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COMPREHENSIVE CANCER CENTER

# A Phase I dose escalation study of Eryaspase in combination with modified FOLFIRINOX in locally advanced and metastatic pancreatic ductal adenocarcinoma

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**Study Drugs:** Eryaspase

**Clinical Phase:** I

**Number of Patients:** 19

# SPONSOR-INVESTIGATOR SIGNATURE PAGE

## Declaration of Sponsor or Responsible Medical Officer

Title: A Phase I dose escalation study of Eryaspase in combination with modified FOLFIRINOX in locally advanced and metastatic pancreatic ductal adenocarcinoma

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

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Marcus Noel, MD Date
Lombardi Comprehensive Cancer Center
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## Figures and Tables

# 1. Study Synopsis

| | |
|---|---|
| **Title** | A Phase I dose escalation study of Eryaspase in combination with modified FOLFIRINOX in locally advanced and metastatic pancreatic ductal adenocarcinoma |
| **Short Title** | rESPECt |
| **Protocol Number** | STUDY00002008 |
| **Clinicaltrials.gov number** | NCT04292743 |
| **Phase** | 1 |
| **Investigational Agents** | Eryaspase |
| **FDA IND number** | 19,437 |
| **Indication** | locally advanced and metastatic pancreatic cancer |
| **Study Overview** | The treatment options for locally advanced and metastatic pancreatic cancer remain limited with poor survival[1,2]. As such, there is a great need for further drug development. In the previous phase II second-line trial the combination of Eryaspase plus gemcitabine or Eryaspase plus FOLFOX (5-fluorouracil [5-FU], leucovorin, and oxaliplatin) was superior to that of chemotherapy alone[3].<br><br>Given this preliminary efficacy signal, this trial is designed to determine safety and perhaps an even larger signal of efficacy in the first-line setting. FOLFIRINOX is the standard of care for the first-line treatment of patients with advanced disease worldwide and thus supports our first line design in combination with Eryaspase.<br><br>Eryaspase is a dispersion for infusion of allogenic erythrocytes encapsulating recombinant E. coli L-asparaginase, in a saline preservative solution. Eryaspase is an off-shelf investigational agent. Eryaspase is produced for each individual patient taking into account blood group and phenotype and dose appropriate for body weight.<br><br>We hypothesize that the addition of Eryaspase to FOLFIRINOX (5-fluorouracil [5-FU], leucovorin, irinotecan, and oxaliplatin) will be safe and demonstrate preliminary signs of efficacy in patients with advanced pancreatic cancer. |
| **Study Duration** | 18 months |
| **Study Center(s)** | ➢ Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC |

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| | ➢ Additional participating centers to be added upon activation |
| **Objectives** | ***Primary Objectives***<br>• The primary objective of this study is to determine the maximum tolerated dose, tolerability and safety of Eryaspase in combination with the dose-modified FOLFIRINOX in patients with newly diagnosed locally advanced or metastatic pancreatic adenocarcinoma<br><br>***Secondary Objectives***<br>• To determine the objective response rate (ORR), progression-free survival (PFS) and the overall survival (OS) |
| **Number of Patients** | Approximately 12-19 subjects, subject to determination of MTD |
| **Diagnosis and Main Inclusion and Exclusion Criteria** | ***Main Inclusion Criteria***<br>• Patients must be able to understand and willing to sign an IRB approved written informed consent document.<br>• Patients must have histologically or cytologically confirmed pancreatic adenocarcinoma, which is locally advanced, or metastatic.<br>• Subject must have received no previous surgery, chemotherapy, radiotherapy or investigational therapy for the treatment of locally advanced or metastatic disease.<br>• If a subject has had adjuvant/neoadjuvant therapy for localized disease, tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the aforementioned therapies.<br>• Patient must have radiographically measurable disease according to RECIST 1.1.<br>• Patient must be > 18 years of age.<br>• Patient must have a life expectancy of ≥ 3 months.<br>• Patient must have an ECOG performance status ≤ 1.<br>• Patient must have normal bone marrow and organ function as defined below:<br>o Absolute neutrophil count ≥1,500/mcl<br>o Platelets ≥100,000/mcl<br>o Hemoglobin ≥9.0 g/dL<br>o Serum Albumin ≥3.0 g/dL<br>o Creatinine should be below the upper limit of normal OR Creatinine clearance ≥ 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal<br>o Plasma antithrombin III ≥ 65%, fibrinogen ≥ 150 mg/dL, international normalized ratio (INR) ≤ |

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| | 1.5, and partial thromboplastin time (PTT) ≤ institutional ULN.<br>○ Total bilirubin ≤ 2.0 x institutional ULN<br>• Patients who have had a stent placed for biliary obstruction can be included in the study.<br>• Female subject of childbearing potential must have a negative urine or serum pregnancy test.<br>• Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.<br>• Male subjects with a female partner of childbearing potential must agree to use two adequate methods or a barrier method plus a method of contraception<br><br>***Main Exclusion Criteria***<br>• Patient must not have evidence of neuroendocrine tumor, duodenal adenocarcinoma, or ampullary adenocarcinoma.<br>• Patient must not have a history of other malignancy ≤ 3 years ago, with the exception of basal cell or squamous cell carcinoma of the skin, which were treated with local resection only or carcinoma in situ of the cervix or ductal carcinoma in situ.<br>• Patient must not be receiving any other investigational agents 28 days prior to the screening process.<br>• Patient must not have brain metastases. Such patients must be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.<br>• Patient must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to asparaginase, 5FU, oxaliplatin, or irinotecan.<br>• Patient must not have an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection , symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, any clinically active malabsorption syndrome, inflammatory bowel disease, any condition that increases the risk of severe irinotecan gastrointestinal toxicity, or psychiatric illness/social situations that would limit compliance with study requirements |

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| | • Has an active autoimmune disease, or a documented history of autoimmune disease or a syndrome that requires steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule.<br>  ○ Has had an allogeneic tissue/solid organ transplant.<br>  ○ Has received or will receive a live vaccine within 30 days prior to the first administration of study medication. Seasonal flu vaccines that do not contain live virus are permitted<br>  ○ Has known active Hepatitis B or C.<br>  ○ Patient must not be pregnant and/or breastfeeding.<br>• Patient must not be known to be HIV-positive on combination antiretroviral treatment. |
| **Study Design** | This will be a single-arm, multi-center, open-label phase 1 study. The standard 3+3 design will be used to determine the maximum tolerated dose (MTD) from 4 possible dose levels.<br><br>mFOLFIRINOX dosing will include 5-fluorouracil 2400 mg/m² over 46 hours, oxaliplatin 85 mg/m², Irinotecan 150 mg/m² plus Eryaspase 75 Units/kg administered on day 1 every 14 days. We will dose escalate to Eryaspase 100 units/kg and also build in 2 dose reduction levels.<br><br>Safety assessments include adverse events, physical examination abnormalities, vital signs, and clinical laboratory tests (including blood chemistry, hematology, and coagulation panel). |
| **Study Statistical Analysis** | **Demographics and Baseline Characteristics**<br>• All subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, physical examination abnormalities, medical history, previous [within 6 months of screening]) and concomitant medications at study entry will be listed by study center and subject number and summarized with appropriate summary statistics.<br>**Establishing Maximum Tolerated Dose (MTD)**<br>• The standard phase I 3+3 design of dose escalation will be used to determine the maximum tolerated dose (MTD) from 5 possible dose levels, including at most 1 escalation level and 3 de-escalation levels.<br>• The maximum tolerated dose (MTD) is defined as the highest dose level where at most 1 of 6 |

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| | patients experience a dose-limiting toxicity (DLT) during the first cycle. If 0 or 1 of 6 patients in Dose Level 1 experience DLT during the first cycle, Dose Level 1 will be presumed to be the MTD. Additional 6 patients will be included at the MTD level.<br>**Safety Analysis**<br>• All subjects who are enrolled and received at least one dose of study medication will be included in the safety population.<br>• The primary safety endpoint is the subject incidence of Grade 3 or 4 adverse events. The number and percentage of all subjects who experience any adverse events (AEs) (Grade 1 through 4), serious adverse events (SAEs), or clinically significant abnormal laboratory results will be reported.<br>• Other safety endpoints include:<br>o Clinically significant changes from baseline in all safety laboratory parameters;<br>o Clinically significant changes from baseline in vital signs;<br>o Incidence and type of clinically significant ECG abnormalities.<br>• All clinical safety and tolerability data will be listed by subject and will be summarized. Treatment-emergent adverse events will be listed and summarized by System Organ Class, by relatedness, and by maximum severity. Serious adverse events and adverse events leading to withdrawal will be listed and summarized. Individual vital signs and change from baseline in vital signs will be listed by subject, and study visit, and summarized descriptively. Laboratory data (actual values and change from baseline) will be listed by subject and study<br>**Efficacy Analysis**<br>• Analysis of secondary endpoints: Due to small sample sizes and dose heterogeneity, no statistical tests of hypotheses are planned for the study. Response data will be collected and summarized. Overall survival, and progression-free survival will also be summarized as preliminary estimates of efficacy in this patient population using a Kaplan Meier estimator/curve. |

# 2. Schedule of Events (Table 1)

**Table 1**

| Study Procedures | Screening Period up to 3 weeks | Up to 5-8 days prior to C1D1 | Treatment (28-day/4-week cycles, **±1-day**) | | | | | End of Treatment Visit (+/- 7 days) | Follow up (every 8 wks, **± 1 week**) |
|---|---|---|---|---|---|---|---|---|---|
| | | | C1D1 | C1D8 | C1D15 | C1D22 | D1 and D15 on subsequent cycles | | |
| Informed consent | X | | | | | | | | |
| Eligibility criteria | X | | X | | | | | | |
| Demography | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Concomitant Medications Collection | X | | X | | X | | X | | |
| Physical exam (including height [screening only] and weight) | X | | X | X | X | X | X | X | |
| Vital signs (temperature, BP, and heart rate) | X | | X | X | X | X | X | X | |
| Performance status [1] | X | | X | X | X | X | X | X | |
| 12-Lead ECG | X | | X[2] | | X[2] | | | X | |
| Radiological assessments (CT or MRI) [3] | X | X (every 8 weeks [±3 days] from time of enrollment until disease progression, or death) | | | | | | | |
| AEs/SAEs [14] | X (collected from the time of informed consent until 30 days after the last study treatment) | | | | | | | | |
| Blood phenotype [4] | X[4] | | | | | | | | |
| Prescription with current weight | | X[5] | X[5] | | X[5] | | X[5] | | |
| Irregular antibody screening test (IAST) [6] | X[6] | | X[6] | | X[6] | | X[6] | | |
| Pre-eryaspase dose complete compatibility test [7] | | | X[7] | | X[7] | | X[7] | | |
| Eryaspase administration [8] | | | X[8] | | X[8] | | X[8] | | |
| FOLFIRINOX | | | X | | X | | X | | |
| Hematology, biochemistry, and coagulation panels; CA19-9 [9] | X[9,10] | | X | | X | | X | X | |
| Pregnancy test, for patients of childbearing potential [11] | X | | X | | X | | X | X | |
| Survival follow-up | | | | | | | | | X[13] |
| Subsequent anti-cancer treatments | | | | | | | | | X |

Tables abbreviations and legends:
D=Day; BP=blood pressure; ECG=electrocardiogram; CT=computed tomography; MRI=magnetic resonance imaging; IAST=irregular antibody screening test; CA19-9=cancer antigen 19-9; ASPNase = Asparaginase.
**[1]** According to the Eastern Cooperative Oncology Group (ECOG)
**[2]** Performed pre-dose Cycle 1 Day 1 and Day 15
**[3]** Radiological assessment (CT C/A/P) to be completed within 3 weeks of screening and then every 8 weeks (±3 days) from the time of enrolment until disease progression or until withdrawal from the study treatment, or death, using the same method throughout.
**[4]** A complete erythrocyte phenotype (including D, C, E, c, e, and K antigens), ABO blood group status, and

Rhesus factor, all assessed on 2 separate samples (can be collected on the same day), to be done at least 5 working days before the first Eryaspase infusion. For group A and AB patients, sub-grouping A1/A1B and A2/A2B is required. If A subgroup, screening of anti-A1 antibodies (Indirect Coombs method) should be performed for A2 and A2B patients. The A2 and A2B patients will require anti-A1 antibodies screening before each administration along with IAST and documented on IAST form.

**[5]** A prescription form indicating the patient's identifiers as well as his/her current weight, the investigator's recipient of the product, and the place and time of the delivery must be sent as soon as possible once the Eryaspase infusion is scheduled, and at the latest 5 working days prior to each Eryaspase infusion. Exact instructions are provided by the IMP Manual.

**[6]** The IAST blood sample and results must be completed within 72 hours prior to each Eryaspase administration and a report provided to the sponsor as soon as possible prior to each Eryaspase infusion.

**[7]** This should be performed by the blood bank at the local institution. If not compatible, eryaspase must not be administered and the sponsor should be notified immediately. A collection of additional blood sample will be required for further investigation.

**[8]** A ±1-day window is permitted for Eryaspase or FOLFIRINOX dosing for scheduling purposes.

**[9]** Laboratory tests to be performed at the local laboratory as follows: Hematology: Complete blood count with differential (hemoglobin, hematocrit, erythrocyte count, white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean corpuscular volume, reticulocytes and platelet count). Serum Chemistry: Sodium, potassium, bicarbonate, calcium, chloride, magnesium, creatinine, albumin, total bilirubin (direct and indirect), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, , glucose, urea, amylase, lipase, inorganic phosphorus, and total protein; Coagulation parameters – international normalized ratio (INR), Partial thromboplastin time, fibrinogen, plasma antithrombin III, D-dimer. Tumor marker: CA19-9

**[10]** Baseline labs to be collected within the first 21 days of the screening period

**[11]** For patients of childbearing potential, serum pregnancy test to be performed during the screening period and at End of Treatment and urine/serum pregnancy test to be performed prior to dosing of any chemotherapy agent

**[13]** Survival follow to be conducted by phone, visit, or medical records review every 8 weeks (± 1 week) from end of treatment visit until patient's death, loss to follow up, or study closure. Subsequent therapy should be collected during this follow up.

Additional lab tests may be required (e.g., weekly monitoring per standard practice or label requirements should be followed) and should be reported if clinically significant

**[14]** SAEs are not required to be reported until after they received the first dose.

# 3. INTRODUCTION

## *3.1 Background*

Pancreatic cancer is a highly aggressive malignancy. In the United States, there will be an estimated 55,440 new cases of pancreatic cancer diagnosed in 2018, with the disease causing an estimated 44,330 deaths. The estimated 5 year survival is poor at 8.5 %[1,4] with a median survival of 10 to 12 months[2]. The poor prognosis for pancreatic cancer is related to a combination of late detection, as most patients present with locally advanced or metastatic disease; and standards of care that consist of relatively ineffective chemotherapeutic regimens. Surgical resection is the only curative treatment for pancreatic cancer, however, only 15-20% of patients present with operable disease[5,6].

Improving survival in metastatic or unresectable disease remains a challenge; for decades many chemotherapy trials were conducted, however, most failed to demonstrate efficacy. For the past decade, we had only two studies that showed meaningful small improvements in survival and changed the practice. The PRODIGE4/ACCORD 11 trial compared FOLFIRINOX (fluorouracil with irinotecan hydrochloride, leucovorin calcium, and oxaliplatin) to single-agent gemcitabine in patients with metastatic pancreatic cancer. FOLFIRINOX demonstrated a significant survival advantage; median overall survival (mOS) of 11.1 months (m) vs. 6.8 m (HR

0.57, P <0.001,)[2]. While the MPACT trial evaluated gemcitabine/nab-paclitaxel combination to gemcitabine alone in patients with metastatic pancreatic cancer, nab-paclitaxel was associated with improved survival; mOS of 8.5 m vs. 6.7 m (HR 0.57, P <0.001)[7]. Unfortunately, since these studies, we have not made any new progress that has changed the outcome of this devastating disease. Hence, new therapeutics that provide greater clinical efficacy in patients with pancreatic cancer are urgently needed.

KRAS (Kirsten rat sarcoma virus) mutations are observed in more than 90% pancreatic ductal adenocarcinomas (PDAC)[8,9]. KRAS mutations provoke a constitutive activation of RAF/MEK/ERK and PI3K/AKT-mTOR pathways, reprogramming of metabolic pathways that allow continued cellular proliferation in the absence of nutrients required by normal cells[10,11]. Consequently, targeting cell metabolism is a novel approach in pancreatic adenocarcinoma[12].

What distinguishes the pancreatic tumor cell's metabolism from normal cells is the dependence on metabolites that are utilized through the non-canonical metabolic pathway[13]. The amino acid glutamine, for instance, has an essential role in sustaining anabolic metabolism and biosynthetic pathways, including the de novo synthesis of asparagine[14,15] . Asparagine is a non-essential amino acid, synthesized intracellularly from glutamine and aspartic acid by the enzyme asparagine synthetase (ASNS). However, this biosynthesis capacity varies between cells[16].

### *3.2 Preclinical Data*

In leukemic cells, the asparagine synthetase (ASNS) is lacking, therefore, it depends on circulating asparagine in the serum[17]. The modulation of glutamine and asparagine metabolism was targeted with L-Asparaginase (L-ASNase). L-ASNase induces an antineoplastic effect through catalyzing the asparagine to ammonia and aspartic acid, consequently, depletion of serum asparagine leading to cycle arrest and cell death. Moreover, ASPNase deplete the serum glutamine as it acts as a substrate for the enzyme, and thus contributing further to cell growth inhibition and apoptosis[18]. Hence, L-ASNase has been tested and used in pediatric acute lymphoblastic leukemia (ALL) and has become one of the cornerstone components of chemotherapy regimens used in ALL.

Interestingly, ASNS expressions are high in normal pancreatic cells. However, more than 50% of pancreatic adenocarcinoma has low or no expression of ASNS[19,20]. Therefore, the modulation of glutamine and asparagine metabolism has become an investigational therapeutic strategy of interest in pancreatic cancer. Unfortunately, L-ASNase has a narrow therapeutic index and was correlated with significant toxicity when it was tested in solid tumors, including pancreatic cancer[21].

Eryaspase is an encapsulated *Escherichia Coli* L-ASNase within erythrocytes. It's a novel way of delivering L-ASNase that led to the delivery of effective doses with less toxic effects. Encapsulation of L-ASNase decreases the rapid degradation of L-ASNase in the blood, thus prolonging activity, with a half-life of approximately two weeks. Furthermore, encapsulation limits exposure to the immune system and, subsequently, decreases its intrinsic immunogenicity and hypersensitivity reactions[22].

### *3.3 Previous Human experience*

Encapsulated L -asparaginase within erythrocytes investigated in GRASPALL 2005 phase I/II, a multicenter randomized controlled trial, investigated the safety profile of three dose levels (50, 100, and 150 IU/kg). The study results suggested a reduction in the number and severity of allergic reactions and a trend towards fewer coagulation disorders. Other adverse events were comparable to those observed with E. coli L-asparaginase, and there was also no difference between the three doses[22].

In pancreatic cancer, two clinical trials have been conducted. The first clinical trial in pancreatic cancer was GRASPA 2008 trial (NCT01523808), a national, multicenter, open-label, phase 1 dose-escalation study, which investigated Eryaspase as a single agent in patients with metastatic pancreatic cancer progressed after two lines of therapy. Twelve patients were enrolled, and they received a single administration of Eryaspase as monotherapy (25, 50, 100, or 150 IU/Kg). No dose-limiting toxicity was reported. The recommended Phase 2 dose was determined to be 100 IU/Kg every two weeks[23].

Subsequently, a Phase 2, multicenter, open-label trial investigating Eryaspase in combination with gemcitabine or mFOLFOX6 (modified FOLinic acid-Fluorouracil-Oxaliplatin-6 regimen) as second-line treatment in patients with metastatic pancreatic cancer was conducted. The trial was completed in 2017. The endpoint of the study was an improvement in progression-free survival (PFS) or overall survival (OS) in patients with no or low ASNS (0/1) expression as determined by immunohistochemistry (IHC), with a target hazard ratio (HR) < 0.85. Secondary endpoints included OS, PFS, objective response rate, safety, and QoL. A total of 141 patients were enrolled and randomized, 95 to Eryaspase plus chemotherapy and 46 to chemotherapy alone. The majority of patients (90%) received gemcitabine during the study. Both co-primary endpoints were met in the ASNS 0/1+ subgroup (Eryaspase, n= 66; control, n= 32), with HRs of 0.67 for PFS and 0.63 for OS[3]. These encouraging results prompted investigators to plan for the Phase III study. However, we sought to test the safety and tolerability of Eryaspase with FOLFIRINOX, the current first line, and standard of care chemotherapy.

Eryaspase's safety and efficacy also have been under investigation in other clinical trials, acute lymphoblastic leukemia (ALL)[24] and acute myeloid leukemia (AML)[25].

### *3.4 Study Rationale*

As previously mentioned, the treatment options for unresectable and metastatic pancreatic cancer remain limited with poor survival. As such, there is a great need for further drug development. In the previous phase II second-line trial the combination of Eryaspase plus gemcitabine or Eryaspase plus FOLFOX was superior to that of chemotherapy alone. Given this preliminary efficacy signal, and this trial is designed to perhaps demonstrate an even larger signal of efficacy in the first-line setting. FOLFIRINOX is the standard of care for the first-line treatment of patients with the unresectable disease worldwide and thus justifies our combination of FOLFIRINOX plus Eryaspase.

### *3.5 Justification for Dose*

We plan to use modified dosing of FOLFIRINOX which has been an accepted practice across recent clinical trials, the infusion 5-FU, Oxaliplatin and are given at a full dose. The Irinotecan

is given at a modified dose in order to minimize Gastrointestinal and hematologic toxicity, and the bolus 5-FU is eliminated in order to minimize myelosuppression. Eryaspase has been previously evaluated in twelve patients at dose levels 25. 50. 100 and 150 units/kg without evidence of a dose limited toxicities. The recommended phase 2 dose was 100 units/kg. We will start with a dose of 75 units/kg, with the goal of reaching 100 units/kg, however, will also build in a -1/-2 dose level of 50/25 units /kg.

# 4. Objectives

## *4.1 Primary Objective*

- The primary objective of this study is to determine the maximum tolerated dose, tolerability and safety of Eryaspase in combination with the dose-modified FOLFIRINOX in patients with newly diagnosed locally advanced or metastatic pancreatic adenocarcinoma.

## *4.2 Secondary Objectives*

- To estimate the objective response rate (ORR)
- To summarize progression-free survival (PFS)
- To summarize overall survival (OS)

# 5. Study Design

## *5.1 Overall Design*

This is an open-label, multicenter, Phase 1 study of Eryaspase combination with FOLFIRINOX in patients with locally advanced or metastatic pancreatic adenocarcinoma. Subjects will undergo screening in order to determine eligibility. The screening period will not exceed 28 days. Eligible patients will receive Eryaspase and it will be administered on Day 1 and 15 of the 4-week cycle combined with mFOLFIRINOX.

## *5.2 Sample Size*

The sample size for the standard 3+3 design is random with a total of anywhere from 9 to 21 subjects possible, but 12-19 subjects most likely, with at most 1 escalation level and 2 de-escalation levels beyond the initial dose level.

## *5.3 Cohorts/Escalation scheme*

The study will use a standard 3+3 method of dose escalation. Patients will be enrolled in cohorts of 3. Four dose levels are planned and include 25, 50, 75, and 100 mg of Eryaspase with reduced dose irinotecan. Subjects will be assigned to a dose level in the order of study entry with at least a 3-day stagger in enrollment between individual subjects. With the 3+3 design to be employed, doses are not escalated unless all patients receiving the current dose have been observed for at least 4 weeks and dose-limiting toxicities (DLTs) have been reported. The MTD is defined as the highest dose level where at most 1 of 6 patients experience a dose limiting toxicity (DLT). Three patients will be treated at dose level 0. If 0/3 experience a DLT, 3 new

patients will be enrolled at the next higher dose level. If 1/3 experience a DLT, 3 additional patients will be enrolled at the same dose level. If 1/6 patients experience a DLT at any dose level except the highest dose level, 3 new patients will be enrolled at the next higher dose level; if 1/6 patients at the highest dose level experience a DLT, it will be deemed the MTD and the trial will be deemed the MTD and we will expand to an additional 6 patients at that dose level. As soon as 2 patients experience a DLT at a given dose level, that dose will be concluded to be above the MTD, dose escalation will cease and 3 new patients will be enrolled at the next lower dose level. If 6 patients were previously treated at that lower dose, the study will halt and that lower dose will be declared the MTD. A subject who withdraws from the escalation phase of the study for reasons other than a DLT will be replaced.

FOLFIRINOX treatment will be given on Day 1 and 15 of the 4 weeks cycle and continued until unacceptable toxicity or disease progression, for a maximum of 12 treatments (6 months) of FOLFIRINOX. Subjects will receive a single intravenous administration of Eryaspase on Day 1 and 15 of 4-weeks cycle.

The study visits are day 1, 8, 15, 22, during cycle 1 and day 1 and 15 during subsequent cycles with a 4-week follow-up period after the end of treatment. Subjects who show at least stable disease based on RECIST 1.1 at the end of the 12-week period (Day 85) are eligible for the continuation of FOLFIRINOX plus eryaspase treatment until disease progression or unacceptable toxicity.

**Table 2**

| Dose Escalation Schedule | | |
|---|---|---|
| **Dose Level** | **Dose** | |
| | **Eryaspase** | **FOLFIRINOX** |
| Level -2 | 25 Units/kg | 5-fluorouracil 2400 mg/m² over 46 hours, oxaliplatin 85 mg/m², Irinotecan **150** mg/m²,leucovorin 400 mg/m2 |
| Level -1 | 50 Units/kg | 5-fluorouracil 2400 mg/m² over 46 hours, oxaliplatin 85 mg/m², Irinotecan **150** mg/m²,leucovorin 400 mg/m2 |
| Level 0 (starting dose) | 75 Units/kg | 5-fluorouracil 2400 mg/m² over 46 hours, oxaliplatin 85 mg/m², Irinotecan **150** mg/m²,leucovorin 400 mg/m2 |
| Level 1 | 100 Units/kg | 5-fluorouracil 2400 mg/m² over 46 hours, oxaliplatin 85 mg/m², Irinotecan **150** mg/m²,leucovorin 400 mg/m2 |

### *5.4 Definition of the Maximum Tolerated dose (MTD)*

The maximum tolerated dose (MTD) is defined as the highest dose level where at most 1 of 6 patients experience a dose-limiting toxicity (DLT) during the first cycle. If 0 or 1 of 6 patients in Dose Level 1 experience DLT during the first cycles, Dose Level 1 will be presumed to be the MTD.

## *5.5 Dose Limiting Toxicities (DLT)*

To the extent possible, any adverse events that are deemed to study drug-related and are ongoing at end of treatment will be followed up to resolution or until a determination is made that the unresolved event is stable.

In general, Grade 1 and 2 toxicities do not require any dose modification for any of the chemotherapy agents or for Eryaspase. However, appropriate supportive care will be provided for the management of drug-related toxicities.

**Hematologic DLT** is defined as any of the following that occurs during the first cycle (total of approximately 28 days) of treatment that is attributed as possibly, probably, or definitely related to Eryaspase alone or the combination of Eryaspase and FOLFIRINOX:

- Grade 4 neutrophil count decrease > 7 day duration
- Febrile neutropenia ≥ Grade 3 of any duration
- Grade 3 or Grade 4 platelet count decrease
- Any Grade 4 platelet count decrease with bleeding

**Non-hematologic DLT** is defined as any grade 3 or grade 4 adverse event, based on NCI CTCAE that occurs during the first cycle (total of approximately 28 days) of treatment that is considered possibly, probably, or definitely related to Eryaspase alone or the combination of Eryaspase and FOLFIRINOX with the following specific exceptions:

- Grade 3 or 4 AST, ALT, alkaline phosphatase, or total bilirubin due to biliary obstruction or infection
- Grade 3 or 4 nausea, vomiting, or diarrhea resolved with maximal supportive care within 7 days
- Grade 3 mucositis resolved with supportive care
- Grade 3 fatigue lasting less than 7 days
- Grade 3 or 4 laboratory abnormalities that are not clinically significant or do not require any clinical intervention.

Any treatment-related toxicity that results in treatment delay for > 21 days cumulatively during the first cycle or > 14 days cumulatively during the second cycle will be considered a DLT, and the patient will be removed from the study. If the treatment delay during the first cycle is due to reasons other than treatment-related toxicity, the patient will be replaced as the subject will be considered to be inevaluable for DLT.

## *5.6 Dose modification*

Dose reduction or modification are only allowed after passing the 28 days DLT period. Recommended mFOLFIRINOX dose modifications are listed in Table 3, however modification may follow investigator or institutional guidelines. Modifications may be made to any or all chemotherapy agents, per investigator discretion.

**Table 3**

| Recommended mFOLFIRINOX 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 | 150 mg/m$^2$ | 125 mg/m$^2$ | 90 mg/m$^2$ |
| Oxaliplatin | 85 mg/m$^2$ | 68 mg/m$^2$ | 50 mg/m$^2$ |

**Table 4. Indications for mFOLFIRINOX Dose Modifications**

**Table 4A**

| A<br>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 | **5-FU** | **Irinotecan** | **Oxaliplatin** |
| 2 | Consider holding, but can treat per Investigator discretion. | Consider holding, but can treat per Investigator discretion. | Consider holding, but can treat per Investigator discretion. |
| 3-4 | 1$^{st}$ occurrence: reduce by 1 dose level | 1$^{st}$ occurrence: reduce by 1 dose level | 1$^{st}$ occurrence: reduce by 1 dose level |
| | 2$^{nd}$ occurrence: reduce by 1 dose level | 2$^{nd}$ occurrence: reduce by 1 dose level | 2$^{nd}$ occurrence: reduce by 1 dose level |
| | 3$^{rd}$ occurrence: discontinue the treatment | 3$^{rd}$ occurrence: discontinue the treatment | 3$^{rd}$ occurrence: discontinue the treatment |

**Table 4B**

| **B**<br>**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** | **5-FU** | **Irinotecan** | **Oxaliplatin** |
| 2 | Consider holding, but can treat per Investigator discretion. | Consider holding, but can treat per Investigator discretion. | Consider holding, but can treat per Investigator discretion. |
| 3-4 | 1st occurrence: reduce by 1 dose level | 1st occurrence: reduce by 1 dose level | 1st occurrence: reduce by 1 dose level |
| | 2nd occurrence: reduce by 1 dose level | 2nd occurrence: reduce by 1 dose level | 2nd occurrence: reduce by 1 dose level |
| | 3rd occurrence: discontinue the treatment | 3rd occurrence: discontinue the treatment | 3rd occurrence: discontinue the treatment |

**Table 4C**

| **C**<br>**General**<br>**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 | |
| 2 | Consider holding, but can treat per Investigator discretion. |
| 3 | Hold all drugs until resolution to ≤ Grade 1. Then resume treatment at the next lower dose level. |
| 4 | Discontinue all protocol treatment |

**Table 4D**

| **D**<br>**Diarrhea** | Patients should be instructed in the use of loperamide as treatment for diarrhea. Patient should not be retreated with irinotecan until recovery from diarrhea, without loperamide for at least 24 hours, has occurred |
|---|---|
| Toxicity Grade | |
| 2 | Consider holding, but can treat per Investigator discretion. |
| 3-4 | 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 |

**Table 4E**

| **E**<br>**Mucositis** | | |
|---|---|---|
| Toxicity Grade | 5-FU | Oxaliplatin |
| 2 | Hold treatment<br>until resolution to ≤ Grade 1,<br>Continue at same dose level | Hold treatment<br>until resolution to ≤ Grade 1,<br>Continue at same dose level |
| 3-4 | Hold treatment<br>until resolution to ≤ Grade 1,<br>Continue at next lower dose level | Hold treatment<br>until resolution to ≤ Grade 1,<br>Continue at next lowest dose level |

**Table 4F**

| **F**<br>**Oxaliplatin related neuropathy** | | Paresthesia or peripheral sensory neuropathy | |
|---|---|---|---|
| **Toxicity Grade** | **Duration of toxicity 1–7 days** | **Duration of toxicity more than 7 day** | **Persistent (duration of toxicity more than 14 days)** |
| **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** |
| **4** | **Discontinue** | **Discontinue** | **Discontinue** |

**Table 4G**

| **G**<br>**Palmar-plantar erythrodysesthesia syndrome** | |
|---|---|
| Toxicity Grade 2 | Consider holding, but can treat per Investigator discretion. |
| Toxicity Grade 3-4 | Reduce 5–5-FU by 1 dose level |

### *5.7 Discontinuation of Eryaspase*

- DLT during dose escalation
- Study completion
- Patient withdraws from the study for any reason, including withdraws consent.
- Progressive disease
- Declared discontinuation due to missed Eryaspase doses.

### *5.8 Duration of therapy*

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for a total of 12 treatments of FOLFIRINOX (approximately 6 months) or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out the continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from the study
- The Sponsor-Investigator or Georgetown decides to close the study

After 12 treatments of FOLFIRINOX, patients have the option to continue FOLFIRINOX plus Eryaspase or can transition to FOLFIRI (dropping Oxaliplatin) plus Eryaspase or 5-FU (dropping Irinotecan and Oxaliplatin) plus Eryaspase, at the investigator's discretion.

### *5.9 Duration of follow-up*

Patients will be followed via chart review or phone interview every 8 weeks for a total of 2 years or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

### *5.10 Women of childbearing potential*

Women of childbearing potential (women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal, or women who have had a tubal ligation) are required to have a negative serum pregnancy test within 14 days prior to the first dose of Eryaspase.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 1 month following the last dose of Eryaspase.

If a patient is suspected to be pregnant, Eryaspase should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 1 month after the last dose of Eryaspase, the investigator must be notified in order to facilitate outcome follow-up.

### *5.11 Study Pause Criteria*

The protocol will be paused with any criteria below being met:

- Any death (other than due to progressive disease)
- The occurrence of 2 or more grade 4 events

## 6. Study Population

### *6.1 Inclusion Criteria*

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

6.1.1 Patient must be able to understand and willing to sign an IRB approved written informed consent document.
6.1.2 Patient must have histologically or cytologically confirmed pancreatic adenocarcinoma, which is locally advanced, unresectable, or metastatic.
6.1.3 Patient must have received no previous surgery, chemotherapy, radiotherapy or investigational therapy for the treatment of locally advanced or metastatic disease.
6.1.4 If a patient has had adjuvant/neoadjuvant therapy for localized disease, tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the aforementioned therapies.
6.1.5 Patient must have radiographically measurable disease according to RECIST 1.1
6.1.6 Patient must be > 18 years of age.
6.1.7 Patient must have a life expectancy of $\geq$ 3 months.
6.1.8 Patient must have an ECOG performance status $\leq$ 1.
6.1.9 Patient must have normal bone marrow and organ function as defined below:
- Absolute neutrophil count $\geq$1,500/mcl
- Platelets $\geq$100,000/mcl
- Hemoglobin $\geq$9.0 g/dL
- Serum Albumin $\geq$3.0 g/dL
- Creatinine should be below the upper limit of normal OR Creatinine clearance (eGFR) $\geq$60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal
- Plasma antithrombin III $\geq$ 65%, fibrinogen $\geq$ 150 mg/dL (1.5g/L), international normalized ratio (INR) $\leq$ 1.5, and partial thromboplastin time (PTT) $\leq$ institutional ULN.
- Total bilirubin ≤ 2.0x institutional ULN

6.1.10 Patients who have had a stent placed for biliary obstruction can be included in the study.
6.1.11 Female subject of childbearing potential must have a negative urine or serum pregnancy test.

6.1.12 Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

6.1.13 Male subjects with a female partner of childbearing potential must agree to use two adequate methods or a barrier method plus a method of contraception

## *6.2 Exclusion Criteria*

Patients meeting any of the following exclusion criteria will not be able to participate in this study:

6.2.1 Evidence of neuroendocrine tumor, duodenal adenocarcinoma, or ampullary adenocarcinoma.

6.2.2 History of other malignancy ≤ 3 years ago, with the exception of basal cell or squamous cell carcinoma of the skin, which were treated with local resection only or carcinoma in situ of the cervix of ductal carcinoma in situ.

6.2.3 Receiving any other investigational agents 28 days prior to the screening process.

6.2.4 Patient with evidence of brain metastases. Such patients must be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

6.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to asparaginase, 5FU, oxaliplatin, or irinotecan.

6.2.6 Any uncontrolled intercurrent illness including, but not limited to, ongoing or active infection , symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, any clinically active malabsorption syndrome, inflammatory bowel disease, any condition that increases the risk of severe irinotecan gastrointestinal toxicity, or psychiatric illness/social situations that would limit compliance with study requirements

6.2.7 Has an active autoimmune disease, or a documented history of autoimmune disease or syndrome that requires steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule.

6.2.8 History of abdominal fistula, gastrointestinal perforation, peptic ulcer, or intraabdominal abscess within 6 months prior to randomization.

6.2.9 Has had an allogeneic tissue/solid organ transplant.

6.2.10 Has received or will receive a live vaccine within 30 days prior to the first administration of study medication. Seasonal flu vaccines that do not contain live virus are permitted

6.2.11 Has known active Hepatitis B or C.

6.2.12 Patient is pregnant and/or breastfeeding.

6.2.13 Known to be HIV-positive on combination antiretroviral.

## *6.3 Randomization and Method of Treatment Assignment*

There is only one treatment group in each part of the study. Therefore, no randomization will be performed

## *6.4 Inclusions of Women and Minorities*

Both Men and Women and all minorities are eligible for participation.

## *6.5 Multicenter Trial Management*

### *6.5.1 Personnel*

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator
- A data manager

In addition, Georgetown University's Multicenter Project Management Office will oversee the conduct of the trial at Lombardi-Georgetown and additional sites. Georgetown University's Multicenter Project Management Office will be the main point of contact for Dr. Noel and the other site PIs for any study related concerns including data management and regulatory.

### *6.5.2 Patient Enrollment*

Enrollment at the sites will be competitive. If a patient is consented and being screened for enrollment, the local research coordinator must send an email within 24 hours containing the Patient registration form to the local PI, Dr. Noel, Georgetown University's Multicenter Project Management Office and Erytech. If a patient is successfully screened, the local research coordinator must send all supporting documentation to Georgetown University's Multicenter Project Management office by secure email to confirm eligibility. Patients should not start therapy until Dr. Noel and Georgetown University's Multicenter Project Management office have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.

### *6.5.3 Data Collection and Management*

Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit.

### *6.5.4 Conference Calls*

A weekly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

### *6.5.5 Trial Auditing*

Georgetown University's Multicenter Project Management Office will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites.

# 7 Study Procedures

## *7.1 Screening and Enrollment*

For patients being considered for enrollment outside of Georgetown-Lombardi, all primary source documentation should be sent to Georgetown University's Multicenter Project Management Office, and the principal investigator, Dr. Noel, for review and approval. Patients must be approved for accrual prior to starting study medications. Patient IDs will be assigned at the time of registration.

Informed consent must be obtained prior to the performance of study related evaluations.

Within 21 days prior to study entry subjects will undergo the following evaluations:

- Demographics, medical history, and concomitant medications
- A physical exam, height, and weight measurements
- Vital signs including temperature blood pressure and heart rate
- A 12-lead ECG will be obtained
- Subject performed status will be assessed via the ECOG scale
- Samples will be collected for serum chemistry hematology, coagulation, and CA-19-9
- Irregular antibody screening test (IAST)
- Blood phenotype
- Radiographic assessments will be obtained during screening and then repeated every 8 weeks from the time of enrollment until disease progression or death

## *7.2 Study Day -8 to Day -5*

The following procedures will be performed at least 5 days prior to Cycle 1 Day 1:

- Prescription with current weight

### *7.3 Study Day 1*

The following procedures will be performed:

- Physical examination
- Vital signs including temperature blood pressure and heart rate
- Subject performed status will be assessed via the ECOG scale
- 12-lead ECG
- Pre-Eryaspase dose complete compatibility test
- Irregular antibody screening test (IAST)
- Samples will be collected for serum chemistry hematology, coagulation, and CA 19-9
- For all women of childbearing potential, a urine pregnancy test will be administered
- Eryaspase Administration
- FOLFIRINOX Administration

### *7.4 Study Day 8*

The following procedures will be performed:

- Physical examination
- Vital signs including temperature blood pressure and heart rate
- Subject performed status will be assessed via the ECOG scale
- All adverse events will be recorded

### *7.5 Study Day 15*

The following procedures will be performed:

- Physical examination
- Vital signs including temperature blood pressure and heart rate
- Subject performed status will be assessed via the ECOG scale
- All adverse events will be recorded
- 12-lead ECG
- Pre-Eryaspase dose complete compatibility test
- Irregular antibody screening test (IAST)
- Samples will be collected for serum chemistry hematology, coagulation, and Ca 19-9
- For all women of childbearing potential, a urine pregnancy test will be administered
- Eryaspase Administration
- FOLFIRINOX Administration

### *7.6 Study Day 22*

The following procedures will be performed:

- Physical examination
- Vital signs including temperature blood pressure and heart rate
- Subject performed status will be assessed via the ECOG scale
- All adverse events will be recorded

### *7.7 Study Day 1 and Day 15 of each subsequent cycle*

The following procedures will be performed:

- Physical examination
- Vital signs including temperature blood pressure and heart rate
- Subject performed status will be assessed via the ECOG scale
- All adverse events will be recorded
- Pre-Eryaspase dose complete compatibility test
- Irregular antibody screening test (IAST)
- Samples will be collected for serum chemistry hematology, coagulation, and CA19-9
- For all women of childbearing potential, a urine pregnancy test will be administered
- Eryaspase Administration
- FOLFIRINOX Administration

### *7.8 End of Treatment/Safety Follow-up*

Subjects will complete an end of treatment (EOT) evaluation 4 weeks (+/- 7 days) after the last day of treatment on study or after tumor progression is documented. In addition, a positive urine test must be confirmed by a serum pregnancy test.

Survival follow up will be conducted by phone, visit, or medical records review every 8 weeks (±1 week) from end of treatment visit until patient's death, loss to follow up, or study closure. Subsequent anti-cancer treatment should be collected during this follow up.

## 8 Study Assessment

### *8.1 Efficacy Assessments*

#### *8.1.1 Tumor Assessment*

**Methods of evaluation of Measurable Disease**

**Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler estimating the size of the lesion, is recommended.

**Conventional CT and MRI:** These guidelines have defined measurability of lesions on CT scans based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slicing thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of **MRI** remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, 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 be performed with breath hold scanning techniques, if possible.

## *8.2 Safety Assessments*

### 8.2.1 Physical Examinations, Vital Signs, and ECGs

A physical examination will be performed during screening, Cycle 1 Days 1, 8, 15, and 22, and Day 1 and Day 15 on all subsequent cycles.

Vital signs will be measured at all study visits. Blood pressure, pulse rate, and body temperature will be measured in accordance with the study site's standard operating procedures. Body weight and height will be measured at screening. Body height will be performed only at the screening period, and body weight will be measured at all visits.

12-Lead ECGs will be acquired during the Screening period, and on Day 1 (pre-dose), Day 15 (pre-dose) of Cycle 1. The ECG recordings will be reviewed for any evidence of abnormalities. In particular, any evidence of QT/QTcF prolongation will be recorded as an adverse event.

### 8.2.2 Clinical Laboratory Assessments

The following tests will be performed at the local laboratories at the visits identified in the Time and Events tables.

- **Hematology:** hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, platelet count, mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean corpuscular volume, reticulocytes

- **Serum Chemistry:** liver panel (total and direct bilirubin, AST, ALT), GGT, renal panel (BUN, creatinine), albumin, sodium, potassium, magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total protein, alkaline phosphatase,, amylase, and lipase.

- **Coagulation:** Coagulation profile, plasma antithrombin III, fibrinogen, D-dimer, the international normalized ratio (INR), and partial thromboplastin time (PTT).

- **Pregnancy test** (for all women of childbearing potential): Serum or Urine β HCG test

- **Tumor Marker:** CA19-9

- **Complete compatibility testing**: To be performed prior to Eryaspase administration by the blood bank at the Institution. If not compatible, eryaspase should NOT be administered and the sponsor notified immediately. Depending on the individual circumstances the patient may receive chemotherapy alone and resume eryaspase at the next dose or delay dose for Erytech to remanufacture and ship the new bag of eryaspase. If incompatibility persists the patient will NOT receive further eryaspase, but can continue chemotherapy alone.

## *8.3 Regulatory and Reporting Requirements*

### 8.3.1 Adverse Events (AE)

Adverse events are defined as any untoward medical occurrence in a subject participating in a clinical trial who is administered an investigational product, at any dose; the adverse event does not necessarily have to have a causal relationship with this product. An adverse event could, therefore, be any unfavorable and/or unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries, and exacerbation of pre-existing conditions.

All adverse events occurring in subjects who have received the treatment will be recorded on the CRF and will be reported in accordance with regulatory requirements. Adverse events reported prior to the commencement of administration of study medication will be considered pretreatment events. All adverse events will be monitored until resolution or, if the AE is determined to be chronic, until a cause is identified. To the extent possible, any adverse events that are deemed to study drug-related and are ongoing at End of Treatment will be followed up to resolution or until a determination is made that the unresolved event is stable. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and the Sponsor's Medical Monitor whether continued follow-up of the adverse event is warranted.

**Laboratory abnormalities** and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An **elective surgery/procedure** scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g.,

surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

#### 8.3.1.1 Grading Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

For AEs not listed, the following scale will be used:

- Mild (Grade 1): no limitation of usual activities
- Moderate (Grade 2): some limitation of usual activities
- Severe (Grade 3): inability to carry out usual activities
- Life-threatening (Grade 4): an immediate risk of death
- Death (Grade 5)

### 8.3.2 Unanticipated Problems

An unanticipated problem is defined as:

- **Unexpected** (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- **Related or possibly related** to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- **Suggests** that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Since it is anticipated that there will be deaths due to pancreatic cancer progression in this study, death will not necessarily be considered unexpected in this study.

### 8.3.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

**Related:** A causal relationship between the medicinal product (and/or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive re-challenge/de-challenge is supportive.

**Not Related:** A causal relationship between the medicinal product (and/or study procedures) and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

For every adverse event, the investigator must attribute whether the adverse event was due to study medication, or other causes. If an investigator's opinion of probably not or not related to study drug(s) is given, an “other” cause of event must be provided by the investigator for the adverse event.

### 8.3.4Serious adverse event (SAE)

A Serious Adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the patient was, in the opinion of the Investigator or Sponsor, at immediate risk of death from the event as it occurred)
- Requires or prolongs hospitalization (unless planned for observation, protocol compliance, elective procedures, social reasons). This does not include an emergency room visit or admission to an outpatient facility.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important and significant medical event that, based on appropriate medical judgment, may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

**Disease progression** is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient’s disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

For patients enrolled outside of Georgetown University, serious adverse events will also be reported, and all supporting documentation emailed to Georgetown University’s Multicenter Project Management Office and to the study PI, Dr. Noel, within 24 hours.

If an adverse event meets any of the following criteria, it will be reported to the Georgetown DSMC as a SAE by the Sponsor-Investigator or designee per DSMC reporting guidelines.

SAEs will be collected and recorded from the time the patient receives the first dose in the study until he/she completes the End of Treatment visit. SAEs brought to the attention of the investigator at any time after cessation of the study drugs and considered by the investigator to be related or possibly related to the study drugs must be reported to the Sponsor-Investigator and Multicenter Project Management Office, if and when they occur.

### 8.3.5Serious Unexpected Suspected Adverse Reaction

A serious unexpected suspected adverse reaction is defined as an unexpected serious adverse event where there is a reasonable possibility that the drug caused the serious

adverse event. For the purposes of expedited safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### 8.3.6 Stopping Criteria

We will follow guidelines for early termination of the study per the 3+3 study design.

### 8.3.7 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. It's the responsibility of the **Site-Investigator** to report any Unexpected Suspected Adverse Reaction to the FDA as follows:

Report any unexpected fatal or life-threatening adverse experiences associated with the use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than 7 calendar days after initial receipt of the information. A life-threatening adverse experience is defined as anyadverse drug experience that places the subject (in the view of the investigator) at immediate risk ofdeath from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Report any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, within 15 calendar days after initial receipt of this information.

All SAEs, regardless of relationship to the study/study drug, will be summarized and reported to the FDA at annual reports by the Sponsor-Investigator.

A serious adverse drug experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity (i.e., substantial disruption of a person’s ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the expectedness assessment with the Section 7 reference safety information of the current investigator brochure (or risk information, if an IB is not required or available).

All MedWatch forms will be sent by the investigator or investigator’s team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Document Control Center
10903 New Hampshire Ave.
Bldg WO71, Rm. G112
Silver Spring, MD 20993-0002
FAX: 1-800-FDA-0178

### 8.3.8 Reporting of Pregnancy

In cases of pregnancy or suspected pregnancy, the patient is to be discontinued immediately (within 24 hours) from the study and the female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. Pregnancy, suspected pregnancy, a positive pregnancy test and pregnancy outcomes must be reported to the study PI, and the Multicenter Project Management Office. If the pregnancy results in spontaneous abortion or stillbirth, the event should be reported as an SAE. If there are any abnormal outcomes that meet the serious criteria, it must be reported as an SAE. Please follow the SAE reporting instructions. Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Pregnancy of the patient's partner is not considered to be an AE. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

### 8.3.9 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be reported to the study PI and Multicenter Project Management Office. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded on the eCRF; dosing information is recorded on the dose administration eCRF. If the overdose results in an AE, the AE must also be recorded as an AE. An overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE.

**Table 5: The timeframe for reporting Adverse Events/Unanticipated Problems**

| | |
|---|---|
| Deaths | |
| Any reportable death while on study or within 30 days of study | Immediately, within 24 hours, to PI, Georgetown Multicenter Project Management Office, ERYTECH (**SUSAR,** suspected unexpected serious adverse reactions, **ONLY**), and to the IRB (Per local IRB policy) |
| Any reportable death while off study | Immediately, within 24 hours, to PI, Georgetown Multicenter Project Management Office, ERYTECH (**SUSAR ONLY**), and to the IRB (Per local IRB policy) |
| Adverse Events/Unanticipated Problems | |
| Any reportable adverse events/unanticipated problems as described in Sections 8.3.2, 8.3.4 and 8.3.5 (other than death) | Immediately, within 24 hours to PI, Georgetown Multicenter Project Management Office, and ERYTECH |

| | |
|---|---|
| | (**SUSAR ONLY**),<br>Within 7 calendar days (or within local IRB guidelines) to the IRB, and<br>Within 7 or 15 calendar days to the FDA, as required |
| All adverse events regardless of grade and attribution should be submitted cumulatively | Entered into CRFs and<br>Include in DSMC reports |

**Erytech Reporting:**
Sites will report events/problems to the PI, Dr. Noel and the Georgetown Multicenter Project Management office and the Georgetown Multicenter Project Management Office will submit information as required to Erytech.

Email:
[redacted]

# 9 Study Drugs and Treatment Plan

## *9.1 Study Drugs Description*

### 9.1.1 Eryaspase

Eryaspase is a dispersion for infusion of allogeneic erythrocytes encapsulating recombinant *E. coli* L asparaginase, in a saline preservative solution. Eryaspase is an off-shelf investigational agent. Eryaspase is produced for each individual patient taking into account blood group and phenotype and dose of ASNase appropriate for body weight.

Eryaspase was previously studied as a single agent in twelve patients with pancreatic cancer. No patient experienced dose limiting toxicities at any dose level. One patient experienced grade 3 lymphopenia one patient experienced grade 1 allergic pruritus. Eryaspase was later studied in combination with chemotherapy in 93 patients with pancreatic cancer, in comparison to the control arm of chemo alone grade 3 and 4 hematological adverse event occurred with similar frequency between treatment arms. The most common adverse events were asthenia (68.8%), nausea (62.4%, anemia (45.2%), thrombocytopenia (43%), emesis (44.1%), abdominal pain (35.5%) and diarrhea (39.8%), however these are most likely secondary to chemotherapy[26].

In previous studies of Eryaspase in acute lymphocytic leukemia the most common adverse events were thrombocytopenia (13.6%), elevated transaminases (13.6%), anemia (8.8%), neutropenia (6.4%), and leukopenia (5.6%)[26].

Further information can be found in the current version of the Eryaspase Investigator's Brochure.

### 9.1.2 FOLFIRINOX (5-FU, Leucovorin, Irinotecan, and Oxaliplatin)

5-FU is an antineoplastic antimetabolite agent. It is commercially available as an injectable solution for IV use. 5-FU will be administered as per institutional procedure.

Leucovorin is folinic acid (the active metabolite of folic acid). It is an essential coenzyme for nucleic acid synthesis and is used to enhance the cytotoxicity of 5-FU. It is commercially available as a powder for reconstitution for IV use. Leucovorin will be administered as per institutional procedure.

Irinotecan is an antineoplastic agent of the topoisomerase I inhibitor class. It is commercially available as an aqueous solution intended for dilution prior to IV infusion. Irinotecan will be reconstituted/used as per the manufacturer's suggestions and will be administered as per institutional procedure.

Oxaliplatin an antineoplastic antimetabolite agent. It is commercially available as an injectable solution for IV use. Oxaliplatin will be administered as per institutional procedure.

## *9.2 Study Drugs Dosing*

### 9.2.1 Eryaspase

At the treatment initiation, Eryaspase will be prepared and dispatched after all screening assessments have been completed and the results reviewed and after it has been confirmed that the patient meets all eligibility criteria. The dose of Eryaspase will follow the dose escalation schema. Eryaspase is administered over approximately 60 minutes per bag, depending on the volume of the bag(s). The entire content of each bag is to be administered unless otherwise specified. Eryaspase administration must be completed before the expiry time clearly stated on the label of the Eryaspase bag. Date of administration, exact start and end times of infusion, and volume administered will be recorded on the Shipment and Administration Form (SAF) as described in the Investigational Medicinal Product (IMP) Manual. A ±1-day window is permitted for Eryaspase dosing for scheduling purposes.

Detailed instructions related to Eryaspase administration and contact information in case of any issues are provided in the IMP Manual.

### 9.2.2 FOLFIRINOX (5-FU, Leucovorin, Irinotecan, and Oxaliplatin)

- 5-fluorouracil 2400 mg/m² continuous infusion over 46 hours
- Oxaliplatin 85 mg/m² (Intravenous infusion)
- Irinotecan 150 mg/m² (Intravenous infusion)
- Leucovorin 400 mg/m2 (Intravenous infusion)

Institutional guidelines should be followed for the administration of FOLFIRINOX. It is recommended the administration be as follows:

1. Oxaliplatin is administered first over 2 hours,
2. Leucovorin over 2 hours (30 minutes prior to Irinotecan),
3. Irinotecan over 1.5 hours.

## *9.3 Other Medication & Supportive Care*

### 9.3.1 Antiemetic Therapy

Given the high incidences of nausea and vomiting associated with the FOLFIRINOX regimen, a combination of aprepitant, 5-HT3 antagonist, and dexamethasone before chemotherapy is strongly recommended.

### 9.3.2 Irinotecan-induced cholinergic syndrome

Atropine 0.25-1.0 mg IV may be given prior, during, or after infusion of irinotecan for irinotecan-induced cholinergic symptoms including lacrimation, rhinorrhea, diaphoresis, flushing, abdominal cramps, diarrhea, etc.

### 9.3.3 Growth Factor Support

Indications for use of GCSF should follow American Society for Cooperative Oncology (ASCO) guidelines. The choice of G-CSF support (filgrastim vs. pegfilgrastim) is at the discretion of the treating physician. Use of the erythropoiesis-stimulating agent is not allowed. It is strongly recommended that patients over the age of 65 receive growth factor support following initiation of treatment.

### 9.3.4 Transfusion of blood products

Transfusions are permitted. However, transfusion of fresh frozen plasma should be minimized, as it provides an exogenous source of asparagine. It is preferable to administer antithrombin III (AT III) concentrates in case of a decrease in AT III following Eryaspase administration. Hemoglobin must be ≥9 g/dL at Cycle 1 Day 1 and must be ≥8 g/dL before all subsequent doses. If hemoglobin is <8 g/dL, then appropriate measures must be taken according to standard clinical practice prior to further administration of chemotherapy.

### 9.3.5 Systemic and inhaled steroid treatment

A standard 3- to 5-day course of dexamethasone following the institutional standard of care is permitted for the prevention of treatment-induced nausea and vomiting. In addition, oral glucocorticoids at a daily dose of 1.5 mg dexamethasone (or equivalent) are permitted.

### 9.3.6 Antidiarrheal medications

Patients should be closely monitored for diarrhea. Dose modification is allowed for diarrhea. Patients should be instructed to take loperamide at the first sign of poorly formed or loose stools. Patients should take loperamide in the following fashion: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours until diarrhea resolved. The total dose of loperamide should not exceed 16 mg/day. Patients are instructed to notify their treating physicians if diarrhea is not resolved within 24 hours. Additional antidiarrheal medications including Lomotil, tincture of opium, or octreotide can be used.

### 9.3.7 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care.

## *9.4 Eryaspase Acquisition, Accountability, Preparation, Storage, and Handling*

### 9.4.1 Acquisition

Eryaspase will be dispatched directly to each site only after receipt of the required information in accordance with ERYTECH procedures.

**Information to be provided at study start**: Erythrocytes phenotype (including D, C, E, c, e, and K antigens), ABO blood group status, and Rhesus factor, all assessed on 2 separate samples, which can be collected on the same day. In addition, results of an irregular antibody screening test (IAST) are required. This information is required at least 5 working days before the first Eryaspase infusion. For group A and AB patients, sub-grouping A1/A1B and A2/A2B is required. If A subgroup, screening of anti-A1 antibodies (Indirect Coombs method) should be performed for A2 and A2B patients. The A2 and A2B patients will require anti-A1 antibodies screening before each administration along with IAST and documented on IAST form.

**Information to be provided during the treatment phase:** Results of IAST performed less than 3 days prior to each Eryaspase infusion.

A prescription form indicating patient identifiers and body weight should be provided at the latest 5 working days prior to each Eryaspase infusion.

The following information is required before Eryaspase can be shipped to the site:

- The name and contact details of the recipient, who should be the Investigator or designee.
- The location for delivery (local pharmacy or blood bank).

Detailed instructions for completing and providing the phenotype, blood group, and Rhesus factor information, the IAST results, and the prescription form are provided in the IMP manual. Eryaspase will be shipped to the Investigator in a qualified container by a specialized carrier who will ensure that the cold chain is maintained between +2-8°C (35-46°F).

If a temperature excursion outside the range of +2°C to +8°C (35-46°F) occurs, the product should be quarantined and ERYTECH Pharma should be contacted to determine the usability of the product. Refer to the IMP manual for ERYTECH contact information.

If it is not used immediately after receipt, it is mandatory that Eryaspase be stored at temperatures between +2 and +8°C (35-46°F).

Eryaspase may be stored at room temperature for up to 6 hours prior to administration, including infusion time; it must not be stored at room temperature for more than 6 hours.

### 9.4.2 Accountability

The Investigator or designee is responsible for IMP accountability, reconciliation, and record maintenance (i.e., records of receipt, reconciliation, and final disposition). Further guidance and information concerning the final disposition of unused IMP are provided in the IMP Manual.

### 9.4.3 Formulation, Appearance, Packaging, and Labelling

Eryaspase is packed in medical-grade polyvinyl chloride (PVC) bags. The final volume of the Eryaspase bag depends on the patient's weight and the dose prescribed. The volume of the bag ranges from 50 mL to 300 mL depending on the individual patient's dose (multiple bags may be required to achieve the full dose).

Three (3) removable segment-tubes are attached to the bag for use in blood compatibility testing before administration.

Label statements are specific to the clinical trial and comply with legal requirements for IMPs. The date and time of Eryaspase expiration will be noted on the label. In addition, the label displays specific information necessary for traceability of source cell material and medicinal product (blood bank identifier for original erythrocytes, phenotype, patient identification Preparation number, etc.) to allow verification of the patient's identity and blood group before administration.

### 9.4.4Preparation

Prior to administration, a complete compatibility test (cross match test) between the patient's blood and Eryaspase, using the removable segment tubes, should be performed to confirm compatibility. In case a patient receives multiple bags of Eryaspase to achieve the intended prescribed dose, a separate test must be performed with each Eryaspase bag to confirm compatibility.

Eryaspase should not be transferred to another container before infusion.
Eryaspase should not be mixed or administered simultaneously with any other products, solutions, or medicinal products.

After Eryaspase administration, partially administered and empty bags may be destroyed locally under the biomedical waste disposal process as approved by the specific institution. However, in case of a product defect or quality issue, ERYTECH must be contacted for further instruction. Additional details will be described in the IMP Manual.

Detailed instructions related to Eryaspase administration and contact information in case of any issues are provided in the IMP Manual.

# 10 Study Monitoring

## *10.1 Data Safety Monitoring Committee at Georgetown*

The Georgetown Lombardi Comprehensive Cancer Center (LCCC) will be responsible for the data and safety monitoring of this trial. As this study is an investigator-initiated phase I study utilizing FDA-approved on label, and off label therapies, it is considered a high-risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC). The Principal Investigator, Dr. Noel, will review the data including safety monitoring at study teleconferences with participating sites. All SAEs are required to be reported to the local and to the Georgetown IRB, per each IRB policy. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 3 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure. DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC Associate Director for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the Associate Director for Clinical Research. Of note, the DSMC will also review the safety data of the patients enrolled outside of Georgetown University. Georgetown University's Multicenter Project

Management Office will be tasked with the job of collecting primary source documentation for patients enrolled outside of Georgetown University. In addition, the data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMC at Georgetown to review.

# 11 STUDY ANALYSIS

## *11.1 Demographics and Baseline Characteristics*

All subject baseline characteristics and demographic data (age, sex, race, ethnicity, weight, height, body mass index, physical examination abnormalities, medical history, previous [within 6 months of screening]) and concomitant medications at study entry will be listed by study center and subject number and summarized with appropriate summary statistics

## *11.2 Safety Analysis*

All subjects who are enrolled and received at least one dose of study medication will be included in the safety population.

The primary safety endpoint is the subject incidence of Grade 3 or 4 adverse events. The number and percentage of all subjects who experience adverse events (AEs), serious adverse events (SAEs), or abnormal laboratory results will be reported.

Other safety endpoints include:
Clinically significant changes from baseline in all safety laboratory parameters;
Clinically significant changes from baseline in vital signs;
Incidence and type of clinically significant ECG abnormalities.

All clinical safety and tolerability data will be listed by subject and will be summarized by the study part. Treatment-emergent adverse events will be listed and summarized by System Organ Class, by relatedness, and by maximum severity. Serious adverse events and adverse events leading to withdrawal will be listed and summarized. Individual vital signs and change from baseline in vital signs will be listed by subject, and study visit, and summarized descriptively. Laboratory data (actual values and change from baseline) will be listed by subject and study.

## *11.3 Analysis of secondary endpoints*

Due to small sample sizes and dose heterogeneity, no statistical tests of hypotheses are planned for the study. Response data will be collected and summarized. Overall survival, and progression-free survival will also be graphically summarized using the Kaplan-Meier method.

# 12 Ethical Considerations

## *12.1 Institutional Review Board (IRB)*

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any serious adverse events that

meet the reporting criteria, as dictated by local regulations, will be reported to the IRB. During the conduct of the study, the investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

### *12.2 Ethical Conduct of the Study*

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

### *12.3 Subject Information and Consent*

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

### *12.4 Protection of Patient Confidentiality*

All patient records, questionnaires, and tissue specimens will be de-identified using a letter and number assigned to their case at the time of enrollment on study. No record or specimen will contain information which could identify the patient. The key which connects patient identifiable information with this assigned number will be held by the Principal investigator. For computer records, the key will be protected by a double password protection system. Any paper records will be contained in a locked cabinet within a locked office to ensure patient’s privacy is protected.

### *12.5 Investigator Responsibilities*

Prior to trial initiation, the Investigator will provide the Sponsor with a fully executed and signed FDA Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms also will be completed for all Sub-Investigators listed on the Form 1572 who will be involved directly in the treatment or evaluation of research subjects in this trial.

The study will be conducted in accordance with the Declaration of Helsinki (amended by the 59th World Medical Association General Assembly, October 2008) and Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines. Specifically, the study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by a properly constituted IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; and each subject will give his/her informed consent before any protocol-specific tests or evaluations are performed.

# 13 Data Management and Confidentiality

## *13.1 Data Sharing Plan*

Data sharing for this study will be conducted in compliance with the February 26, 2003 NIH Statement on Data Sharing (NOTICE: NOT-OD-03-032). The collaborating sites for this study generate a wide variety of scientific and clinical data and Data Sharing and Archiving will be handled by in accordance with NIH Statement on Data sharing, institutional internal document retention policies and all application rules, regulations and statutes. Subject to institutional policies, local IRB guidelines, and local, state and Federal laws and regulations including the Privacy Rule and the Bayh-Dole Act, we will make finished research data available through scientific presentations, publications (paper, web and other), depositing gene sequence, gene expression and other data in searchable electronic repositories, attendance at scientific meetings and extending invitations to scientists from other institutions for discussion. In accordance with the NIH policy, such data shall be made widely and freely available while safeguarding the privacy of participants and protecting Lombardi's confidential and proprietary data.

The participating sites will maintain awareness, and may participate in, discussions between members of multiple scientific and technical disciplines and their professional societies concerning data sharing, standards and best practices, and to create an environment that supports and develops data sharing tools. We will participate in or make ourselves aware of the outcome of any workshops the NIH or AACR will convene to address data sharing and which may address areas such as cleaning and formatting data, writing documentation, redacting data to protect subjects' identities and proprietary information, and estimating costs to prepare documentation and data for sharing.

The NIH has recognized the need to protect patentable and other proprietary data and notes the restrictions on the sharing of data that may be imposed by agreements with third parties. Under the Bayh-Dole Act, grantees have the right to elect and retain title to subject inventions developed with Federal funding, and further, to commercialize any invention to which they retain title. Since it is not the stated intent of the NIH statement on Data Sharing to discourage, impede or prohibit the development of commercial products from federally funded research, our collaborating sites will continue to perform inventive activities, to seek patent protection for inventions that relate to data generated and may choose to defer publication or enter into agreements with third parties that may result in certain restrictions on data sharing. We note that seeking patent protection results in publication of the patent application into the public domain and, thus, may result in the data being broadly disseminated.

All specimens submitted to any of the shared resource laboratories will be bar-coded upon receipt and assigned a unique identifier using a common software program. Tracking of specimens and their utilization will be carried out using a web-based system that will represent a modification of the systems presently in place at Georgetown (including but not limited to G-DOC, Georgetown Database of Cancer, Medidata Rave, REDCap), which will also give us the ability to track sample utilization. These systems have an "honest broker" interface which ensures HIPAA compliance and protection of any human subjects. As the same sample may well be used for genomic, proteomic, histopathological and clinical interrogation, assignment of a unique identifier as well as a common administrative structure ensures efficient cross-database interrogation.

## *13.2 Data security*

The rights and privacy of people who participate in sponsored clinical research will be protected at all times. In the event that data is intended for broader use, it will be de-identified and would not permit linkages to individual research participants and variables that could lead to deductive disclosure of the

identity of individual subjects. No efforts will be made to identify individual cases, and any shared archive data will not be linked to other identifiable data. The following de-identification and security procedures will be followed to share information with collaborators part of the study:

1) Deletion of 18 HIPAA identifiers
    a. Non-identifiable unique patient ID will be generated in G-DOC
2) Secure netID-based single sign-on (netID is Georgetown's LDAP based secure login system)
3) Users will have to *authenticate* themselves prior to accessing controlled data
4) Furthermore, based on their roles, users will require *authorization* to see specific studies
5) Auditing and security assessments will be performed on a quarterly basis to ensure appropriate de-identification procedures and use of data.

For future studies involving new data types that are not covered in the descriptions above, NIH policy on data sharing will be followed where applicable. For example, Genome Wide Association Studies, if conducted, will comply with *NIH Guidelines* NOT-OD-07-088 (http://grants.nih.gov/grants/gwas/) for data release. Following these guidelines, GWAS data will be submitted to NCBI's dbGAP (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap) or other tools as the NIH's policy on GWAS evolves.

### *13.3 Data Disclosure*

GUMC (Georgetown University Medical Center) has a Confidentiality and Non-Disclosure policy that pertains only to proprietary information belonging to GUMC. The disclosure of research information such as microarray analysis results is at the discretion of the faculty and staff. Notably, investigators with NIH funding are expected to make their data and results public in a reasonable time frame (Please see the University plan for sharing and distributing biomedical research resources at http://otc.georgetown.edu/documents/inventors/NIHGrantLetter_ModelOrganismsUpdate_6-27-05.doc . To protect institutional intellectual property, the institution does have an internal review process prior to submission of journal manuscripts. This process will be propagated to other study sites as well.

### *13.4 Record Retention*

The Investigator must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The Investigator must consult a Sponsor CRA before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Records must be retained for the longest of the following two periods:

- For two years following the date a marketing application is approved, or
- For two years after the development of the drug is discontinued if there is no marketing application

### *13.5 Use of Information and Publication*

It is understood by the Investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

The Sponsor recognizes the importance of communicating study data, whether positive or negative, in accordance with ICH GCP Section 6.15 and Article 30 of the Declaration of Helsinki, version 2008.

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## APPENDIX A: ECOG Performance Scale

| Grade | ECOG |
|---|---|
| 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 all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only 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. |