5 years of follow-up, type 1 error of 10%, and 80% power.

Assuming a 10% ineligibility rate, 7-20 patients will be accrued to yield 6-18 eligible patients for the Phase I portion of the trial and 152 patients will be accrued to yield 138 eligible patients for the Phase II portion of the trial. Based on **S0205** and **S0727** it is anticipated that accrual will be approximately 6 patients per month from SWOG. SWOG vigorously monitors accrual of ongoing studies. If the accrual rate to this study is less than 50% of projected after one year, consideration will be given to early closure. This decision would be made in conjunction with NCI staff.

11.2 Phase IB Run In

Section 7.3 provides the details of the study design for the Phase I Portion of the study. The Phase I Portion will be a limited dose-de-escalation. To be evaluable, patients must have received full PEGPH20 dose in Cycle 1.

The primary objective of the Phase I Portion will be to determine the MTD of PEGPH20 used in combination with mFOLFIRINOX in patients with newly diagnosed metastatic pancreatic adenocarcinoma. The regimen will be considered safe and the optimal dose determined if the dose-limiting toxicity rate is ≤ 17%. In the unlikely event of > 17% PEGPH20 toxicities at the end of the third and final dose level, the study will be placed on hold pending discussion of further dose de-escalation and a protocol amendment.

Prior to implementation of the Phase II Portion, a temporary closure will occur in order to assess dose and to evaluate the safety profile more fully.

11.3 Phase II Trial

The primary analysis of overall survival will be conducted in all eligible patients according to the intent-to-treat principle, using the logrank test. The final analysis will take place

upon the observation of approximately 110 deaths. An interim analysis will be performed when one-third of the events (approximately 37 deaths) have been observed (anticipated to occur when approximately 75% of accrual is reached). Evidence suggesting early termination would consist of rejection at a one-sided 0.07 level of the test for the alternative hypothesis (1.5 hazard ratio for overall survival).

Secondary endpoints include progression-free survival, response rate, and toxicity. With 69 eligible patients in each arm, progression-free survival at a particular timepoint, and rates of response and of specific toxicities can be estimated to within ± 12% with 95% confidence. Any toxicity occurring with at least a 5% probability is highly likely (> 95% chance) to be seen at least once.

Three interim analyses will be performed to monitor the incidence of thromboembolic (TE) events when approximately 40, 80 and 120 patients have completed 2 cycles of treatment. Sufficient evidence suggesting that the incidence of TE events in the experimental arm is greater than the rate in the control arm will be taken to be an observed odds ratio of 1.3 or greater for TE events by arm. If this outcome is observed, the study will be halted temporarily and evaluated by the independent Data and Safety Monitoring Committee (DSMC). This rule yields an approximate 30% chance of suspending the study under a true TE event rate of 25% in both arms, a 70% chance of stopping under true TE event rates of 25% in the control arm and 37.5% in the experimental arm, and 80% chance of stopping under true TE event rates of 30% in the control arm and 45% in the experimental arm.

The first of these three interim TE event analyses was performed in May 2016. Among the first 41 patients completing at least 2 cycles of treatment, we observed eight versus two thromboembolic events (Grade 2-5 occurring *any* cycle) in the PEGPH20 arm versus the control arm (OR=5.5, 95% CI 1.0-30.5). However, a higher than expected TE event incidence in the PEGPH20 arm had previously been recognized through ongoing data monitoring, and prophylactic administration of low molecular weight heparin (LMWH) (Enoxaparin) was instituted in February 2016. Thus, future interim analyses to monitor TE event incidence by treatment arm will be performed when approximately 40 and 80 patients *enrolled after February 2016* have completed 2 cycles of treatment.

A single safety interim analysis to compare toxicity rate across treatment arms will also be performed after at least 40 patients (20 in each arm) have completed their second treatment cycle. Toxicities included in this analysis are defined in Section 8.3. If we observe sufficient evidence to suggest that the incidence of toxicities in the experimental arm is 1.5 times higher than that in the control arm, the study will be halted temporarily and evaluated by the DSMC. Sufficient evidence will be taken to be an observed odds ratio of 1.4 or greater for toxicity events in the experimental compared to the control arm. The probability of suspending the trial according to this stopping rule under various true data scenarios was estimated from 5,000 Monte Carlo simulations per scenario. These probability estimates show that there is a 31% chance of suspending the study under a true toxicity event rate of 33% in both arms (null hypothesis), but that the study is likely to be suspended when the true toxicity event rate in the experimental arm is ≥ 1.5 times that in the control arm (for example, 73% chance under true toxicity event rates of 33% in control arm and 50% in experimental arm; 82% chance under true toxicity rates of 33% in control arm and 55% in experimental arm).

11.4 Translational Medicine

The planned accrual is 138 eligible patients to the Phase II portion of the clinical study. Previous SWOG pancreatic cancer trials, **S0205** and **S0727**, had specimen submission rates of 99% and 59%, respectively. Based on these trials, we expect at least 85% submission of archival tissue, which is approximately 120 samples for evaluation of HA immunohistochemistry. IHC will be converted to high (2+ or greater) versus low (0 or 1+). It is expected that in this population, approximately 70% of cases will fall into the 'high'

category. Survival is hypothesized to be better in those with low HA by IHC. With this sample size, there is low power to assess the prognostic value of IHC in the control group alone. For example, under the hypothesis that median survival is 10 months in the control population, if the HR between low and high IHC is 1.75 (corresponding to medians of approximately 8 and 14 months in the high and low groups respectfully), the power would only be 60% (based on a 10% type one error). It is of special interest to explore whether treatment with PEGPH20 selectively improves outcome in those with high HA. This corresponds to an interaction between IHC level and treatment effect. Under the alternative, if we assume that all of the treatment effect occurs in the high HA group (corresponding to median survival in the experimental arm of 16 months in the high, and 14 months in the low), this translates into approximately an interaction hazard ratio of 2, which can be detected with less than 50% power. Thus, these analyses will be highly exploratory in nature.

For the assessment of circulating HA levels, we anticipate that we will have more than 95% submission of blood samples for at least the baseline and 48 hour draws, with some drop off at later time periods. We will approach the analysis of these data in several ways. Initially, we will assess the distributions of these assays both at baseline, and between baseline and the 48 hour draw. An increase is HA is expected to reflect a successful target, but how it is influenced by the baseline value will need to be evaluated, and the variability of these measures is not well known. We will evaluate circulating levels as potential prognostic or predictive values for overall and progression-free survival using Cox regression. As with the discussions related to IHC, it is anticipated that power may be poor and that these analyses will be exploratory.

CA19-9 levels will be measured pre-study and every 4 weeks during the study. Percentage decrease in CA19-9 levels from baseline and time to maximum decrease in CA19-9 will be examined in descriptive analyses. Decrease in CA 19-9 levels will be defined as high (≥ 50% decrease) versus low (< 50% decrease). It is expected that approximately 75% of cases will fall into the 'high' category. Survival and response rates are hypothesized to be better in patients with high percentage decrease in CA19-9 levels. With this small sample size, there is low statistical power to assess the prognostic value of CA19-9 in the control group alone. For example, under the hypothesis that median survival is 10 months in the control population, if the HR between high and low change in CA19-9 is 1.5 (corresponding to medians of approximately 11 and 7 months in the high and low groups respectively), the power would only be 55% (based on a 10% type one error). Thus, these analyses will be exploratory in nature.

11.5 Data and Safety Monitoring

The Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

In addition to the above DSMC review, toxicity and accrual monitoring are done routinely by the Study Chair; study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Serious Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than one working day prior to planned start of treatment).

13.2 Slot Reservation (Phase I)

Patients planning to enroll on this study must first have a slot reserved in advance of the registration, even if the site plans to enroll right away.

All site staff will use OPEN to create a slot reservation. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench. Please refer to the 'Slot Reservation Quick Reference Site User Guide' within the OPEN tab on the CTSU members' website under 'Training and Demonstration Materials' for detailed instructions.

The individual making the slot reservation for the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Patient Initials

e. Patient's Date of Birth

f. ZIP Code

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

Slot reservations expire within 7 calendar days. A warning email will be sent 48 hours before the expiration date. The reservation can be renewed any time before it expires as long as at least 1 slot is still available. After it expires, you must create a new slot reservation for this patient before you can enroll to this trial. You may also withdraw your reservation at any time.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access

OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

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

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

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

i. Country of Residence

j. ZIP Code

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

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

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

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

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

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

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.
2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email

c. technicalquestion@crab.org.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1313 Onstudy Form

Baseline Tumor Assessment Form

Pathology Report documenting metastatic disease

Radiology reports from all scans performed to assess disease at baseline.

b. WITHIN 28 DAYS OF REGISTRATION:

Specimens as outlined in Section 15.0.

c. FOR PHASE I PATIENTS ONLY: AT THE END OF EACH WEEK OF CYCLE 1 TREATMENT ONLY (See Section 14.4d for remaining cycles.):

Submit the **S1313** Adverse Event Form

d. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT:

Submit the following:

S1313 Treatment Form

S1313 Adverse Event Form

e. WITHIN 14 DAYS AFTER EACH CA19-9 TEST (every 4 weeks):

Record the CA 19-9 lab results on the **S1313** CA19-9 Form and submit.

f. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (every 8 weeks) UNTIL PROGRESSION:

Submit the following:

Follow Up Tumor Assessment Form documenting results of assessment

Radiology reports from all scans used to assess disease

g. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1313 Treatment Form

S1313 Adverse Event Form

h. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following

Follow Up Tumor Assessment Form

Radiology reports from all scans used to assess disease

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

i. AFTER OFF TREATMENT, EVERY 3 MONTHS FOR 3 YEARS FROM REGISTRATION

Submit the following:

Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reporting)

j. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and a final S1313** Treatment Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Correlative Studies and Banking

a. Specimens must be submitted at the following times (see Section 9.0):

1. All patients at baseline: Minimum of 5-10mm^3 paraffin embedded tissue (FFPE) (If block is not available, ten unstained, freshly cut 5 micron tissue positively charged slides must be submitted.) with pathology report from diagnosis of metastatic disease. If multiple biopsies from different anatomical locations are available from most recent biopsy, it is preferred that tissue from primary site (1st choice), liver metastasis (2nd choice), or lung metastasis (3rd choice) be sent. The biopsy must contain pancreatic adenocarcinoma.

2. Patients in Phase I or Arm 2 (FOLFIRINOX+PEGPH20) of Phase II only: 10 mL whole blood in two 5 mL lavender top (K3EDTA) tubes at baseline, 48 hours after the first PEGPH20 dose, prior to Cycle 2, and prior to Cycle 3. Blood samples must be centrifuged and plasma separated (into four chilled 1.8 mL cryovials) prior to storage or shipping. Plasma samples must be frozen at -20°C or below after preparation and can be batch shipped on dry ice.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

15.2 Phase I Portion: Mandatory Conference Calls

A mandatory conference call will take place every week. The call will update participants on the current status of the trial and will include representatives from the study team, investigators from all participating institutions and representatives from Halozyme. At this time any serious toxicities encountered will be discussed and appropriate action taken. In between these regularly scheduled conference calls, investigators will be informed of important study decisions via e-mail.

Institutional participation on these calls requires the identification of an investigator contact and a CRA contact. Prior to registration of the first patient, each institution must provide the contact names, e-mail addresses, and phone numbers to the SWOG Operations Office. Institutions will be responsible for keeping this information up-to-date and must notify the study Protocol Coordinator (Kimberly Kaberle, e-mail: kkaberle@swog.org or phone: 210/614-8808) of any changes. The investigator and the contact CRA will receive e-mail reminders with the conference call information.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner

to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808, or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in the Phase I portion of the study and in Arm 2 of the Phase II portion of this study is PEGPH20. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Patients on the Phase I Portion and Early Phase II Portion, Arm 1: Expedited Reporting Requirements for Adverse events that Occur on Studies under an Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a non-CTEP-IND:**

1. **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2. The adverse events listed below also require expedited monitoring for this trial:

- Thromboembolic events, any Grade regardless of attribution

g. **Expedited reporting for <u>commercial</u> agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used in both arms of this study are 5-FU, filgrastim, irinotecan, oxaliplatin, and pegfilgrastim. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on Phase II portion, study Arm 1 who have received the commercial drug(s) listed in 16.1g above within 30 days of the last administration of the commercial agent(s).

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known,

accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm,

17.0 BIBLIOGRAPHY

1 Páez D, Labonte MJ, Lenz HJ. Pancreatic cancer: medical management (novel chemotherapeutics). Gastroenterol Clin North Am 1:189-209; 2012.

2 Hidalgo M. Pancreatic cancer. The New England Journal of Medicine 362(17):1605-17, 2010.

3 Burris HA, 3rd, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. Journal of Clinical Oncology 15(6):2403-2413, 1997.

4 Páez D, Labonte MJ, Lenz HJ. Pancreatic cancer: medical management (novel chemotherapeutics). Gastroenterol Clin North Am 1:189-209; 2012.

5 Hidalgo M. Pancreatic cancer. The New England Journal of Medicine 362(17):1605-17, 2010.

6 Von Hoff DD, Ervin TJ, Arena FP, et al. Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). J Clin Oncol 30:(suppl 34: abstr LBA148), 2012.

7 Conroy T, Desseigne F, Ychou M et al. PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-25; 2011.

8 Conroy T, Desseigne F, Ychou M et al. PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-25; 2011.

9 Lowery MA, Yu KH, Adel NG et al, Activity of front-line FOLFIRINOX (FFX) in stage III/IV pancreatic adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC) A4057. ASCO 2012.

10 Jiang P, Li X, Thompson CB, Huang Z et al. Effective targeting of the tumor microenvironment for cancer therapy. Anticancer Res 32:1203-12; 2012.

11 Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21:418-29: 2012.

12 Jacobetz MA, Chan DS, Neesse A, Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut 62(1): 112-20, 2013.

13 Tredan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. Journal of the National Cancer Institute 99(19):1441-54, 2007.

14 Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21:418-29: 2012.

15 Jacobetz MA, Chan DS, Neesse A, Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut 62(1): 112-20, 2013.

16 Whatcott CJ, Han H, Posner RG, et al. Targeting the tumor microenvironment in cancer: why hyaluronidase deserves a second look. Cancer Discovery 1:291e6; 2011.

17 Toole BP. Hyaluronan: from extracellular glue to pericellular cue. Nature Reviews Cancer 4(7): 528-39, 2004.

18 Borad MJ, Ramanathan RK, Bessudoet A al. Targeting hyaluronan (HA) in tumor stroma: A phase I study to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of pegylated hyaluronidase (PEGPH20) in patients with solid tumors. A2579 ASCO 2012.

19 Von Hoff DD, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. Journal of Clinical Oncology 29(34): 4548-54, 2011.

20 Hidalgo M. Pancreatic cancer. The New England Journal of Medicine 362(17):1605-17, 2010.

21 Burris HA, 3rd, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. Journal of Clinical Oncology 15(6):2403-2413, 1997.

22 Von Hoff DD, Ervin TJ, Arena FP, et al. Randomized phase III study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). J Clin Oncol 30:(suppl 34: abstr LBA148), 2012.

23 Conroy T, Desseigne F, Ychou M et al. PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-25; 2011.

24 Mahadevan D, Von Hoff DD. Tumor-stroma interactions in pancreatic ductal adenocarcinoma. Molecular Cancer Therapeutics 6(4): 1186-97, 2007.

25 Lowery MA, Yu KH, Adel NG et al, Activity of front-line FOLFIRINOX (FFX) in stage III/IV pancreatic adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC) A4057. ASCO 2012.

26 Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21:418-29: 2012.

27 Whatcott CJ, Han H, Posner RG, et al. Targeting the tumor microenvironment in cancer: why hyaluronidase deserves a second look. Cancer Discovery 1:291e6; 2011.

28 Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21:418-29: 2012.

29 Jacobetz MA, Chan DS, Neesse A, Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. Gut 62(1): 112-20, 2013.

30 Whatcott CJ, Han H, Posner RG, et al. Targeting the tumor microenvironment in cancer: why hyaluronidase deserves a second look. Cancer Discovery 1:291e6; 2011.

31 Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21:418-29: 2012.

32 Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21:418-29: 2012.

33 Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med. 2012;9(7):e1001275.

34 Epstein AS, O'Reilly, EM. Exocrine pancreas cancer and thromboembolic events: A systematic literature review. J Natl Compr Canc Netw. 2012 Jul 1;10(7):835-46.

35 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.

18.0 APPENDIX

18.1 Translational Medicine Studies

18.1 Translational Medicine Studies

a. Background

Until very recently, the uniformly accepted standard of care for pancreatic ductal adenocarcinoma (PDA) was single agent gemcitabine, which provided modest object response rates (7-10%) and similarly modest improvements in both median and one-year survival. *(1,2)* Recently, two regimens have suggested that different outcomes may be possible. In a Phase II study, patients with Stage IV disease received a combination of gemcitabine plus nab-paclitaxel, an albumin-coated nanoparticle, resulting in a median survival of 12.2 months (historical norm for gemcitabine monotherapy is approximately 6 months). *(3)* More recently, a Phase III trial of the multi-drug regimen, FOLFIRINOX, conferred a median survival of 11.1 months compared with 6.8 months for single agent gemcitabine ($p<0.0001$). *(4)* Interestingly, these two regimens share one notable feature: sustained exposure of the tumor to circulating drug concentrations which can help overcome the pronounced interstitial fluid pressures that oppose drug penetration (see below). This study proposes a strategy to overcome these barriers and extend the efficacy observed with FOLFIRINOX.

An emerging concept in pancreatic cancer pathophysiology is the extent to which the associated robust desmoplastic reaction erects physical barriers to systemic therapies. These barriers limit the ability to achieve therapeutic drug concentrations and serve as primary and underappreciated mechanisms of drug resistance. Detailed analyses of the tumor microenvironment in PDA are revealing an unusually complex cellular and extracellular matrix composition that includes stromal fibroblasts; various classes of immunosuppressive cells; and a dense network of glycosaminoglycans (GAG), proteoglycans, and proteins that collectively conspire to create a drug-free and immune privileged sanctuary for the disease. (5) One especially abundant GAG, hyaluronan or hyaluronic acid (HA), is the primary determinant of inordinately high interstitial fluid pressure (IFP) that rivals mean arterial pressure and causes widespread vascular collapse. (6) HA is a large linear polymer composed of alternating units of N-acetyl glucosamine and glucuronic acid units with viscoelastic properties that contribute to the architecture and malleability of tissues, particularly during dynamic processes such as embryogenesis and oncogenesis. (7,8) The viscoelastic properties of HA underlie its role in clinical and cosmetic applications. In PDA, HA functions as a hydrogel, trapping and retaining water, which both serves to elevate IFP and further retard drug perfusion by inhibiting convection. (9) The investigators have recently defined a strategy in their Murine Clinical Trials Program (MCTP) to overcome these prohibitive IFPs in PDA and restore both diffusive and convective components of drug delivery. (10) Systemic administration of a chemically modified form of recombinant hyaluronidase (PEGPH20) normalizes IFP and mobilizes intratumoral fluid permitting chemotherapies to freely penetrate the tumor bed. Phase I studies with single agent PEGPH20 have already established that it is well-tolerated and appears to have similar effects on tissue perfusion as observed in the genetically engineered mouse studies. *(11)* A Phase III randomized trial is currently underway comparing the control arm of nab-paclitaxel/gemcitabine to the same regimen + PEGPH20 in patients with advanced pancreatic cancer. (Halo-301, NCT02715804). This study is sponsored by Halozyme Therapeutics and is a registration study. Eligibility requires tumor samples to have high HA content. Halozyme has partnered with Roche-Ventana systems and a CLIA-certified companion assay (Ventana HA CDx) is used to prospectively identify HA-High patients for inclusion in the study.

mFOLFIRINOX (modified or dose-reduced FOLFIRINOX) is now a standard regimen for advanced PDA and the investigators hypothesize that the combination with PEGPH20 will substantially improve overall survival. Testing this hypothesis in the Phase II portion of the trial, the investigators will perform correlative studies to determine: 1) if intratumoral HA content can serves as a useful prognostic and predictive marker; and 2) whether circulating levels of HA metabolites during the course of treatment can serve to demonstrate target degradation and whether this can also predict survival benefit.

b. **Experimental Approach and Analysis**

Intratumoral HA content: Formalin-fixed, paraffin-embedded (FFPE) material from tissue biopsies at time of diagnosis will be recovered and archived in a central repository. It is anticipated that most these specimens will represent core biopsies from liver lesions with a minority of samples from the primary pancreatic tumor. Affinity-histochemical studies will be performed for HA content to determine its prognostic value. These assays will be performed independently by Ventana Medical Systems using the Ventana HA CDx assay.

Circulating HA levels: All patients will have serum HA levels assessed at baseline, 48 hours after PEGPH20 dosing, then at 2 and 4 weeks into study. An additional blood sample will be drawn at time of disease progression if possible. In Phase I studies, peak concentration of circulating HA catabolites occurred at approximately 48 hours. A dissacharide assay is used to measure catabolites. Control levels in patients are less than 1 mcg/ml and peak circulating concentrations in patients receiving the expected study dose ranged from 10 – 50 mcg/ml. In preclinical studies, peak circulating HA concentrations appear to reflect baseline intratumoral HA content and also successful target ablation.

Additional assays: Additional assays will be done on archived material, contingent upon acquiring additional funding support. The Hingorani laboratory has extensive experience with assays of HA and other markers in pancreatic cancer. *(12)* These studies would include immunohistochemical (IHC) and/or immunofluorescence (IF) analyses of degree of apoptosis in stromal and epithelial compartments (dual IF for cleaved caspase 3 (CC3) and αSMA or CK19, respectively); proliferation in each compartment (using Ki-67, for example, in similar dual IF assays); and vascular content and morphology (CD34). Once the study required assays are done, the investigators will evaluate remaining specimens and, in collaboration with Dr. Hingorani, apply for additional funding.

c. **Statistical Plan**

Due to early study closure, the investigators expect to have approximately 100 samples for evaluation of HA affinity-immunohistochemistry. IHC will be converted to high (2+ or greater) versus low (0 or 1+). It is expected that in this population, approximately 40% of cases will fall into the 'high' category. Survival is hypothesized to be better in those receiving PEGPH20 and with high HA by IHC. With this sample size, there is sufficient power to detect a strong prognostic effect of IHC in the control group alone: under the hypothesis that median survival is 10 months in the control population, if the HR between low and high IHC is 1.75 (corresponding to medians of approximately 7 and 12 months in the high and low groups respectfully), the power would be 70% (based on a 1-sided 10% type one error). It is of special interest to explore whether treatment with PEGPH20 selectively improves outcome in those with high HA. This corresponds to an interaction between IHC level and treatment effect. Under the alternative, if it is assumed that all of the treatment effect occurs in the high HA group (corresponding to median survival in the experimental arm of 21 months in the

high, and 12 months in the low), this translates into approximately an interaction hazard ratio of 3, which can be detected with 86% power.

For the assessment of circulating HA levels, it is anticipated that more than 95% of blood samples will be submitted for at least the baseline and 48 hour draws, with some drop off at later time periods. The investigators will approach the analysis of these data in several ways. Initially, the distributions of these assays will be assessed both at baseline, and between baseline and the 48 hour draw. An increase in HA is expected to reflect a successful target, but how it is influenced by the baseline value will need to be evaluated, and the variability of these measures is not well known. Circulating levels will be evaluated for potential prognostic or predictive values using Cox regression.

d. **Procedures**

Paraffin Embedded Tissue (FFPE)

All study sites will be requested to obtain baseline tumor blocks if available, or at least 5 unstained, consecutive tissue sections cut at 4-5 microns on positively charged slides.

Please review Section 15.1 for specimen submission procedures.

The SWOG Repository will ship baseline tissue specimens for HA testing to:

Ventana Medical Systems, Inc
CDx Pharma Service CAP/CLIA Laboratory
1910 E Innovation Dr
Tucson, AZ 85755
Crystal Robles (520-229-4685, crystal.robles@roche.com)

Blood Samples

Four 1 mL samples of blood drawn at pre-study, 48 hours after PEGPH20 dosing, and at 2 and 4 weeks after beginning treatment is required (4 serial samples). An additional blood sample will be obtained at time of disease progression if possible.

Please review Section 15.1 for specimen processing and submission procedures.

The SWOG Repository will ship blood/plasma specimens for HA testing to:

MicroConstants, Inc.
9050 Camino Santa Fe
San Diego, CA 92121
Katie Jeltema, Project Manager, 858-652-4600 ext. 4618,
KJeltema@MicroConstants.com

e. **VENTANA HA RxDx**

The VENTANA HA RxDx Assay is intended for the histochemical assessment of hyaluronan (HA) in formalin fixed, paraffin embedded (FFPE) tissue comprising of pancreatic ductal adenocarcinoma stained on a BenchMark ULTRA automated staining instrument. Specimens have already been collected during the SWOG **S1313** study.

Pathologists at Ventana agreed on a method of scoring hyaluronan content in PDA tissue specimens via evaluation of the percentage of hyaluronan staining of the extracellular matrix (at any staining intensity above background) throughout the entire tumor surface. The resulting hyaluronan score is the percent of the VENTANA HA RxDx Assay stained tumor extracellular matrix compared to the total tumor surface. The scoring algorithm for the VENTANA HA has been verified through Ventana's intra- and inter-reader precision studies. As the scoring yields HA as a continuous variable a cut-off to distinguish hyaluronan High and Low content and its potential ability to be used as a predictive biomarker was confirmed in the analysis of samples collected from HALO-109-202 stage 2 ("validation set") and is currently also used in the patient selection for the Phase 3 clinical study (HALO-109-301) in pancreatic cancer. In addition, on March 9, 2016 the FDA approved an IDE for the VENTANA RxDx for the use in Halozyme's Phase III study (Approval No G160029).

1. Analytical Performance

The VENTANA HA RxDx assay will be performed in one central lab in a retrospective fashion.

Normal skin and normal liver slides containing HA positive and negative elements, are stained with VENTANA HA RxDx Assay to serve as system-level controls. In addition, individual patient samples will be treated with hyaluronidase and serve as intra-patient negative control.

Pathologists at Ventana agreed on a method of scoring hyaluronan content in PDA tissue specimens via evaluation of the percentage of hyaluronan staining of the extracellular matrix (at any staining intensity above background) throughout the entire tumor surface. The resulting hyaluronan score is the percent of the VENTANA HA RxDx Assay stained tumor extracellular matrix compared to the total tumor surface. As the scoring yields HA as a continuous variable a cut-off to distinguish hyaluronan High and Low content and its potential ability to be used as a predictive biomarker was confirmed in the analysis of samples collected from HALO-109-202 stage 2 ("validation set") and is currently also used in the patient selection for the Phase 3 clinical study (HALO-109-301) in pancreatic cancer. In addition, on March 9, 2016 the FDA approved an IDE for the VENTANA RxDx for the use in Halozyme's Phase 3 study (Approval No G160029). As part of the IDE submission the technical validation included the following assays.

All assays passed the acceptance requirements.

- Accelerated Stability Assessment of VENTANA HA RxDx Assay
- Reactivity Assessment of VENTANA HA RxDx Assay Binding in Normal and Neoplastic Tissues
- Intra-day Repeatability and Inter-day Intermediate Precision of VENTANA HA RxDx Assay on PDA
- Cut Slide Stability of VENTANA HA RxDx Assay on Pancreatic Ductal Adenocarcinoma
- Cut Slide Stability of VENTANA HA RxDx Assay on System Level Control Slides
- Intermediate Precision (Inter-HA Lot, Inter-Detection Kit Lot, and Intra-Platform) of VENTANA HA RxDx Assay Staining in PDA
- Reader Precision (Inter-Reader Repeatability) Study for VENTANA HA RxDx Assay in Pancreatic Ductal Adenocarcinoma

- Tissue Thickness Verification of VENTANA HA RxDx Assay Staining in Pancreatic Ductal Carcinoma (PDA)
- Tissue Thickness Verification of VENTANA HA RxDx Assay Staining on System Level Control Tissues (Normal Liver and Skin)
- Intermediate Precision (Inter-HA Lot, Inter-Detection Kit Lot, and Intra-Platform) of VENTANA HA RxDx Assay Staining in System Level Control Tissue
- VENTANA HA RxDx Assay Staining Repeatability (Intra-day) and Intermediate Precision (Inter-day) Verification in System-Level Tissue Controls (Normal Skin and Normal Liver)

2. Clinical Utility

The assay is exploratory and neither integrated nor integral. HA is a large linear polymer composed of alternating units of N-acetyl glucosamine and glucuronic acid units with viscoelastic properties that contribute to the architecture and malleability of tissues, particularly during dynamic process such as embryogenesis and oncogenesis. The viscoelastic properties of HA underlie its role in clinical and cosmetic applications. In PDA, HA functions as a hydrogel, trapping and retaining water, which both serves to elevate IFP and further retards drug perfusion by inhibiting convection. We (Hingorani Lab) have recently defined a strategy in our Murine Clinical Trials Program (MCTP) to overcome these prohibitive IFPs in PDA and restore both diffusive and convective components of drug delivery. Systemic administration of a chemically modified form of recombinant hyaluronidase (PEGPH20) normalizes IFP and mobilizes intratumoral fluid permitting chemotherapies to freely penetrate the tumor bed. Phase 1 studies with single agent PEGPH20 have already established that it is well-tolerated and appears to have similar effects on tissue perfusion as observed in the genetically engineered mouse studies ([13]).

An appropriate scoring method for the VENTANA HA RxDx Assay Assay based on clinical outcome data was developed using a set of tissue samples from patients previously enrolled in stage 1 (“training set”) of the Halozyme-sponsored Phase 2 clinical trial (HALO-109-202). A cut-off to distinguish hyaluronan High and Low content and its potential ability to be used as a predictive biomarker was confirmed in the analysis of samples collected from HALO-109-202 stage 2 (“validation set”). 279 pts were randomized; 231 are evaluable for efficacy. In study HALO-109-202 of 246 pts with HA data, 84 (34%) were HA-High. As of December 16, 2016, the primary PFS endpoint was statistically significant for PAG vs AG (HR 0.73, 95% CI 0.53-1.00; p=0.048). PFS in HA-High pts was also statistically significant in the PAG vs AG arm (HR 0.51; 95% CI 0.26-1.00; p=0.048). ORR in HA-High pts was 46% (PAG) vs 34% (AG). Overall survival in HA-High pts (exploratory) was 11.5 months (mo) (PAG) and 8.5 mo (AG) (HR 0.96, 95% CI 0.57-1.61). TE events were similar (PAG 14% vs AG 10%) following enoxaparin initiation. Randomized Phase II study met both primary endpoints (PFS and TE event rate), with the largest improvement in the secondary endpoint of PFS in HA-High pts. These data support HA as a potential predictive biomarker for patient selection of PEGPH20 in pancreatic cancer such as in the ongoing global Phase 3 HALO 301 study or SWOG S1313.

Thus the preclinical studies and preliminary results of the Halo-201 study support further evaluation of HA assays in **S1313**.

3. Expected Distribution of Biomarker in Study Population

The VENTANA HA RxDx assay will be performed in one central lab in a retrospective fashion to assess any potential correlation of HA status with outcome in study SWOG S1313. Based on data of the HALO-109-202 study approximately 30-40% of the patients are expected to be HA High.

4. Cutpoints to be Used in Analysis

This analysis is exploratory and little data are available.

S1313 expects at least 85% submission of archival tissue, thus approximately 100 samples are available for evaluation of HA affinity-immunohistochemistry. IHC will be converted to high (2+ or greater) versus low (0 or 1+). It is expected that in this population, approximately 40% of cases will fall into the 'high' category. Survival is hypothesized to be better in those receiving PEGPH20 and with high HA by IHC. With this sample size, there is sufficient power to detect a strong prognostic effect of IHC in the control group alone: under the hypothesis that median survival is 10 months in the control population.

5. Access to Assay Results

Individual reports will not be given to treating physician or patients. The study is closed to accrual and most patients are expected to be off protocol therapy soon

18.1 Bibliography

1 Burris HA, 3rd, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 15(6):2403-2413, 1997.

2 Hidalgo M. Pancreatic cancer. The New England journal of medicine 362(17):1605-1617, 2010.

3 Von Hoff DD, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29(34):4548-4554, 2011.

4 Conroy T, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. The New England journal of medicine 364(19):1817-1825, 2011.

5 Mahadevan D & Von Hoff DD Tumor-stroma interactions in pancreatic ductal adenocarcinoma. Molecular cancer therapeutics 6(4):1186-1197, 2007.

6 Provenzano PP, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer cell 21(3):418-429, 2012.

7 Toole BP. Hyaluronan: from extracellular glue to pericellular cue. Nature reviews. Cancer 4(7):528-539, 2004.

8 Whatcott CJ, Han H, Posner RG, Hostetter G, & Von Hoff DD. Targeting the tumor microenvironment in cancer: why hyaluronidase deserves a second look. Cancer discovery 1(4):291-296, 2011.

9 Tredan O, Galmarini CM, Patel K, & Tannock IF. Drug resistance and the solid tumor microenvironment. Journal of the National Cancer Institute 99(19):1441-1454, 2007.

10 Provenzano PP, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer cell 21(3):418-429, 2012.

11 Ramanathan RK, et al. Abstract #A2579, ACSO, 2012.

12 Provenzano PP, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer cell 21(3):418-429, 2012.

13 Borad MJ, Ramanathan RK et al., Abstract #A2579, ASCO 2012

Informed Consent Model for **S1313**

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	60.5 (targeted above 55)
Flesch-Kincaid Grade Level	8.7 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Study Title for Study Participants: Testing the addition of pegylated recombinant human hyaluronidase (PEGPH20) to usual chemotherapy in metastatic pancreatic cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: S1313, "A Phase IB/II Randomized Study of Modified FOLFIRINOX + Pegylated Recombinant Human Hyaluronidase (PEGPH20) versus Modified FOLFIRINOX Alone in Patients with Good Performance Status Metastatic Pancreatic Adenocarcinoma"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

What is the usual approach to my metastatic pancreatic cancer?

You are being asked to take part in this study because you have metastatic pancreatic cancer. People who are not in a study are usually treated with a combination of chemotherapy drugs. Drugs such as gemcitabine are used alone or in combination with other agents. In this study, a combination of 5-fluorouracil (5-FU), oxaliplatin, irinotecan, and leucovorin is used, commonly called the mFOLFIRINOX regimen. Please note the modified FOLFIRINOX regimen differs from the FOLFIRINOX regimen that was reported (in the 2011 *New England Journal of Medicine*) to improve the survival of patients with pancreatic cancer. *(1/20/14)* The modification was made to possibly reduce side effects of this regimen. Filgrastim or pegfilgrastim are given with the mFOLFIRINOX regimen to increase the white blood cell count. This helps to lower your risk of getting infections. *(sentence added 1/20/14)*

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

If you decide not to take part in this study, you have other choices. For example:

- **you may choose to have the usual approach described above**
- **you may choose to take part in a different study, if one is available**
- **or you could decide not to be treated for cancer, but you may want to receive comfort care to relieve symptoms.**
- **Comfort care, also called palliative care, helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**

Why is this study being done?

The purpose of this study is to compare the safety and test the good and bad effects of the study drug pegylated recombinant human hyaluronidase (PEGPH20) with combination chemotherapy. In this study, you will receive the usual combination chemotherapy called mFOLFIRINOX with or without PEGPH20. Other studies have shown the PEGPH20 can damage the outer layer of a tumor which can let more chemotherapy reach the tumor and possibly increase effectiveness. PEGPH20 is an investigational agent in this study. There will be about 172 people taking part in this study (7-20 in Part I and 152 in Part II).

What are the study groups?

This study will be conducted in 2 parts. Patients will take part in either Part I or Part II, not both.

Part I of the study is being done to test the safety of giving all of these drugs together. The first few patients will get a higher dose of PEGPH20. If the side effects are too great, the next few patients will get a reduced dose. The dose will reduce every few patients until we find the most appropriate dose for the combination.

All patients in Part I will receive mFOLFIRINOX, filgrastim or pegfilgrastim, and PEGPH20. mFOLFIRINOX and PEGPH20 will be given into a vein.*(1/20/14)* Filgrastim or pegfilgrastim will be given as a shot under the skin. *(sentence added 1/20/14)* Each two week period is called a "cycle". For every cycle, you will receive PEGPH20 on the first day. The next day you will receive oxaliplatin over a 2 hour period, then leucovorin and irinotecan over a 2 hour period, then 5-FU spread out over a 46-hour period, then 4 days of filgrastim or 1 dose of pegfilgrastim after 5-FU is discontinued. You will receive daily enoxaparin (or similar low molecular weight heparin) to reduce the risk of blood clots. *(updated 1/20/14)*

The 46-hour 5-FU infusion will require placement of a special central venous catheter. This will be a tube placed into a large vein in your chest. This tube can be of two basic types: (1) It can come out through your skin or (2) be attached to a small chamber with all of the device under your skin. In most patients, these can be placed under local anesthesia in an operating room and can remain indefinitely. However, you may need to be in the hospital for one day to have the catheter put in. Blood samples can be taken from the catheter so you may not have to be stuck with a needle. The placement of this catheter carries a small risk of infection, bleeding and penetration of your lung. The risk of infection and bleeding may be reduced by the strict attention to the care of the catheter. Your doctor will teacher you how to care for the catheter. The catheter may be removed easily at any time that it is no longer necessary.

Once safety of the combination has been established in Part I, this part of the study will end and the second part will start.

Patients in Part II will be put into one of two groups. Group 1 will receive the same treatment, exams, and scans that is described above except you will only get mFOLFIRINOX and filgrastim or pegfilgrastim, without PEGPH20. Group 2 will receive the exact same treatment that is given in Part I.

A computer will randomly put you in a study group. This is done because no one knows if one study group is better, the same, or worse than the other group. Once you are put in one group, you cannot switch to the other group. Neither you nor your doctor can choose which group you will be in.

How long will I be in this study?

You will receive the study drugs as long as your disease does not get worse and the side effects are not too severe. After you finish the study drugs, your doctor will continue to watch you for side effects and follow your condition for up to three years.

What extra tests and procedures will I have if I take part in this study?

(section updated 1/20/14)
Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer.

Small pieces of cancer tissue removed by a previous surgery or biopsy and a blood sample will be taken for the study before you begin the study. Additional blood samples will be taken at 48 hours, 2 weeks and 4 weeks into the study. These samples are required in order for you to take part in this study because the research on the samples is an important part of the study. Researchers will be looking at the samples to see if a tumor marker, CA19-9, for pancreatic cancer decreases during treatment.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the samples that will be used for this study. You and your study doctor will not receive the results of any tests done on your samples.

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

If you choose to take part in this study, there is a risk that you may:

- **Lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **Be asked sensitive or private questions which you normally do not discuss**

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**

- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

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

Possible side effects of mFOLFIRINOX (all patients in Part I and Part II): *(section updated 7/8/14)*

COMMON, SOME MAY BE SERIOUS In 100 people receiving mFOLFIRINOX (Leucovorin, 5-Fluorouracil, Irinotecan, and Oxaliplatin), more than 20 and up to 100 may have:
• **Severe diarrhea** • **Constipation, nausea, vomiting, diarrhea** • **Weakness** • **Infection, especially when white blood cell count is low** • **Hair loss** • **Loss of appetite, weight loss** • **Anemia which may require a blood transfusion** • **Fever, pain** • **Dizziness, tiredness** • **Cough, shortness of breath** • **Rash, increased risk of sunburn, itching** • **Bruising, bleeding** • **Sores in mouth which may cause difficulty swallowing** • **Redness, pain or peeling of palms and soles** • **Numbness and tingling of the arms and legs** • **Feeling of "pins and needles" in arms and legs** • **Heartburn** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving mFOLFIRINOX (Leucovorin, 5-Fluorouracil, Irinotecan, and Oxaliplatin), from 4 to 20 may have:

- **A tear or hole in internal organs that may require surgery**
- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**
- **Blood clot which may cause swelling, pain, shortness of breath**
- **Scarring of the lungs**
- **Chest pain**
- **Abnormal heartbeat which may cause fainting**
- **Hoarseness**
- **Abnormal eye movement, watering eyes, discomfort from light, blurred vision with chance of blindness**
- **Swelling and redness of the eye**
- **Problem with eyelid**
- **Hearing loss**
- **Dry eye, mouth, skin**
- **Fluid in the belly**
- **Difficulty walking, opening mouth, talking, with balance and hearing, smelling, eating, sleeping, emptying the bladder**
- **Swelling of the body which may cause shortness of breath**
- **Blockage of the airway which may cause shortness of breath, cough, wheezing**
- **Bleeding from multiple sites including vaginal bleeding, bleeding of the testis, or bleeding of the brain**
- **Internal bleeding which may cause black tarry stool, blood in vomit or urine, or coughing up blood**
- **Damage to organs which may cause shortness of breath**
- **Chills**
- **Swelling and redness at the site of the medication injection**
- **Liver damage which may cause yellowing of eyes and skin**
- **Kidney damage which may require dialysis**
- **Weight gain, dehydration, passing gas**
- **Changes in taste, voice**
- **Stroke which may cause paralysis, weakness**
- **Inability to move shoulder or turn head**
- **Muscle weakness**
- **Seizure**
- **Worry, confusion, depression**
- **Increased urination**
- **Stuffy nose, hiccups, sinus problems**
- **Increased sweating, flushing, hot flashes**
- **High blood pressure**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving mFOLFIRINOX (Leucovorin, 5-Fluorouracil, Irinotecan, and Oxaliplatin), from 4 to 20 may have:
• **Low blood pressure which may cause feeling faint**
RARE, AND SERIOUS **In 100 people receiving mFOLFIRINOX (Leucovorin, 5-Fluorouracil, Irinotecan, and Oxaliplatin), 3 or fewer may have:**
• **A new cancer resulting from treatment of earlier cancer** • **Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness**

Possible Side Effects of Filgrastim *(section added 1/20/14) (section reinserted 10/9/14)*

COMMON, SOME MAY BE SERIOUS **In 100 people receiving Filgrastim, more than 20 and up to 100 may have:**
• **Nausea, vomiting** • **Pain in bone**

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving Filgrastim, from 4 to 20 may have:**
• **Anemia which may cause tiredness, or may require transfusion** • **Damage to the lungs which may cause shortness of breath** • **Internal bleeding which may cause coughing up blood** • **Swelling or tenderness of vessels**

RARE, AND SERIOUS **In 100 people receiving Filgrastim, 3 or fewer may have:**
• **Rupture of the spleen leading to bleeding in the belly**

Possible Side Effects of Pegfilgrastim *(section reinserted 10/9/14)*

COMMON, SOME MAY BE SERIOUS **In 100 people receiving Pegfilgrastim, more than 20 and up to 100 may have:**
• **Pain in bone**

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving Pegfilgrastim, from 4 to 20 may have:**
• **Anemia which may cause tiredness, or may require transfusion** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Damage to the lungs which may cause shortness of breath**

RARE, AND SERIOUS **In 100 people receiving Pegfilgrastim, 3 or fewer may have:**
• **Rupture of the spleen with bleeding in the belly**

In addition to side effects outlined above, people who are in Part I and Part II Study Group 2 may also experience the additional possible side effects of PEGPH20 and enoxaparin listed below. *(3/4/16)*

COMMON, SOME MAY BE SERIOUS **In 100 people receiving PEGPH20, more than 20 and up to 100 may have:**
• **Changes in voice** • **Muscle spasms** • **Swelling of the body** • **Blood clot which may cause swelling, pain, shortness of breath** *(moved 7/8/14)*

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving PEGPH20, from 4 to 20 may have:**
• **Weight gain** • **Infection** • **Muscle weakness**

Possible Side Effects of Enoxaparin *(Section added 3/4/16)*

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving enoxaparin, from 4 to 20 may have:
• **Anemia which may cause tiredness, or may require blood transfusions** • **Blood clot** • **Bleeding** • **Fever**

RARE, AND SERIOUS In 100 people receiving enoxaparin, 3 or fewer may have:
• **Diarrhea** • **Nausea** • **Bruising** • **Abnormal heartbeat** • **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Bleeding in the brain which may cause headache, confusion** • **Infection**

The incidence of blood clots to the legs, lungs, heart and brain (stroke) may be increased by administration of PEGPH20. For this reason any symptoms such as leg swelling, shortness of breath, chest pain, difficulty breathing, headache, weakness of arms, legs etc should be immediately be reported to your study doctor. *(added 7/8/14)* **If you are in Group 2, you will need to take enoxaparin daily by injection into your skin while on study in order to reduce this risk.** *(added 5/19/15, revised 3/4/16)*

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study and for 4 weeks after stopping study drug.

What possible benefits can I expect from taking part this study?

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

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.
The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The PEGPH20 will be supplied at no charge while you take part in this study. The cost of getting the PEGPH20 ready and giving it to you is not paid by the study sponsor so you or your

insurance company may have to pay for this. It is possible that the PEGPH20 may not continue to be supplied free while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of managing any side effects. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- *[List relevant* organizations *like study sponsor(s), local IRB, etc.]*
- The study sponsor and any drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

NOTE: Use the following types of format only when the "additional studies" are optional for the patient. When mandatory, the description should be imbedded as a part of the study description in the main consent.

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

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

1. Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

2. Optional Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in the main study, a sample of tissue from your previous biopsy and four blood samples (one when you start, after 48 hours, 2 weeks, and 4 weeks of treatment) will be collected. The researchers ask your permission to store and use your leftover samples from the planned research and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to allow your samples to be stored and used in future research, here is what will happen next:

1) Your blood and tissue will be collected as described above and will be sent to the Biobank.
2) Your sample and some related information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

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

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option (*include only applicable questions)*:

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

(section deleted 1/20/14)

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).