# Eryaspase
# Protocol GRASPANC 2018-01

## A Randomized, Phase 3 Study of Eryaspase in Combination with Chemotherapy versus Chemotherapy Alone as Second-Line Treatment in Patients with Pancreatic Adenocarcinoma

### TRYbeCA-1 – TRial of erYaspase in pancreatic CAncer

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| **Protocol Number:** | **GRASPANC 2018-01** |
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| **Version Number:** | 2.0 (Amended protocol), 14 December 2020 |
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# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# SPONSOR SIGNATURES

| | |
|---|---|
| Protocol ID: | GRASPANC 2018-01 |
| Protocol Title: | A Randomized, Phase 3 Study of Eryaspase in Combination with Chemotherapy versus Chemotherapy Alone as Second-Line Treatment in Patients with Pancreatic Adenocarcinoma |
| Protocol Version and Date: | Version 2.0 (Amended protocol), 14th December 2020 |

This amended clinical study protocol has been reviewed and approved by the study Sponsor.

*Signature* *Date*

Iman El Hariry, MD, PhD

Chief Medical Officer

# COORDINATING INVESTIGATOR SIGNATURES

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This amended clinical study protocol has been reviewed and approved by:

*Signature* *Date*

Pascal Hammel, MD, PhD

Coordinating Investigator

*Signature* *Date*

Manuel Hidalgo, MD, PhD

Coordinating Investigator

# INVESTIGATOR'S AGREEMENT

| | |
|---|---|
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| **Protocol Version and Date:** | Version 2.0 (Amended protocol), 14th December 2020 |

I have read the **Protocol GRASPANC 2018-01, Version** 2.0 (Amended protocol), 14th December 2020. I agree to abide by all provisions set forth herein. I will conduct the study as outlined herein, in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki, and will comply with the obligations and requirements of clinical investigators and all other requirements listed in the International Council for Harmonization (ICH) guideline for GCP.

I agree to comply with all regulations regarding clinical research that apply in the country where I am based. I agree to comply with all legislation regarding protection of privacy that applies in the country where I am based. I understand that all information concerning eryaspase and this protocol is confidential, and I agree to not use this information for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of ERYTECH Pharma.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

_____ _____

*Signature* *Date*

_____

*Printed Name of Investigator*

*Institution:*

# SYNOPSIS

**Study No.:** GRASPANC 2018-01

**Title of Study:** A Randomized, Phase 3 Study of Eryaspase in Combination with Chemotherapy versus Chemotherapy Alone as Second-Line Treatment in Patients with Pancreatic Adenocarcinoma

**Number of Study Centers:** approximately 100 study centers

Phase of Development: 3

**Objectives:**

**Primary Objective:**

To determine whether the addition of eryaspase to chemotherapy improves overall survival (OS) in second-line treatment of pancreatic adenocarcinoma compared to chemotherapy alone.

**Secondary Objectives:**

- To compare progression-free survival (PFS) between the two treatment arms.
- To compare the objective response rate (ORR) and duration of response (DoR) between the two treatment arms.
- To compare the disease control rate (DCR) between the two treatment arms.
- To evaluate the safety and tolerability of eryaspase in combination with chemotherapy versus chemotherapy alone.
- To assess the effect of eryaspase on quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).
- To determine the pharmacokinetics of eryaspase.
- To assess the immunogenicity of eryaspase in terms of the induction of anti-asparaginase (ASNase) antibodies and neutralizing antibodies.
- To evaluate the relationship of clinical outcome with relevant biomarkers and genetic changes present in tumor tissues and blood and/or serum samples.
- To investigate the predictive relationship between the patient's deoxyribonucleic acid (DNA) sequence variation, e.g. exploratory single nucleotide polymorphism [SNP] genotyping in select candidate genes, and their response to combination treatment in terms of safety and tolerability (pharmacogenetics [PGx]).

**Endpoints:**

**Primary Endpoint:**

Overall Survival (OS) in the ITT population.

**Secondary Endpoints:**

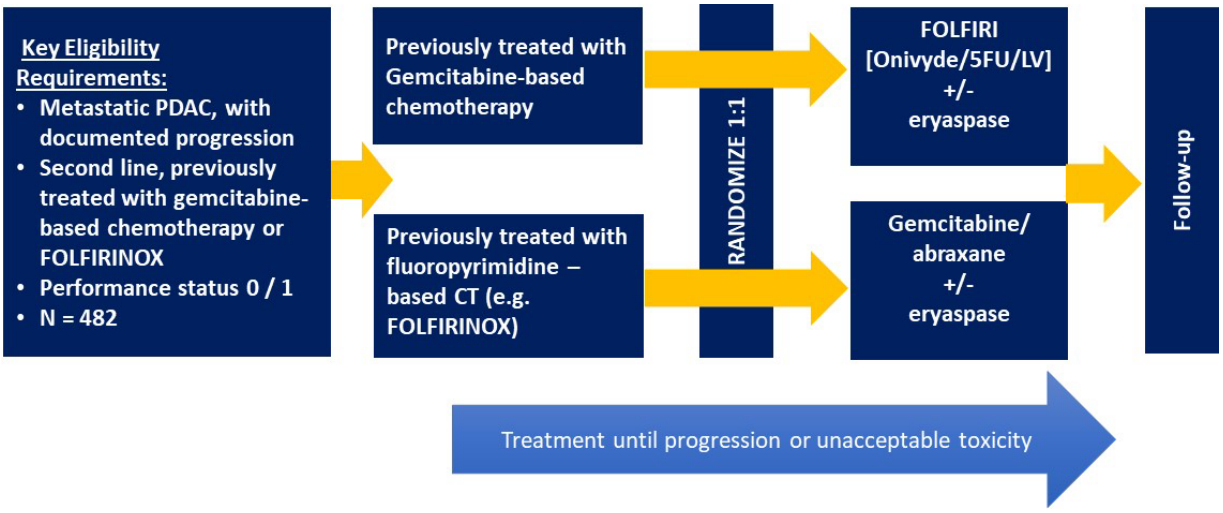
- Progression-free Survival (PFS),
- Objective Response Rate (ORR)

- Duration of Response (DoR)
- Disease Control Rate (DCR)
- Pharmacokinetics and Pharmacodynamics
- Anti- ASNase antibodies
- Adverse events AEs
- Quality of life (QoL)
- Biomarkers

**Trial Design/Methodology:**

This is an open-label, multicenter, randomized, Phase 3 study in patients with adenocarcinoma of the pancreas who have failed only one prior line of systemic anti-cancer therapy for advanced pancreatic cancer and have measurable disease as defined by the modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. After provision of informed consent and conduct of screening assessments, patients who meet all inclusion and no exclusion criteria will be randomized in a 1:1 ratio to one of the following treatment arms (see figure below):

- Arm A (investigational arm): eryaspase in combination with either gemcitabine/Abraxane or irinotecan-based therapy (FOLFIRI [FOLinic acid-Fluorouracil-IRInotecan regimen] or Onivyde®/5-fluorouracil/leucovorin),
- Arm B (control arm): gemcitabine/Abraxane or irinotecan-based therapy (FOLFIRI or Onivyde/5-fluorouracil/leucovorin).




The study will be divided into the following phases:

- **Screening Phase:** Screening assessments should occur within 3 weeks of randomization for assessment of the patient's overall eligibility.
- **Randomization Phase:** Randomization will occur after the patient has been determined to be eligible.

- **Treatment Phase:** The first dose of chemotherapy will be administered within 3 days after randomization. Treatment will continue until objective disease progression, unacceptable toxicity, or the patient's withdrawal of consent. Unacceptable toxicity is determined at investigator's discretion, but as a guidance, unacceptable toxicity could consist of prolonged Grade 3 or 4 toxicity lasting more than 2 weeks.
- In the investigational treatment arm (Arm A), eryaspase will be administered on Day 1 and Day 15 of each 4-week cycle in combination with chemotherapy. Eryaspase will be administered by intravenous (IV) infusion over approximately 60 minutes, followed by one hour of rest and then followed by chemotherapy infusion.
- Chemotherapy will be one of the following two treatment regimens:
  - Gemcitabine and Abraxane combination chemotherapy or
  - Irinotecan-based therapy: FOLFIRI (FOLinic acid-Fluorouracil-IRInotecan regimen) or Onivyde/5-fluorouracil (5-FU)/leucovorin (LV).
- The choice of the chemotherapy regimen for a particular patient will be determined by the prior treatment received in the first-line setting. Thus:
  - If a patient received prior gemcitabine/Abraxane in the first-line setting, then on disease progression, the patient will be assigned to FOLFIRI (or Onivyde/5-FU/LV) in the current study.
  - If a patient received prior irinotecan-based therapy (FOLinic acid-Fluorouracil-IRInotecan-Oxaliplatin; FOLFIRINOX), then on disease progression, the patient will be assigned to gemcitabine/Abraxane in the current study.
- **Follow-up Phase:** Patients will be monitored for survival at 8-week intervals. Patients who discontinue treatment for reasons other than disease progression will continue to be assessed radiologically every 8 weeks until disease progression, or until withdrawal from the study, or death.

Randomization will occur through an interactive web response system (IWRS). Patients will be randomized in a 1:1 ratio to chemotherapy with or without eryaspase. Randomization will be stratified according to the following factors:

- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1),
- Chemotherapy regimen in this study (gemcitabine/Abraxane or irinotecan-based treatment [FOLFIRI or its equivalent Onivyde/5-FU/LV]), and
- Time interval since initial diagnosis of advanced disease to date of randomization in the study (<6 months or ≥6 months).

An Independent Data Monitoring Committee (IDMC) will be established to review safety and efficacy data at regular intervals, including the interim and final analyses.

In addition, the safety of eryaspase in combination with irinotecan-based therapy or gemcitabine/Abraxane regimen will be reviewed by the IDMC after at least 10 patients are enrolled per regimen and have received at least one cycle of study therapy. The specific responsibilities and composition of the IDMC will be outlined in a separate document, the IDMC Charter.

**Safety and Efficacy Evaluations**

Assessments and timing of data collection are detailed in the Schedule of Events (Table 1).

**Safety Evaluations**

Clinical and laboratory parameters and adverse events will be assessed in all patients to evaluate disease status and toxicity. Patients will have safety assessments (laboratory tests, physical exams, vital signs including temperature, heart rate, and blood pressure, electrocardiograms [ECGs; to be performed during screening and then as clinically indicated], and performance status score) performed on Day 1 and Day 15 of each cycle and at the end of treatment.

Adverse event reporting will begin at the time of informed consent signature. Adverse events and concomitant medications will be collected until 90 days after the last dose of study treatment, or until start of a new anti-cancer treatment whichever is sooner.

**Efficacy Evaluations**

Tumor assessments utilizing thoraco-abdominal computed tomography (CT)/magnetic resonance imaging (MRI) scans will be repeated every 8 weeks, calculated from the date of randomization, until disease progression, or until withdrawal from the study, or death. Every effort should be made to adhere to the assessment schedule. The same imaging technique must be used throughout the study. For patients who discontinue treatment for reasons other than objective disease progression, and patients who start new anti-cancer treatment without evidence for objective disease progression, disease status evaluation will continue to be repeated every 8 weeks, calculated from the date of randomization, until disease progression. All radiological images must be collected in a de-identified manner, quality controlled, stored, and available for future review, including independent radiological review as necessary.

Survival information will be collected by phone, follow-up visit, or medical records review every 8 weeks from the date of the EOT visit until the patient's death, until the patient is lost to follow-up, or until study closure. Survival follow-up information will include collection of any subsequent anticancer therapy received after discontinuation from study medication.

Quality of life (QoL) assessment (EORTC QLQ-C30) will be performed, at Day 1 of each cycle prior to dosing, at the end of treatment visit and every 8 weeks during survival follow up.

**Pharmacokinetics, Pharmacodynamics, and Translational Research**

Where possible, blood and plasma samples will be collected in the eryaspase arm for pharmacokinetic (PK) (ASNase activity) and pharmacodynamic determination, and for immunogenicity evaluation.

Blood/plasma samples for PK and pharmacodynamic assessments will be collected at the following time points of Cycles 1 and 3 of study treatment: Day 1 prior to eryaspase administration, at 5-10 minutes post-eryaspase-infusion, at 5-8 days post-infusion (at the Investigator's discretion), and at Day 15 pre-dose. Samples will be analyzed for whole blood

and plasma concentrations of ASNase and amino acids. The sparse PK data will be combined with previous data as part of a Population PK (POP PK) analysis.

Samples for assessment of anti-L-ASNase antibodies and neutralizing antibodies will be collected pre-dose at Cycle 1 Day 1 and Day 15, at Day 1 of every second cycle thereafter, upon determination of disease progression and at the End of Treatment (EOT) visit, as specified in the Schedule of Events (Table 1).

Exploratory biomarker analyses will examine potential predictive biomarkers correlating with eryaspase activity. Tissue samples will be collected at study start. In addition, blood/plasma samples for biomarker analysis will be collected from all patients at Cycle 1 Day 1 and Day 15, at Day 1 of every second cycle thereafter, upon determination of disease progression, and at the EOT visit.

A blood sample for pharmacogenetic (PGx) analysis will be obtained once during the study, preferably during the screening phase, for patients who consent to this optional procedure.

**Number of Patients**: The target sample size is 482 patients.

**Criteria for Inclusion:**

A patient will be eligible for the study if all the following criteria are met:

1. Must be 18 years of age or older.
2. Must have histologically confirmed pancreatic adenocarcinoma.
3. Must have Stage III or IV disease (see **APPENDIX 1**).
4. Must have received one line of systemic chemotherapy in the advanced setting with or without targeted agents, immunotherapy, or radiotherapy for treatment of advanced pancreatic adenocarcinoma. NOTE: patients whose disease progresses on, or within 3 months of neo(adjuvant) chemotherapy may be considered eligible
5. Must have radiological evidence of disease progression following most recent prior treatment, defined as appearance of any new lesion or increase of >20% of one or more existing lesions.
6. Must have measurable lesion(s) per RECIST version 1.1 by CT scan with contrast (or MRI, if the patient is allergic to CT contrast media).
   - Measurable disease may be in the field of prior irradiation; however, at least 4 weeks must have elapsed between the completion of radiation therapy and the baseline scan documenting disease status.
   - Bone disease is considered radiologically measurable only if there is at least a 50% lytic component.

   **NOTE:** Bone disease consisting of blastic lesion only is not measurable.
7. Archival or fresh tumor tissue must be available for evaluating relevant biomarkers. Formalin-fixed paraffin-embedded [FFPE] block preferred, or a minimum of 10 unstained FFPE slides of one archived block is required. NOTE: if archival tissue is unavailable and an elective biopsy can't be scheduled due to COVID, this will be waived.

**NOTE**: Cytology samples from fine needle aspirates or brushing biopsies are not sufficient.

8. Must have adequate performance status (see **APPENDIX 2** and **APPENDIX 3**):
   a. ECOG Performance Status (PS) score of 0, or
   b. ECOG PS score one and score ≥80 on Karnofsky Performance Status (KPS) scale.

   **NOTE:** Must have body mass index (BMI) ≥18.5 kg/m$^2$ (obtained <14 days prior to randomization.
9. Must have life expectancy of >12 weeks according to the investigator's clinical judgment.
10. Females of childbearing potential must have a negative pregnancy test at screening and additional negative pregnancy test prior to first dose. Males and females of childbearing potential must agree to use a highly effective method of contraception during treatment and for at least 6 months after the last dose of study treatment. These include, but not limited to:
    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
       i. intravaginal
       ii. transdermal
    b. progestogen-only hormonal contraception associated with inhibition of ovulation:
       i. injectable
       ii. implantable
    c. intrauterine device (IUD)
    d. bilateral tubal occlusion
    e. vasectomised partner
    f. sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) is intended. The true abstinence is when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
    g. males with partners of childbearing potential must agree to use condoms

    **NOTE:** Since an indirect interaction between components of the oral contraceptives and ASNase cannot be ruled out, oral contraceptives are not considered acceptable as contraceptive methods in the current clinical trial. A method other than oral contraception should be used in women of childbearing potential.

    **NOTE:** All chemotherapeutic agents may be teratogenic and excreted in breast milk. Patients who are breast feeding should consider alternative methods.
11. Must have adequate laboratory parameters at baseline (obtained <14 days prior to randomization). Laboratory parameters outside of these ranges that are deemed clinically insignificant should be discussed with the medical monitor:
    a. Absolute neutrophil count ≥1.5 x 10$^9$/L.

b. Hemoglobin ≥9 g/dL. Patients with a baseline Hemoglobin ≥13 g/dL should be discussed with the medical monitor.
c. Platelet count ≥100,000/$mm^3$ (100 x $10^9$/L).
d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) (≤5 x ULN in presence of liver metastases).
e. Total bilirubin ≤ 1.5 x institutional ULN.
f. Serum creatinine within normal limits or calculated clearance >60 mL/min/1.73 $m^2$ for patients with serum creatinine levels above or below the institutional normal range.
g. Acceptable coagulation parameters: plasma antithrombin III >70% and fibrinogen ≥1.5 g/L.
h. Serum albumin ≥3.0 g/dL.

12. Patients requiring biliary stent placement must have the biliary stent placed >7 days prior to screening and must have normalization of bilirubin level after stenting.
13. Must not be receiving therapy in a concurrent clinical study and must agree not to participate in any other interventional clinical studies during their participation in this trial while on study treatment. Patients taking part in surveys or observational studies are eligible to participate in this study.
14. Must be able to understand and comply with the conditions of the protocol and must have read and understood the consent form and provided written informed consent.

**Criteria for Exclusion:**

A patient is not eligible to participate in the study if any of the following criteria are met:

1. Resectable or borderline resectable pancreatic adenocarcinoma at the time of signing the informed consent.
2. Histology other than pancreatic adenocarcinoma (for example, but not inclusive: neuroendocrine, adenosquamous, etc.).
3. More than one line of prior treatment in advanced or metastatic setting.
4. Patient has experienced medically significant acute decline in clinical status including
   a. Decline in ECOG PS to >1 (or KPS <70) between baseline visit and within 72 hours prior to randomization.
   b. Weight loss of ≥10% during screening.
5. Presence of active or symptomatic untreated central nervous system (CNS) metastases.

   **NOTE:** Patients with asymptomatic or stable CNS metastases are eligible, provided that the CNS metastases are radiologically and clinically stable, and the patient is off high-dose steroid treatment for at least one month prior to randomization.
6. Prior radiotherapy to the only area of measurable disease.

   **NOTE:** Patients must have completed treatment and recovered from all acute treatment-related toxicities prior to administration of the first dose of eryaspase or chemotherapy.
7. Bone as the only site of metastatic disease from pancreatic cancer (bone-only disease).

8. History of recent clinical pancreatitis, according to revised Atlanta criteria, within 3 months of randomization.

   **NOTE:** The revised Atlanta classification [1] requires that two or more of the following criteria be met for the diagnosis of acute pancreatitis: (a) abdominal pain suggestive of pancreatitis, (b) serum amylase or lipase level ≥3 x ULN, or (c) characteristic imaging findings using CT or MRI.

9. Neurosensory neuropathy > Grade 2 at baseline.
10. Pregnancy or breastfeeding.
11. History of infection with human immunodeficiency virus (HIV) and/or active infection with hepatitis B or hepatitis C.

    **NOTE:** Patients with unknown status of hepatitis B or C must be tested and declared negative before randomization.

12. Hypersensitivity to any of the components of the chemotherapy or ASNase.

    **NOTE:** Patients known to be homozygous for UGT1A1*28 who are assigned to an irinotecan-containing regimen must have the initial irinotecan dose reduced unless they have previously tolerated full doses of irinotecan. Subjects whose UGT1A1 status is not known but are being considered for irinotecan-based chemotherapy must be screened for UGT1A1*28 allele unless they have previously tolerated full doses of irinotecan before enrollment into the trial and must have the initial irinotecan dose reduced if demonstrated to be homozygous for the UGT1A1*28 allele.

    **NOTE:** Patients assigned to the irinotecan/5-FU arms in the study should not have dihydropyridine dehydrogenase deficiency (DPD). Patients whose DPD status is unknown at time of screening should be tested before enrollment in the irinotecan/5-FU arm unless they have previously tolerated full doses of 5-FU.

13. Patients who have received live or live attenuated vaccines within 3 weeks of randomization.
14. History of other malignancies

    **NOTE:** Adequately treated non-melanoma skin cancer or curatively treated in-situ cancer of the cervix may be eligible.

    **NOTE:** Patients successfully treated for other malignancies and are disease-free for at least 5 years may be eligible.

15. Any other severe acute or chronic condition/treatments that may increase the risk of study participation including:

    a. History of abdominal fistula, gastrointestinal perforation, peptic ulcer, or intra-abdominal abscess within 6 months prior to randomization.
    b. Current or history within 6 months prior to randomization of medically significant cardiovascular disease including symptomatic congestive heart failure >New York Heart Association (NYHA) Class II, unstable angina pectoris, clinically significant cardiac arrhythmia.
    c. Patients with pre-existing coagulopathy (e.g. hemophilia).

d. Psychiatric illness/social situations or any other serious uncontrolled medical disorders in the opinion of the Investigator that would limit compliance with study requirements.

**Investigational Product, Dosage and Mode of Administration:**

Eryaspase is a dispersion for infusion of homologous (allogeneic) erythrocytes encapsulating recombinant *E. coli* L--ASNase, in a saline preservative solution.

The dose of eryaspase is 100 U/Kg administered every two weeks (Day 1 and Day 15) until disease progression, unacceptable toxicity, or the patient's withdrawal of consent.

Eryaspase will be administered intravenously over approximately 60 minutes, followed by one hour of rest and then followed by chemotherapy infusions.

**Standard Chemotherapy dose and mode of administration:**

**Gemcitabine plus Abraxane (albumin-bound paclitaxel)** administered on Days 1, 8, and 15 of each 4-week cycle as follows:

- Abraxane (125 mg/m$^2$) IV over 30-40 minutes followed by
- Gemcitabine (1000 mg/m$^2$) IV over 30 minutes.

**Onivyde (irinotecan nanoliposomal) + 5-FU/leucovorin** administered on Days 1 and 15 of each 4-week cycle as follows:

- Onivyde 70 mg/m$^2$ IV over 90 minutes (recommended starting dose of Onivyde in patients homozygous for UGT1A1*28 is 50 mg/m$^2$),

  **NOTE:** The approved dose of Onivyde is based on the NAPOLI-1[36] trial, in which Onivyde was given at a dose of 80 mg/m$^2$ (i.e. equivalent of 70 mg/m$^2$ of irinotecan free base).

- Leucovorin 400 mg/m$^2$ IV over 30 minutes, and
  **NOTE**: Modifications to the leucovorin dose per sites standard administration protocol may be allowed in the study following approval from the medical monitor.
- 5-FU 2400 mg/m$^2$ over 46 hours.

**FOLFIRI (irinotecan, 5-FU, and leucovorin)** administered on Days 1 and 15 of each 4-week cycle as follows:

- Irinotecan 180 mg/m$^2$ IV infusion over 90 minutes (recommended starting dose of irinotecan in patients homozygous for UGT1A1*28 is 150 mg/m$^2$),
- Leucovorin 400 mg/m$^2$ IV infusion over two hours,
  **NOTE:** Modifications to the leucovorin dose per sites standard administration protocol may be allowed in the study following approval from the medical monitor.
- 5-FU 400 mg/m$^2$ IV bolus injection over 2-4 minutes, immediately following leucovorin infusion, and
- 5-FU 2400 mg/m$^2$ IV continuous infusion over 46 hours immediately following bolus 5-FU (Days 1 and 2, and Days 15 and 16).

**Rationale for Sample Size Estimation:**

With a power of 88.4% and an overall one-sided type I error of 2.5%, and including one interim analysis for efficacy with an O'Brien-Fleming-type stopping rule, a total of 390 deaths are required to detect a treatment effect hazard ratio of 0.725 for eryaspase plus chemotherapy versus chemotherapy alone. The interim analysis for efficacy will take place once 261 (67%) events have been observed.

Assuming a recruitment period of 26 months, a median overall survival in the control group of 6.0 months, a 10% probability of dropping out during the course of the study, and a minimum follow-up of 9 months, the study size will be based on the recruitment of 482 patients.

**Analysis Populations:**

**Intent to Treat (ITT) population:** All patients randomized, irrespective of whether they receive study medication.

**Safety population (SP):** All randomized patients who receive at least one dose of study medication (eryaspase or chemotherapy).

**Per-Protocol (PP) population:** The PP population is a subset of the ITT population, and consists of all randomized patients who meet the major inclusion criteria and none of the major exclusion criteria and who receive at least one cycle of treatment.

**Interim and Final Analyses:**

This study will have one interim analysis for superiority after 67% of the initial targeted numbers of events are observed.

**Primary Analysis:**

The primary analysis will be the comparison of OS between the two treatment arms in the ITT population using the one-sided stratified log-rank test, stratified for ECOG status, chemotherapy regimen, and time from diagnosis of advanced disease.

**Key Secondary Analyses:**

Progression-free survival (PFS) will be compared between the two treatment arms using the same method of analysis as for OS.

The following efficacy analyses will also be performed in the ITT population:

- ORR, defined as the proportion of patients who achieve objective tumor response (complete response [CR] or partial response [PR]) per RECIST 1.1. Each patient's best overall response (BOR) will be summarized (CR, PR, stable disease [SD], progressive disease [PD], or unknown).
- DCR (disease control rate), defined as the proportion of patients who achieve CR, PR and SD.

- DoR will be evaluated in patients who achieve CR/PR. It will be measured from the time CR/PR (whichever is first recorded) is first met to until the first date that recurrence or PD is objectively documented.

Extensive evaluation of the consistency of treatment effect for OS and PFS across the population as a whole will be undertaken by providing analyses in subgroups, with displays in forest plots and p-values for interaction.

All efficacy analyses will be repeated in the PP population.

Confirmatory testing for the primary and secondary efficacy endpoints will be performed hierarchically (OS followed by PFS followed by DCR followed by ORR) in order to account for multiplicity. Any statistically significant findings occurring below a non-significant result in the hierarchy will be considered as exploratory findings.

Safety and tolerability of eryaspase in combination with chemotherapy versus chemotherapy alone will be assessed by analyzing AEs (incidence, intensity, seriousness, and causal relationship of AEs to the study drug, action taken following AE), drug exposure (duration of treatment), dosing information/compliance, concomitant medications, clinical laboratory results, ECG findings, vital signs, physical examination, body weight, ECOG PS, and treatment and study termination status data.

# SCHEDULE OF EVENTS

**Table 1 Schedule of Events**

| Study Procedures | Selection period (within 3 weeks of Randomization) | Up to 3 days prior to Cycle 1 Day 1 | Treatment (28-day/4-week cycles) Cycle 1, 2, 3… | | | | | End of Treatment Visit | Follow-Up every 8 weeks |
|---|---|---|---|---|---|---|---|---|---|
| | | | D1 (+3 days)[1] | D8 | D15 (+ 3 days)[1] | D21 | D28 End of Cycle Evaluation (or D1 subsequent cycle) | | |
| Informed consent | X | | | | | | | | |
| Eligibility criteria | X | | X | | | | | | |
| Demography | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Pancreatic cancer disease history (including previous anti-cancer therapies) | X | | | | | | | | |
| Physical exam (including height [screening only] and weight) | X | | X | | X | | X | X | |
| Vital signs (temperature, BP, and heart rate) | X | | X | | X | | X | X | |
| Performance status[2] | X | | X | | X | | X | X | |
| 12-Lead ECG[3] | X | | X | | | | | | |
| Radiological assessments (CT or MRI)[4] | X | | X (every 8 weeks [±3 days] from time of randomization until disease progression, or death) | | | | | | |
| Randomization[5] | | X | | | | | | | |
| QoL assessment (EORTC QLQ-C30) | | | X | | | | | X | X[6] |
| AEs/SAEs | X (collected from time of informed consent until 90 days after the last study treatment or start of new anti-cancer treatment, whichever is sooner) | | | | | | | | |

**Table 1 Schedule of Events**

| Study Procedures | Selection period (within 3 weeks of Randomization) | Up to 3 days prior to Cycle 1 Day 1 | Treatment (28-day/4-week cycles) Cycle 1, 2, 3… | | | | | End of Treatment Visit | Follow-Up every 8 weeks |
|---|---|---|---|---|---|---|---|---|---|
| | | | D1 (+3 days)[1] | D8 | D15 (+ 3 days)[1] | D21 | D28 End of Cycle Evaluation (or D1 subsequent cycle) | | |
| Concomitant medications | X (record all medications taken 14 days prior to randomization to 90 days after the last study treatment or start of new anti-cancer treatment, whichever is sooner) | | | | | | | | |
| Study Drug | | | | | | | | | |
| Blood phenotype[7] | X[7] | | | | | | | | |
| Prescription with current weight | | | X[8] | | X[8] | | | | |
| Irregular antibody screening test (IAST) | X[7] | | X[9] | | X[9] | | | | |
| IAST historical result if available | X | | | | | | | | |
| Pre-eryaspase dose complete compatibility test | | | X[10] | | X[10] | | | | |
| Eryaspase administration | | | X | | X | | | | |
| Chemotherapy | | | Per standard of care | | | | | | |
| Gemcitabine/abraxane | | | X | X | X | | | | |
| Irinotecan-based regimen | | | X | | X | | | | |
| Biological Exams | | | | | | | | | |
| Hematology, biochemistry, and coagulation panels; CA19-9[11] | X[11,12] | | X | X[17] | X | X[17] | X | X | |
| Pregnancy test, for patients of childbearing potential[13] | X | | X | | | | | X | |
| Tumor tissue (for biomarker analysis, mandatory) | X | | | | | | | | |

**Table 1 Schedule of Events**

| Study Procedures | Selection period (within 3 weeks of Randomization) | Up to 3 days prior to Cycle 1 Day 1 | Treatment (28-day/4-week cycles) Cycle 1, 2, 3… | | | | | End of Treatment Visit | Follow-Up every 8 weeks |
|---|---|---|---|---|---|---|---|---|---|
| | | | D1 (+3 days)[1] | D8 | D15 (+ 3 days)[1] | D21 | D28 End of Cycle Evaluation (or D1 subsequent cycle) | | |
| Pharmacogenetic (PGx) sample (optional) | X (once during the study, preferably during the screening phase) | | | | | | | | |
| Plasma biomarkers such as ctDNA, proteomics, and transcriptomics (central labs) | | | X[18] | | X[14] | | | X | |
| Pharmacokinetic (ASNase activity) and pharmacodynamic (amino acid) sample (eryaspase arm only) | | | X[15] | | X[15] | | | | |
| Immunogenicity sample for anti-ASNase antibodies and neutralizing antibodies (eryaspase arm only) | | | X[18] | | X[14] | | | X | |
| Survival follow-up | | | | | | | | | X[16] |
| Subsequent anti-cancer treatments | | | | | | | | | X |

Abbreviations: D=Day; Rand=Randomization; BP=blood pressure; ECG=electrocardiogram; CT=computed tomography; MRI=magnetic resonance imaging; QoL=quality of life; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; AE=adverse event; SAE=serious adverse event; IAST=irregular antibody screening test; CA19-9=cancer antigen 19-9; ctDNA=circulating tumor deoxyribonucleic acid; ASNase=asparaginase.

1. There must be a minimum of 10 days between 2 eryaspase injections.
2. Per Eastern Cooperative Oncology Group (ECOG) /Karnofsky scales (KPS (if required per ECOG score) only during screening and at Cycle 1 Day 1) (See **APPENDIX 2** and **APPENDIX 3**).
3. Performed during screening, and then as clinically indicated.
4. Radiological assessment to be completed within 3 weeks of randomization and then every 8 weeks (±3 days) from time of randomization until disease progression, start of subsequent anti-cancer therapy or until withdrawal from the study, or death, using the same method throughout. Tumor assessments will continue in patients, who start new cancer treatment without evidence of disease progression Every effort should be made to adhere to

the evaluation schedule, irrespective of any treatment delays or modifications. Bone and/or brain scans are to be repeated every 12 weeks if clinically indicated.

5. Randomization performed via interactive web response system (IWRS) within 3 days of 1st chemotherapy dose.
6. During follow-up, questionnaire is to be completed every 8 weeks.
7. A complete RBC phenotype (including D, C, E, c, e, K and other antigens tested as per site practice), ABO blood group status, and Rhesus factor, all assessed on two separate samples (can be collected on the same day), to be done as soon as possible but preferably at least 5 working days before the first eryaspase infusion. Exact instructions are provided in the Investigational Medicinal Product (IMP) Manual. Historical results of IAST can be used at screening if known and available.
8. Prescription form indicating the patient's identifiers as well as his/her most recently collected weight, the Investigator 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 Cycle 1 Day 1 and then 5 working days prior to each subsequent eryaspase infusion. Exact instructions are provided in the IMP Manual.
9. IAST must be completed within 72 hours prior to each eryaspase administration. The results (of the previous infusion) will be provided to the Sponsor along with the prescription form prior to subsequent eryaspase infusion.
10. In case of incompatibility, collection of an additional blood sample will be required for further investigation.
11. Laboratory tests to be performed at local laboratory as follows:
    Hematology: Complete blood count with differential (hemoglobin, hematocrit, RBC count, white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).
    Biochemistry: Sodium, potassium, bicarbonate, calcium, chloride, creatinine, albumin, ammonia, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase, glucose, urea, triglycerides, total cholesterol, amylase, lipase and uric acid; Coagulation parameters – fibrinogen, antithrombin III.
    Tumor marker: CA19-9
12. Baseline labs to be collected within 14 days of randomization.
13. For patients of childbearing potential, serum pregnancy test to be performed during screening period and at End of Treatment and urine pregnancy test to be performed prior to dosing of any chemotherapy agent Day 1 of each cycle. Additional pregnancy testing should be performed in case of delayed menstrual period and is recommended to be performed monthly and until the end of treatment exposure extended by 30 days, in case of sexual activity.
14. Pre-dose Day 15 sample to be collected only during Cycle 1.
15. Where possible, samples to be collected Cycles 1 and 3 of study treatment on Day 1 prior to eryaspase administration, 5-10 minutes post-eryaspase infusion, 5 to 8 days post-infusion, and on Day 15 pre-dose.
16. Survival follow to be conducted 8 weeks after the patient's End of Treatment visit by phone, visit, or medical records review every 8 weeks (±3 days) from the date of the EOT visit (or date of last dose of study medication if patient is unable to come in due to declining health) until patient's death, lost to follow up, or study closure. Subsequent therapy should be collected during this follow-up.
17. For patients under eryaspase arm, in addition to regular evaluation of liver function tests before treatment administration, patients will be monitored on weekly basis in the event of occurrence of ≥Grade 2 elevation of liver enzymes and bilirubin levels.
18. Performed pre-dose Cycle 1 Day 1 and then pre-dose Day 1 of every second cycle thereafter i.e., Cycle 3 Day 1, Cycle 5 Day 1, upon determination of disease progression, or EOT, whichever is sooner.as clinically indicated.

** Additional lab tests may be required (e.g., weekly monitoring per standard practice or label requirements should be followed) and should be reported in the electronic Case Report Form (eCRF) if clinically significant.

# ABBREVIATIONS

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | Adverse event |
| ALL | Acute lymphoblastic leukemia |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukemia |
| ANC | Absolute neutrophil count |
| ANSM | *Agence nationale de sécurité du médicament et des produits de santé* |
| ASCO | American Society for Cooperative Oncology |
| ASN | Asparagine |
| ASNase | Asparaginase |
| ASNS | Asparagine synthetase |
| ASNS 0/1+ | Subgroup of patients with patients with low or no ASNS expression |
| ASNS 2+/3+ | Subgroup of patients with high ASNS expression |
| AST | Aspartate aminotransferase |
| AT III | Antithrombin III |
| BP | Blood pressure |
| BMI | Body Mass Index |
| BOR | Best overall response |
| CA19-9 | Cancer antigen 19-9 |
| CD | Compact disc |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CNS | Central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | Coronavirus Disease 2019 |
| CRO | Contract Research Organization |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CR | Complete response |
| CSR | Clinical Study Report |
| DNA | Deoxyribonucleic acid |
| ctDNA | Circulating tumor DNA |
| DCR | Disease control rate |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| DCR8 | Disease control rates when stable disease is required to last for at least 8 weeks |
| DCR12 | Disease control rates when stable disease is required to last for at least 12 weeks |
| DCR16 | Disease control rates when stable disease is required to last for at least 16 weeks |
| DoR | Duration of response |
| DPD | Dihydropyrimidine dehydrogenase deficiency |
| ECG | Electrocardiogram |
| ECOG | European Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic data capture |
| EMA | European Medicines Agency |
| EOT | End of Treatment |
| EORTC QLQ-C30 | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 |
| EU | European Union |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed paraffin-embedded FFPE |
| FOLFIRI | FOLinic acid-Fluorouracil-IRInotecan regimen |
| FOLFIRINOX | FOLinic acid-Fluorouracil-IRInotecan-Oxaliplatin regimen |
| mFOLFOX6 | Modified FOLinic acid-Fluorouracil-Oxaliplatin-6 regimen |
| GCP | Good Clinical Practice |
| GCSF | Granulocyte colony-stimulating factor |
| GGT | Gamma-glutamyl transferase |
| HCL | Hydrochloride |
| HHS | Health and Human Services |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| IAST | Irregular antibody screening test |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| ID | Identification |
| IDMC | Independent Data Monitoring Committee |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IMP | Investigational medicinal product |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ITT | Intent to Treat |
| IV | Intravenous |
| IWRS | Interactive web response system |
| Kg | Kilogram |
| KPS | Karnofsky Performance Status |
| KRAS | Kirsten rat sarcoma viral oncogene |
| LD | Longest diameter |
| LDH | Lactate dehydrogenase |
| LLN | Lower limit of normal |
| LV | Leucovorin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| mL | Milliliter |
| MRI | Magnetic resonance imaging |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| ND | No disease |
| NE | Non-evaluable |
| NYHA | New York Heart Association (classification) |
| OR | Objective response |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PAC | Pancreatic adenocarcinoma |
| PFS | Progression-free survival |
| PGx | Pharmacogenetics |
| PK | Pharmacokinetic |
| POP PK | Population pharmacokinetic |
| PP | Per Protocol |
| PR | Partial response |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| PS | Performance status |
| PVC | Polyvinyl chloride |
| QA | Quality assurance |
| QC | Quality control |
| QoL | Quality of life |
| RBCs | Red blood cells (erythrocytes) |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic acid |
| SA | Short axis |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Stable disease |
| SNP | Single-nucleotide polymorphism |
| SOE | Schedule of Events |
| SP | Safety population |
| SUSAR | Suspected unexpected serious adverse reaction |
| TRALI | Transfusion-related acute lung injury |
| TRYbeCA | TRial of erYaspase in pancreatic CAncer |
| U | Units |
| UGT | Uridine 5'-diphosphate glucuronosyltransferase |
| ULN | Upper limit of normal |
| US | United States |
| WBC | White blood cell |
| 5-FU | 5-fluorouracil |

# 1 INTRODUCTION

## 1.1 BACKGROUND

### 1.1.1 Pancreatic Cancer

Pancreatic adenocarcinoma (PAC) is one of the most aggressive and fatal malignancies, and is ranked as the seventh leading cause of cancer death.[2] The overall prognosis for PAC is poor, with a 5-year survival rate of 7%.[3] This is attributable to the difficulty of diagnosing pancreatic cancer in the early stages, poor tumor resectability, and poor response to chemotherapy.[4] Indeed, most patients with pancreatic cancer progress to either metastatic or locally advanced disease in the asymptomatic phase.[5]

Current treatment strategies for non-resectable, metastatic disease focus on conventional cytotoxic therapies. Established first-line treatment options include gemcitabine-based chemotherapy, either alone or in combination with nab-paclitaxel, or the FOLFIRINOX regimen (a combination of leucovorin [LV], 5-fluorouracil [5-FU], irinotecan, and oxaliplatin).[5] Gemcitabine treatment results in only modest improvements in overall survival (OS) and quality of life (QoL).[6] While the FOLFIRINOX regimen has demonstrated a robust clinical benefit compared with gemcitabine,[7] this regimen should only be considered for patients with good performance status (Eastern Cooperative Oncology Group Performance Status [ECOG PS] 0 or 1) due to considerable toxicity.[5 8]

In the second-line setting, there remains a lack of consensus regarding the standard of care. Treatment options are dependent on the risk-benefit balance for the patient and the treatment received in the first line.[5] In 2017, treatment guidelines were updated to recommend that the combination of nanoliposomal irinotecan (Onivyde®) with fluoropyrimidine regimens (i.e., 5-FU with LV) can be considered an active and tolerable treatment option in fit patients (ECOG PS ≥2) previously treated with gemcitabine-based therapy.[8 9] This combination extended survival by 1.9 months compared with patients treated with 5-FU in combination with LV.[10] No formal recommendations are available for patients who have progressed on first-line FOLFIRINOX; although gemcitabine is widely used in this setting, disease control is only achieved in one in 5 patients.[11] The limited efficacy provided by cytotoxic therapies is driving the need to identify novel targets for which to develop more effective therapeutic strategies.[4]

### 1.1.2 Tumor Cell Metabolism

Targeting tumor cell metabolism is one of the prospective therapeutic approaches.[12] PAC is characterized by extensive reprogramming of cellular metabolism, which enables tumor cells to proliferate in a nutrient-poor, hypoxic microenvironment. The acquisition of activating mutations in the oncogenic KRAS (Kirsten rat sarcoma virus) gene, which are observed in more than 90% of PACs, is central to this process.[13] Mutations in KRAS mediate the reprogramming of metabolic pathways that allow continued cellular proliferation in the absence of nutrients required by normal cells.[14 15] However, such reprogramming leads to dependence on metabolites that are utilized through non-canonical metabolic pathways, distinguishing these cells from normal cells. One such dependency is on the amino acid glutamine, which fuels anabolic metabolism and maintains redox balance with PAC cells.[16 17] Glutamine deprivation

or inhibition of enzymes downstream of KRAS in this aberrant metabolic pathway results in suppression of PAC growth.[16]

KRAS also regulates expression of amino acid transporters, which provide most of the biomass for growing cells.[18] This is despite the increased levels of glucose and glutamine consumption, which indicates that KRAS-mediated regulation of amino acid transporters is vital for tumor growth. In pancreatic cancer, KRAS has been shown to regulate macropinocytosis of proteins, yielding amino acids including glutamine and asparagine that may then enter the tricarboxylic acid cycle.[19]

Although glutamine is important for many cellular processes, including anaplerosis and lipid/nucleotide synthesis through its catabolism to glutamate, asparagine is the only amino acid that requires glutamine for *de novo* synthesis. A non-essential amino acid, asparagine is synthesized from glutamine and aspartic acid by the enzyme asparagine synthetase (ASNS).[20] Enhanced ASNS expression is a mechanism through which PAC cells adapt to hypoxia and glucose deprivation.[21] ASNS protects PAC cells from apoptosis induced by glucose deprivation through suppression of JNK/SAPK activation.[21]

Furthermore, it has also been demonstrated that KRAS, through ATF4 regulation, adapts amino acid uptake and asparagine biosynthesis.[22] As KRAS activation increases dependency on glutamine, knock-down of KRAS in low glutamine conditions results in poor clinical outcome.[22] Expression of ASNS – a target of ATF4 – has been identified as a key regulator of cancer cell proliferation, and contributes to apoptotic suppression, protein biosynthesis, and mTOR pathway activation.[22] Together, the modulation of glutamine and of asparagine levels leads to a critical vulnerability of PAC cells, which may be exploited in cancer therapeutics.

### 1.1.3 Asparaginase

Asparaginase is a key component of multi-agent chemotherapy used in the treatment of childhood acute lymphoblastic leukemia (ALL). In ALL, as leukemic cells lack ASNS, ASNase exerts its anti-tumor effect through depletion of serum asparagine by catalyzing the deamination of asparagine to aspartic acid.[20] This starves susceptible cells of asparagine required for protein synthesis, which results in cell cycle arrest and, ultimately, apoptosis.[20 23] As glutamine also acts as a substrate for the enzyme,[24] ASNase treatment also depletes serum glutamine levels, contributing further to cell growth inhibition.[20]

Several *in vitro* studies have demonstrated that reductions in both asparagine and glutamine levels are associated with inhibition of the mTOR pathway, which results in suppression of ribosomal protein synthesis.[25] Early experiments utilizing pancreatic cell lines demonstrated that inhibition of protein synthesis by ASNase could be reversed by supplementation with glutamine but not asparagine.[26] More recently, in cell lines expressing high levels of ASNS, glutamine was demonstrated to maintain the viability of cells in asparagine-deprived medium.[27] This suggests that glutaminase activity is an important component of the anti-tumor effect of ASNase, especially against tumors with high ASNS expression.[27]

Despite this *in vitro* sensitivity, clinical studies in solid tumors have been limited due to the challenge of a narrow therapeutic index for ASNase. Excessive toxicity of native and pegylated ASNase (peg-ASNase) formulations has been observed in clinical studies of solid tumors (pancreatic, ovarian) and multiple myeloma.[28-30] Indeed, a recent phase 1 study evaluating

peg-ASNase in combination with gemcitabine in patients with metastatic solid tumors and lymphoma was terminated early due to toxicity.[31]

## 1.2 CLINICAL EXPERIENCE WITH ERYASPASE

Encapsulation of ASNase within RBCs through a proprietary process is a novel approach to the delivery of ASNase at biologically effective doses with reduced propensity for toxic effects. The encapsulated ASNase remains biologically active, with a half-life of approximately two weeks.[32] It has been demonstrated that encapsulation has no effect on the permeability of RBCs to asparagine.[33] Thus, asparagine is actively transported across a concentration gradient into the RBC where it is de-aminated into aspartic acid and ammonia, depleting the serum of asparagine. It is postulated that the same process occurs with glutamine.

Encapsulation prevents the rapid degradation of ASNase in the blood, thus prolonging activity, and limits exposure to the immune system, thus impeding its intrinsic immunogenicity, and in particular hypersensitivity reactions.[32]

To date, five clinical trials have been conducted with eryaspase in pediatric and adult patients with ALL and acute myeloid leukemia (AML), and two clinical trials have been conducted in pancreatic cancer. The total number of patients treated thus far in the eryaspase clinical trial program is 307, as of a cut-off date of 28 Feb 2017. In the two studies in PAC, the total number of patients treated is 104.

## 1.3 ERYASPASE IN THE TREATMENT OF PANCREATIC CANCER

The potential of eryaspase in advanced PAC is being evaluated. GRASPANC 2008-02, a Phase 1 dose-escalation study, investigated eryaspase as a single agent in patients with metastatic PAC with at least two prior lines of therapy. Twelve patients received a single administration of eryaspase as monotherapy (25, 50, 100, or 150 U/Kg). No dose-limiting toxicity was reported. The recommended Phase two dose was determined to be 100 U/Kg every two weeks.[34] [35]

GRASPANC 2013-03, a phase 2 trial in advanced PAC, was completed in 2017. This was a multicenter, open-label study investigating eryaspase in combination with gemcitabine or mFOLFOX6 (modified FOLinic acid-Fluorouracil-Oxaliplatin-6 regimen) as second-line treatment in patients with metastatic PAC. Patients were randomized in a 2:1 ratio to either eryaspase plus chemotherapy or chemotherapy alone, and were stratified according to chemotherapy regimen. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS) in patients with low or no ASNS expression (ASNS 0/1+). Secondary endpoints included PFS and OS in the Intent to Treat (ITT) and high-ASNS expression (ASNS 2+/3+) populations, objective response, and toxicity. It should be noted that the study was not powered for the co-primary endpoints of PFS and OS. The conclusions regarding the efficacy of eryaspase when used in combination with gemcitabine or mFOLFOX6 chemotherapy in relation to these endpoints was to be based on observed hazard ratio (HR), with the study being considered positive if the HR for OS or for PFS was <0.85.

A total of 141 patients were randomized, 95 to eryaspase plus chemotherapy and 46 to chemotherapy alone. The majority of patients (~90%) received gemcitabine during the study. Baseline demographics and disease characteristics were generally well-balanced between

treatment arms. Median age (range) was 63 years (37–84) in the eryaspase arm compared with 63 years (43–80) with chemotherapy alone.

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, Table 2.

**Table 2 Key Efficacy Outcomes in the ITT Population and ASNS Subpopulations in GRASPANC 2013-03**

| | **Overall Survival (OS)** | | | | | |
|---|---|---|---|---|---|---|
| | **ITT** | | **ASNS 0/1+** | | **ASNS 2+/3+** | |
| | **Eryaspase + Chemo-therapy (95)** | **Chemo-therapy Alone (46)** | **Eryaspase + Chemo-therapy (66)** | **Chemo-therapy Alone (32)** | **Eryaspase + Chemo-therapy (29)** | **Chemo-therapy Alone (14)** |
| Event rate, N (%) | 82 (86.3) | 42 (91.3) | 55 (83.3) | 28 (87.5) | 27 (93.1) | 14 (100.0) |
| OS (weeks), Median (95% CI) | 26.1 (21.0, 28.9) | 19.0 (13.0, 21.7) | 27.0 (22.3, 31.1) | 21.3 (13.0, 31.0) | 21.0 (14.9, 29.4) | 11.9 (6.9, 19.7) |
| HR (95% CI) | 0.60 (0.41, 0.87) | | 0.63 (0.39, 1.01) | | 0.52 (0.26, 1.04) | |
| Log-Rank p-value | 0.008 | | 0.056 | | 0.063 | |
| OS rate at 24 weeks | 56.2% | 35.8% | 59.8% | 46.0% | 48.1% | 14.3% |
| | | | | | | |
| | **Progression-Free Survival (PFS)** | | | | | |
| | **ITT** | | **ASNS 0/1+** | | **ASNS 2+/3+** | |
| | **Eryaspase + Chemo-therapy (95)** | **Chemo-therapy Alone (46)** | **Eryaspase + Chemo-therapy (66)** | **Chemo-therapy Alone (32)** | **Eryaspase + Chemo-therapy (29)** | **Chemo-therapy Alone (14)** |
| Event rate, N (%) | 70 (73.7) | 36 (78.3) | 50 (75.8) | 23 (71.9) | 20 (69.0) | 13 (92.9) |
| PFS (weeks), Median (95% CI) | 8.6 (7.6, 14.6) | 6.9 (6.0, 7.6) | 8.6 (7.6, 14.6) | 7.6 (6.1, 16.3) | 8.0 (7.0, 14.9) | 6.0 (4.4, 6.9) |
| HR (95% CI) | 0.56 (0.37, 0.84) | | 0.67 (0.40, 1.12) | | 0.38 (0.18, 0.83) | |
| p-value | 0.005 | | 0.127 | | 0.015 | |
| PFS rate at 24 weeks | 18.7% | 5.8% | 20.4% | 9.0% | 14.3 | 0% |
| | | | | | | |
| | **Objective Response Rate (ORR)** | | | | | |
| | **ITT** | | **ASNS 0/1+** | | **ASNS 2+/3+** | |
| | **Eryaspase + Chemo-therapy (95)** | **Chemo-therapy Alone (46)** | **Eryaspase + Chemo-therapy (66)** | **Chemo-therapy Alone (32)** | **Eryaspase + Chemo-therapy (29)** | **Chemo-therapy Alone (14)** |
| Response rate, % (95% CI) | 12 (12.6) (6.7, 21.0) | 3 (6.5) (1.4, 17.9) | 10 (15.2) (7.5, 26.1) | 3 (9.4) (2.0, 25.0) | 2 (6.9) (0.8, 22.8) | 0 (0.0, 23.2) |

**Table 2 Key Efficacy Outcomes in the ITT Population and ASNS Subpopulations in GRASPANC 2013-03**

| | | | | | | |
|---|---|---|---|---|---|---|
| SD | 34 (35.8) | 8 (17.4) | 21 (31.8) | 7 (21.9) | 13 (44.8) | 1 (7.1) |
| PD | 42 (44.2) | 31 (67.4) | 32 (48.5) | 18 (56.3) | 10 (34.5) | 13 (92.9) |
| NE | 7 (7.4) | 4 (8.7) | 3 (4.5) | 4 (12.5) | 4 (13.8) | 0 |
| | | | | | | |
| | **Disease Control Rate (DCR)** | | | | | |
| | **ITT** | | **ASNS 0/1+** | | **ASNS 2+/3+** | |
| | **Eryaspase + Chemo-therapy (95)** | **Chemo-therapy Alone (46)** | **Eryaspase + Chemo-therapy (66)** | **Chemo-therapy Alone (32)** | **Eryaspase + Chemo-therapy (29)** | **Chemo-therapy Alone (14)** |
| DCR (CR+PR+SD), % (95% CI) | 46 (48.4) (38.0, 58.9) | 11 (23.9) (12.6, 38.8) | 31 (47.0) (34.6, 59.7) | 10 (31.3) (16.1, 50.0) | 15 (51.7) (32.5, 70.6) | 1 (7.1) (0.2, 33.9) |

OS: overall survival; ITT: Intent to Treat; ASNS: asparagine synthetase; CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; ORR: objective tumor response rate; SD: stable disease; PD: progressive disease; NE: Non-evaluable (no follow-up scans [4 consent withdrawal; 4 randomized but not treated; 1 fatal event; 1 target lesions unassessed; 1 treated but discontinued treatment before follow-up scans]; NE was similar between Investigator and independent review); DCR: disease control rate; CR: complete response; PR: partial response.
Response was determined per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria, based on independent radiological review.

In the ITT population, OS was statistically significantly longer in the eryaspase arm compared to the chemotherapy arm alone. Median OS improved from 19.0 weeks in the control arm to 26.1 weeks in the eryaspase arm, with an HR of 0.60 (95% CI: 0.41, 0.87; stratified log rank p = 0.008), Table 2 and Figure 1.

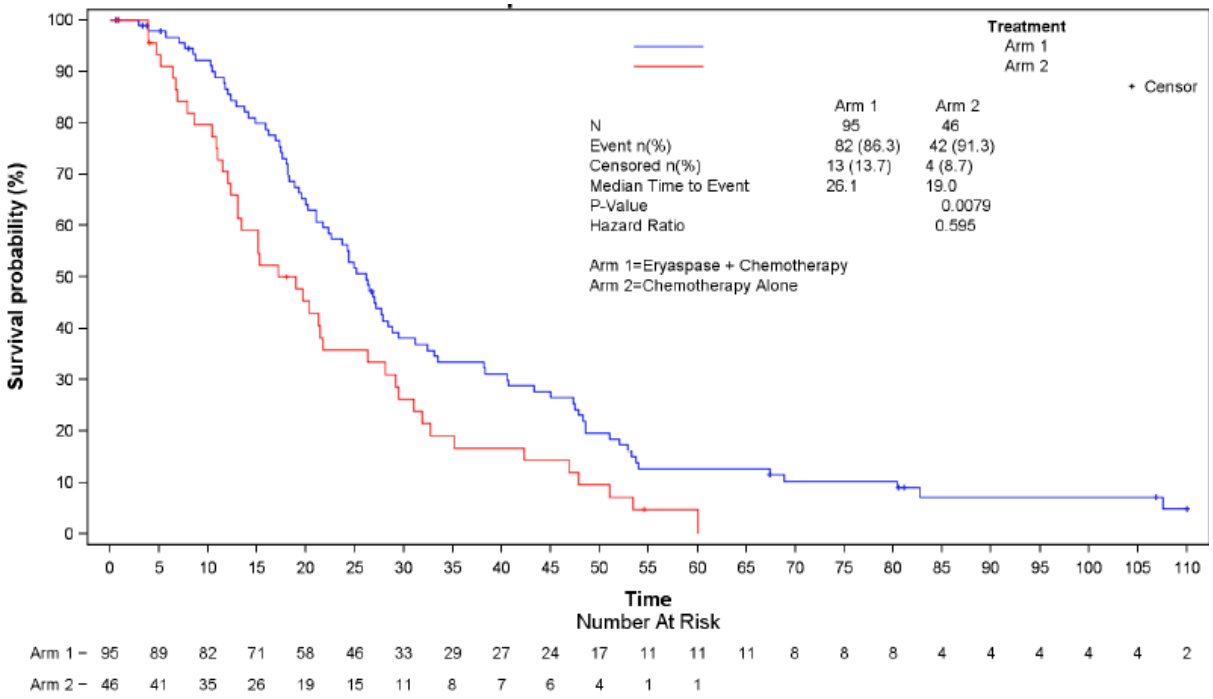



**Figure 1 GRASPANC 2013-03: OS Kaplan-Meier Curves – Full ITT Population**

The objective response rate was also higher in the eryaspase arm (12.6%) compared to the control arm (6.5%), as assessed by independent radiological review. Notably, there was one patient who achieved complete response in the eryaspase arm, Figure 2 and Figure 3. Similarly, the disease control rate (DCR) was also higher in the eryaspase arm (48.4% compared with 23.9% in the control arm).

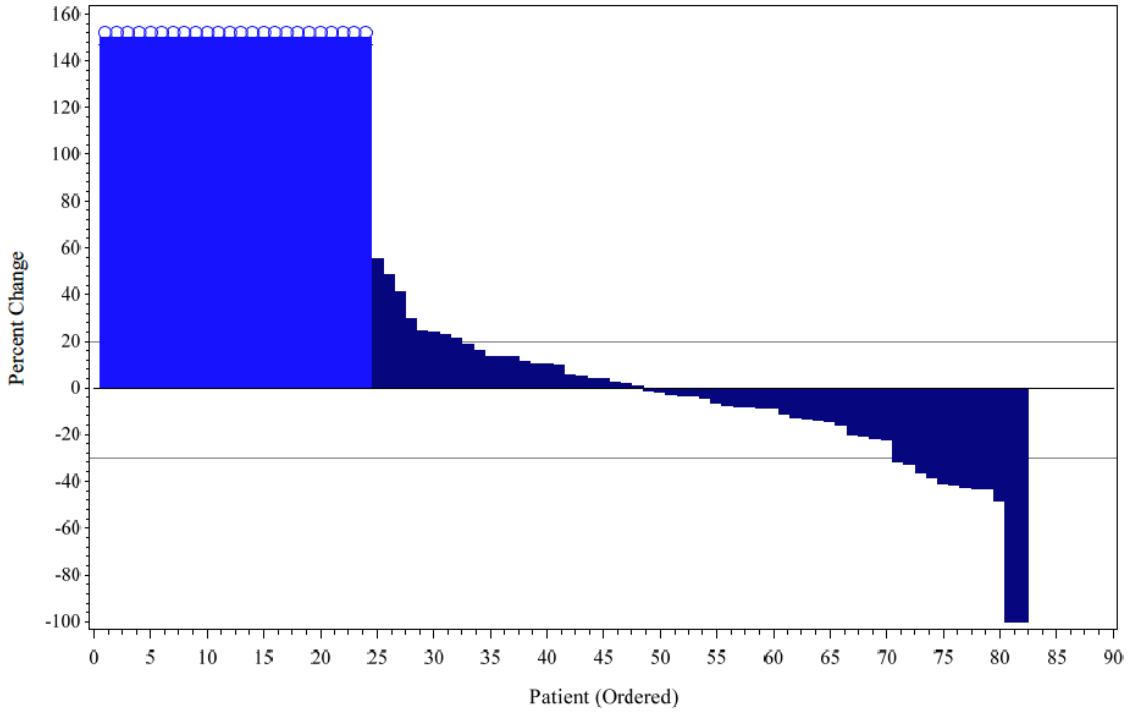



**Figure 2** **GRASPANC 2013-03: Best Response – Waterfall Plot (Percent Change from Baseline) (Eryaspase + Chemotherapy)**

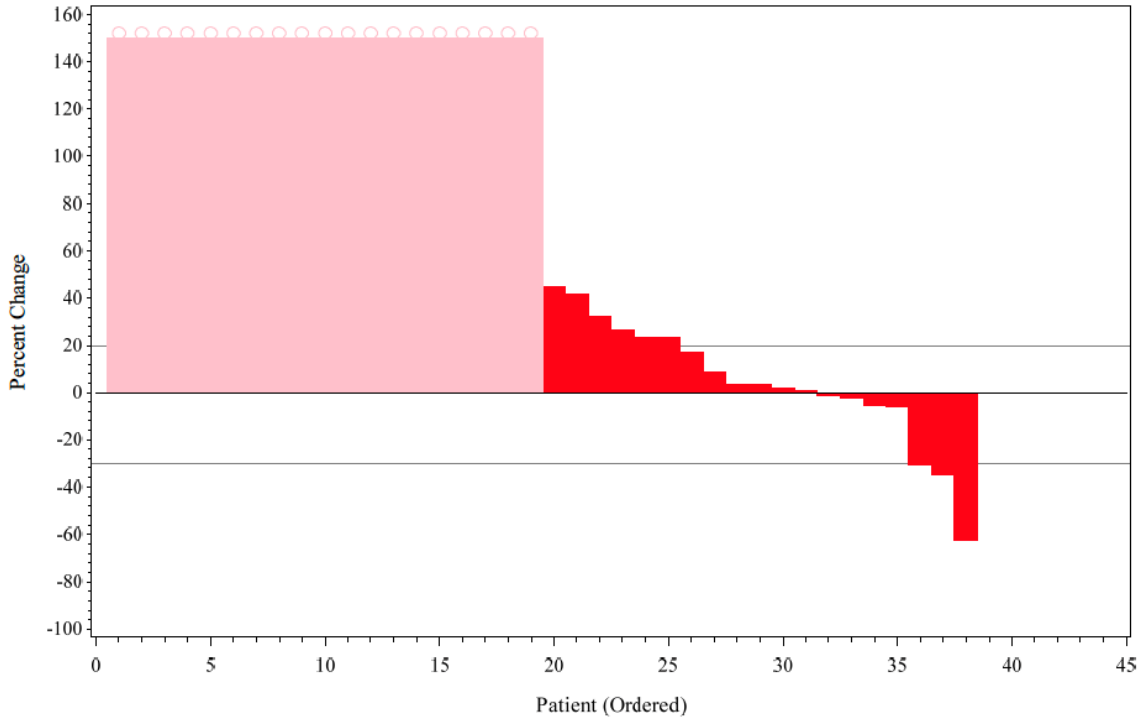



**Figure 3** **GRASPANC 2013 03: Best Response – Waterfall Plot (Percent Change from Baseline) (Chemotherapy Alone)**

Adverse events (AEs, Table 3) and serious adverse events (SAEs, Table 4) were slightly more frequent in the eryaspase arm; however, AEs resulting in treatment discontinuation and fatal outcomes were less frequent in the eryaspase arm. The safety profile of eryaspase added to chemotherapy revealed no unexpected findings, and eryaspase did not appear to add to the toxicity of chemotherapy.

**Table 3 Incidence of Treatment-Related Treatment-Emergent Adverse Events Reported in at Least 10% of Patients by MedDRA Preferred Term - Safety Population**

| Preferred Term | Eryaspase +Chemotherapy (N = 93) | Chemotherapy Alone (N = 44) |
|---|---|---|
| **Patients with at least one Adverse Event, n (%)** | **86 (92.5)** | **42 (95.5)** |
| Asthenia | 44 (47.3) | 24 (54.5) |
| Nausea | 40 (43.0) | 20 (45.5) |
| Thrombocytopenia | 40 (43.0) | 16 (36.4) |
| Anemia | 30 (32.3) | 16 (36.4) |
| Vomiting | 30 (32.3) | 10 (22.7) |
| Diarrhea | 20 (21.5) | 11 (25.0) |
| Neutropenia | 23 (24.7) | 7 (15.9) |
| Decreased appetite | 11 (11.8) | 13 (29.5) |
| Pyrexia | 15 (16.1) | 9 (20.5) |
| Fatigue | 10 (10.8) | 5 (11.4) |
| Stomatitis | 12 (12.9) | 3 (6.8) |
| Positive IAST | 14 (15.1) | 0 |

MedDRA: Medical Dictionary for Regulatory Activities; IAST: Irregular antibody screening test.
The Safety population includes all randomized patients who received at least 1 dose of study drug.

**Table 4 Treatment-Emergent Serious Adverse Events Reported in at Least 5% of Patients by MedDRA Preferred Term – Safety Population**

| Preferred Term | Eryaspase + Chemotherapy (N = 93) | Chemotherapy Alone (N = 44) |
|---|---|---|
| **Patients with at least one SAE, n (%)** | **42 (45.2)** | **22 (50.0)** |
| General physical health deterioration | 7 (7.5) | 4 (9.1) |
| Abdominal pain | 4 (4.3) | 1 (2.3) |
| Gastrointestinal hemorrhage | 2 (1.1) | 3 (6.8) |

| | | |
|---|---|---|
| Jaundice | 3 (3.2) | 1 (2.3) |

MedDRA: Medical Dictionary for Regulatory Activities: SAE: Serious adverse event.
The Safety population includes all randomized patients who received at least one dose of study drug.

## 1.4 STUDY RATIONALE

PAC is characterized by aberrant metabolic pathways, such as constitutive activation of KRAS signaling, that utilize asparagine and glutamine to circumvent the hypoxic and nutrient-poor tumor microenvironment. Perturbation of these pathways through deprivation of glutamine and asparagine results in loss of cell viability.

The potential benefit of ASNase therapy in PAC has been explored previously; however, these studies were stopped early due to the excessive toxicity of the ASNase.[28]

In the Phase 2 GRASPANC 2013-03 study, eryaspase demonstrated clinical benefits in terms of OS, PFS, and objective response rate (ORR) in the second-line treatment of metastatic PAC. The study met its primary endpoints, and the benefits of eryaspase (in terms of OS and PFS) reached statistical significance in the ITT population.

Given the results of this Phase 2, proof-of-concept study, eryaspase has the potential to add to the limited treatment options available for second-line PAC.

## 1.5 RISK/BENEFIT ASSESSMENT

### 1.5.1 Known Potential Risks

Eryaspase is a combination of two recognized products, RBCs and ASNase, whose safety profiles are well documented. Thus, the potential toxicity of eryaspase may arise from 3 main mechanisms: ASNase, RBCs, or a combination of the two components.

Please refer to the investigator's Brochure (IB) for additional details.

To date, there have been 8 clinical studies which have evaluated eryaspase in 307 patients. Specifically, two studies have been conducted in PAC, with eryaspase administered to 104 patients. Table 5 shows the adverse events reported in >10% of patients in the combined eryaspase-treated populations (ALL, AML, PAC), regardless of severity or attribution to treatment.

In the Phase 2 GRASPANC 2013-03 study, the safety profile of eryaspase added to chemotherapy revealed no unexpected findings, and eryaspase did not appear to add to the toxicity of chemotherapy.

**Table 5 Overview of AEs Affecting >10% of Patients in the Pooled Safety Population**

| **Preferred Term** | **All Patients N = 307** |
|---|---|
| **Patients with at least one AE, n (%)** | **303 (98.7)** |
| Thrombocytopenia | 168 (54.7) |

**Table 5 Overview of AEs Affecting >10% of Patients in the Pooled Safety Population**

| Preferred Term | All Patients N = 307 |
|---|---|
| Anemia | 131 (42.7) |
| Neutropenia | 119 (38.8) |
| Asthenia | 116 (37.8) |
| Leukopenia | 100 (32.6) |
| Pyrexia | 92 (30.0) |
| Stomatitis | 90 (29.3) |
| Nausea | 89 (29.0) |
| Transaminases increased | 84 (27.4) |
| Lymphopenia | 72 (23.5) |
| Diarrhea | 71 (23.1) |
| Hypokalemia | 68 (22.1) |
| Febrile bone marrow aplasia | 67 (21.8) |
| Abdominal pain | 66 (21.5) |
| Vomiting | 63 (20.5) |
| Antithrombin III decreased | 62 (20.2) |
| Gamma-glutamyl transferase (GGT) increased | 62 (20.2) |
| Hypoalbuminemia | 62 (20.2) |
| Musculoskeletal pain | 61 (19.9) |
| Hyperbilirubinemia | 54 (17.6) |
| Hyperglycemia | 52 (16.9) |
| Constipation | 48 (15.6) |
| Lipase increased | 45 (14.7) |
| Hyponatremia | 41 (13.4) |
| Decreased appetite | 40 (13.0) |
| Drug hypersensitivity | 39 (12.7) |
| Edema | 35 (11.4) |
| General physical health deterioration | 34 (11.1) |
| Febrile neutropenia | 32 (10.4) |
| Headache | 30 (9.8) |
| Peripheral neuropathy | 30 (9.8) |

### 1.5.2 Known Potential Benefits

The potential benefit for patients can be measured in terms of improvements in quality of life (QoL), OS, and PFS, factors associated with improved tumor control. The GRASPANC 2013-03 study evaluated eryaspase in combination with chemotherapy in the second-line treatment of PAC. This study demonstrated improved OS and PFS in the ITT population, with an acceptable tolerability profile.

### 1.5.3 Assessment of Potential Risks and Benefits

The potential benefit of ASNase therapy in PAC has been explored previously; however, these studies were stopped early due to the excessive toxicity of the ASNase.[28]

In the Phase 2 GRASPANC 2013-03 study, eryaspase demonstrated clinical benefits in terms of OS, PFS, and ORR in the second-line treatment of metastatic PAC.

The addition of eryaspase to chemotherapy did not lead to unexpected safety findings and did not appear to enhance the toxicity of chemotherapy.

Overall, the potential benefits of eryaspase outweigh the expected risks of participation in the study.

# 2 OBJECTIVES AND ENDPOINTS

## 2.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine whether the addition of eryaspase to chemotherapy improves overall survival (OS) in second-line treatment of pancreatic adenocarcinoma compared to chemotherapy alone.

## 2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To compare progression-free survival (PFS) between the two treatment arms.
- To compare the objective response rate (ORR) and duration of response (DoR) between the two treatment arms.
- To compare the disease control rate (DCR) between the two treatment arms.
- To evaluate the safety and tolerability of eryaspase in combination with chemotherapy versus chemotherapy alone
- To assess the effect of eryaspase on quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).
- To determine the pharmacokinetics of eryaspase.
- To assess the immunogenicity of eryaspase in terms of the induction of anti-ASNase antibodies and neutralizing antibodies.
- To evaluate the relationship of clinical outcome with relevant biomarkers and genetic changes present in tumor tissues and blood and/or serum samples.
- To investigate the predictive relationship between the patient's DNA sequence variation, e.g. exploratory SNP genotyping and their response to combination treatment in terms of safety and tolerability (pharmacogenetics [PGx]).

## 2.3 ENDPOINTS:

**Primary Endpoint:**

Overall Survival (OS) in the ITT population.

**Secondary Endpoints:**

- Progression-free Survival (PFS),
- Objective Response Rate (ORR)
- Duration of Response (DoR)
- Disease Control rate (DCR)
- Pharmacokinetics and pharmacodynamics
- Anti- ASNase antibodies

- Adverse events AEs
- Quality of life (QoL)
- Biomarkers

# 3 STUDY DESIGN

## 3.1 OVERALL DESIGN

This is an open-label, multicenter, randomized Phase 3 study in patients with adenocarcinoma of the pancreas who have failed only one prior line of systemic anti-cancer therapy for advanced disease and have measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. After provision of informed consent and conduct of screening assessments, patients who meet all inclusion and no exclusion criteria will be randomized in a 1:1 ratio to one of the following treatment arms, Table 4:

- Arm A (investigational arm): eryaspase in combination with either gemcitabine/Abraxane or irinotecan-based therapy (FOLFIRI [FOLinic acid-Fluorouracil-IRInotecan regimen] or Onivyde/5-fluorouracil/leucovorin),
- Arm B (control arm): gemcitabine/Abraxane, or irinotecan-based therapy (FOLFIRI or Onivyde/5-fluorouracil/leucovorin).

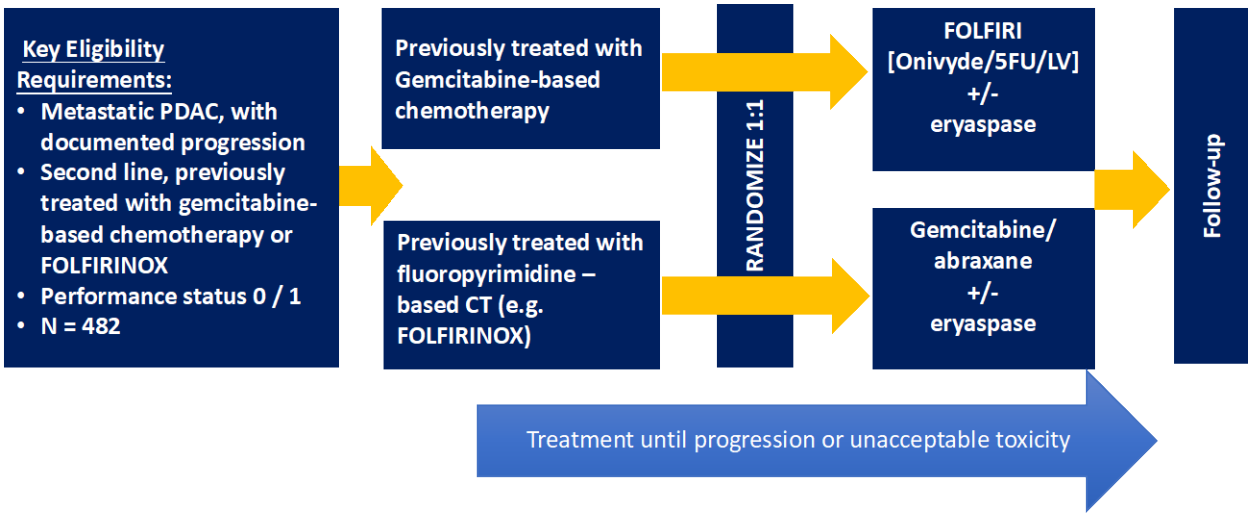



**Figure 4 Study Schema**

The study will be divided into the following phases:

**Screening Phase:** Screening assessments should occur within 3 weeks of randomization for assessment of the patient's overall eligibility.

**Randomization Phase:** Randomization will occur after the patient has been determined to be eligible.

**Treatment Phase:** The first dose of chemotherapy will be administered within 3 days after randomization. Treatment will continue until objective disease progression, unacceptable toxicity, or the patient's withdrawal of consent. Unacceptable toxicity is determined at investigator's discretion, but as a guidance, unacceptable toxicity could consist of prolonged Grade 3 or 4 toxicity lasting more than two weeks.

In the investigational treatment arm (Arm A), eryaspase will be administered on Day 1 and Day 15 of 4-week cycle in combination with chemotherapy. Eryaspase will be administered by intravenous (IV) infusion over approximately 60 minutes, followed by one hour of rest and then followed by chemotherapy infusion.

Chemotherapy will consist of one of the following two treatment regimens:

- Gemcitabine and Abraxane combination chemotherapy
- Irinotecan-based therapy: FOLFIRI (FOLinic acid-Fluorouracil-IRInotecan regimen) or Onivyde/5-fluorouracil (5-FU)/leucovorin (LV)

The choice of the chemotherapy regimen for a particular patient will be determined by the prior treatment received in the first-line setting. Thus:

- If a patient received prior gemcitabine/Abraxane in the first-line setting, then on disease progression, the patient will be assigned to FOLFIRI (or Onivyde/5-FU/LV) in the current study.
- If a patient received prior irinotecan-based therapy (FOLFIRINOX), then on disease progression, the patient will be assigned to gemcitabine/Abraxane in the current study.

**Follow-up Phase:** Patients will be monitored for survival at 8-week intervals. Patients who discontinue treatment for reasons other than disease progression will continue to be assessed radiologically every 8 weeks until disease progression, or until withdrawal from the study, or death.

Randomization will occur through an interactive web response system (IWRS). Patients will be randomized in a 1:1 ratio to chemotherapy with or without eryaspase. Randomization will be stratified according to the following factors:

- ECOG Performance Status(PS) score (0 or 1),
- Chemotherapy regimen in this study (gemcitabine/Abraxane or irinotecan-based treatment [FOLFIRI or its equivalent Onivyde/5-FU/LV]), and
- Time interval since initial diagnosis of advanced disease to randomization date (<6 months or ≥6 months).

An Independent Data Monitoring Committee (IDMC) will be established to review safety and efficacy data at regular intervals, including the interim and final analyses.

In addition, the safety of eryaspase in combination with irinotecan-based therapy or gemcitabine/Abraxane regimen will be reviewed by the IDMC after at least 10 patients are enrolled per regimen and have received at least one cycle of study therapy. The specific responsibilities and composition of the IDMC will be outlined in a separate document, the IDMC Charter.

**Safety and Efficacy Evaluations**

Assessments and timing of data collection are detailed in the Schedule of Events in Table 1.

**Safety Evaluations**

Clinical and laboratory parameters and adverse events will be assessed in all patients to evaluate disease status and toxicity. Patients will have safety assessments (laboratory tests, physical

exams, vital signs including temperature, heart rate, and blood pressure, electrocardiograms [ECGs performed during screening and then as clinically indicated], and performance status score performed on Day 1 and Day 15 of each cycle and at the End of Treatment visit.

Adverse event reporting will begin at the time of informed consent signature. Adverse events and concomitant medications will be collected until 90 days after the last dose of study treatment or until start of new anti-cancer treatment, whichever is sooner.

**Efficacy Evaluations**

Tumor assessments utilizing computed tomography (CT)/magnetic resonance imaging (MRI) scans will be repeated every 8 weeks, calculated from the date of randomization, until disease progression, or until withdrawal from the study, or death. Every effort should be made to adhere to the assessment schedule. The same imaging technique must be used throughout the study. Patients who discontinue treatment for reasons other than disease progression will continue to be assessed radiologically every 8 weeks until disease progression, or until withdrawal from the study, or death. For patients who discontinue treatment for reasons other than objective disease progression, and patients who start new anti-cancer treatment without evidence for objective disease progression, disease status evaluation will continue to be repeated every 8 weeks, calculated from the date of randomization, ,until disease progression. All radiological images must be collected in a de-identified manner, quality controlled, stored, and available for future review, including independent radiological review as necessary.

Survival information will be collected by phone, follow-up visit, or medical records review every 8 weeks from the date of the EOT visit until the patient's death, until the patient is lost to follow-up, or until study closure. Survival follow-up information will include collection of any subsequent anticancer therapy received after discontinuation from study medication.

QoL (EORTC QLQ-C30) assessment will be performed, at Day 1 of each cycle prior to dosing, at the End of Treatment visit, and every 8 weeks during survival follow up.

Blood and plasma samples will be collected in the eryaspase arm for pharmacokinetic (PK) and pharmacodynamic determination and for immunogenicity evaluation.

**Pharmacokinetics, Pharmacodynamics, and Translational Research**

Where possible, blood/plasma samples for PK and pharmacodynamic assessments will be collected at the following time points of Cycles 1 and 3 of study treatment: Day 1 prior to eryaspase administration, at 5-10 minutes post-eryaspsase infusion, at 5-8 days post-infusion (at the Investigator's discretion), and at Day 15 pre-dose. Samples will be analyzed for whole blood and plasma concentrations of ASNase and amino acids. The sparse PK data will be combined with previous data as part of a Population PK (POP PK) analysis.

Samples for assessment of anti-ASNase antibodies and neutralizing antibodies will be collected pre-dose at Cycle 1 Day 1 and Day 15, at Day 1 of every second cycle thereafter, upon determination of disease progression, and at the End of Treatment (EOT) visit, as specified in the Schedule of Events (Table 1).

Exploratory biomarker analyses will examine potential predictive biomarkers correlating with eryaspase activity. Tissue samples will be collected at study start. In addition, blood/plasma samples for biomarker analysis will be collected from all patients at Cycle 1 Day 1 and Day 15,

at Day 1 of every second cycle thereafter, upon determination of disease progression, and at the End of Treatment (EOT) visit, as specified in the Schedule of Events (Table 1).

A blood sample for pharmacogenetic (PGx) analysis will be obtained once during the study, preferably during the screening phase, for patients who consent to this optional procedure.

An effective contraception must be used by all patients during eryaspase treatment and for at least 6 months after discontinuation from eryaspase treatment. Since an indirect interaction between components of the oral contraception and free ASNase cannot be ruled out (potential increase in the risk of a change in coagulation parameters and thrombosis), oral contraceptives are not considered sufficiently reliable when co-administered with ASNase products. A method other than oral contraception should be used in women of childbearing potential.

## 3.2 NUMBER OF PATIENTS

The target sample size is 482 patients.

## 3.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

### 3.3.1 Choice of Chemotherapy (Control)

There is currently no standard of care for locally advanced or metastatic pancreatic cancer that has progressed following either FOLFIRINOX or a gemcitabine-based regimen. While there are potential options, there is no proven benefit for any regimen, and treatment choice is generally an extrapolation from front-line studies. Based on systematic reviews and National Comprehensive Cancer Network (NCCN) guidelines, gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based chemotherapy. Fluoropyrimidine-based chemotherapy regimens are acceptable second-line options for patients who received prior gemcitabine-based therapy. Based the recent Phase 3 NAPOLI-1 trial [36], Onivyde was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in combination with 5-FU/leucovorin for use following gemcitabine-based therapy. Therefore, the choices of chemotherapy as the backbone of treatment in both treatment arms are justified.

## 3.4 JUSTIFICATION FOR DOSE

The choice of dose and schedule for eryaspase (100 U/Kg given on Days 1 and 15 of each 4-week cycle) is based on safety and tolerability data from the phase 1 monotherapy study in PAC patients [37]. This dose and schedule were evaluated in Study GRASPANC 2013-03, and have demonstrated encouraging signs of clinical benefit in terms of OS, PFS, and DCR in patients treated with eryaspase combined with chemotherapy compared to chemotherapy alone.

The dosing schedule of chemotherapy agents will follow the label and standard practice for each respective agent.

## 3.5 END OF STUDY DEFINITION

A patient is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events, Table 1.

The end of the study is defined as completion of the last patient's last visit.

# 4 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the Investigator's team before patients are enrolled.

## 4.1 INCLUSION CRITERIA

A patient will be eligible for the study if all the following criteria are met:

1. Must be 18 years of age or older.
2. Must have histologically confirmed pancreatic adenocarcinoma.
3. Must have Stage III or IV disease (see **APPENDIX 1**).
4. Must have received one line of systemic chemotherapy in advanced setting with or without targeted agents, immunotherapy, or radiotherapy for treatment of advanced pancreatic adenocarcinoma.
   **NOTE:** patients whose disease progresses on, or within 3 months of neo(adjuvant) chemotherapy may be considered eligible
5. Must have radiological evidence of disease progression following most recent prior treatment, defined as appearance of any new lesion or increase of >20% of one or more existing lesions.
6. Must have measurable lesion(s) per RECIST version 1.1 by CT scan with contrast (or MRI, if the patient is allergic to CT contrast media).
   - Measurable disease may be in the field of prior irradiation; however, at least 4 weeks must have elapsed between the completion of radiation therapy and the baseline scan documenting disease status.
   - Bone disease is considered radiologically measurable only if there is at least a 50% lytic component.

   **NOTE:** Bone disease consisting of blastic lesion only is not measurable.
7. Archival or fresh tumor tissue must be available for evaluating relevant biomarkers. Formalin-fixed paraffin-embedded [FFPE] block preferred, or a minimum of 10 unstained FFPE slides of one archived block is required.
   **NOTE:** if archival tissue is unavailable and an elective biopsy can't be scheduled due to COVID, this will be waived.

   **NOTE**: Cytology samples from fine needle aspirates or brushing biopsies are not sufficient.
8. Must have adequate performance status (see **APPENDIX 2** and **APPENDIX 3**):
   a. ECOG Performance Status (PS) score of 0, or
   b. ECOG PS score one and score ≥80 on Karnofsky Performance Status (KPS) scale.

   **NOTE:** Must have body mass index (BMI) ≥18.5 kg/m$^2$ (obtained <14 days prior to randomization.
9. Must have life expectancy of >12 weeks according to the investigator's clinical judgment.

10. Females of childbearing potential must have a negative pregnancy test at screening and additional negative pregnancy test prior to first dose. Males and females of childbearing potential must agree to use a highly effective method of contraception during treatment and for at least 6 months after the last dose of study treatment. These include, but not limited to:

    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        i. intravaginal
        ii. transdermal
    b. progestogen-only hormonal contraception associated with inhibition of ovulation:
        i. injectable
        ii. implantable
    c. intrauterine device (IUD)
    d. bilateral tubal occlusion
    e. vasectomised partner
    f. sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments) is intended. The true abstinence is when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
    g. males with partners of childbearing potential must agree to use condoms

    **NOTE:** Since an indirect interaction between components of the oral contraceptives and ASNase cannot be ruled out, oral contraceptives are not considered acceptable as contraceptive methods in the current clinical trial. A method other than oral contraception should be used in women of childbearing potential.

    **NOTE:** All chemotherapeutic agents may be teratogenic and excreted in breast milk. Patients who are breast feeding should consider alternative methods.

11. Must have adequate laboratory parameters at baseline (obtained <14 days prior to randomization). Laboratory parameters outside of these ranges that are deemed clinically insignificant should be discussed with the medical monitor:

    a. Absolute neutrophil count $\geq 1.5 \times 10^9$/L.
    b. Hemoglobin ≥9 g/dL. Patients with a baseline Hemoglobin ≥13 g/dL should be discussed with the medical monitor
    c. Platelet count ≥100,000/mm$^3$ ($100 \times 10^9$/L).
    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x upper limit of normal (ULN) (≤5 x ULN in presence of liver metastases).
    e. Total bilirubin ≤ 1.5 x institutional ULN.
    f. Serum creatinine within normal limits or calculated clearance >60 mL/min/1.73 m$^2$ for patients with serum creatinine levels above or below the institutional normal range.
    g. Acceptable coagulation parameters: plasma antithrombin III >70% and fibrinogen ≥1.5 g/L.
    h. Serum albumin ≥3.0 g/dL.

12. Patients requiring biliary stent placement must have the biliary stent placed >7 days prior to screening and must have normalization of bilirubin level after stenting.
13. Must not be receiving therapy in a concurrent clinical study and must agree not to participate in any other interventional clinical studies during their participation in this trial while on study treatment. Patients taking part in surveys or observational studies are eligible to participate in this study.
14. Must be able to understand and comply with the conditions of the protocol and must have read and understood the consent form and provided written informed consent.

## 4.2 EXCLUSION CRITERIA

A patient is not eligible to participate in the study if any of the following criteria are met:

1. Resectable or borderline resectable pancreatic adenocarcinoma at the time of signing the informed consent.
2. Histology other than pancreatic adenocarcinoma (for example, but not inclusive: neuroendocrine, adenosquamous, etc.).
3. More than one line of prior treatment in advanced or metastatic setting.
4. Patient has experienced medically significant acute decline in clinical status including
   a. Decline in ECOG PS to >1 (or KPS <70) between baseline visit and within 72 hours prior to randomization.
   b. Weight loss of ≥10% during screening.
5. Presence of active or symptomatic untreated central nervous system (CNS) metastases.

   **NOTE:** Patients with asymptomatic or stable CNS metastases are eligible, provided that the CNS metastases are radiologically and clinically stable, and the patient is off high-dose steroid treatment for at least one month prior to randomization.
6. Prior radiotherapy to the only area of measurable disease.

   **NOTE:** Patients must have completed treatment and recovered from all acute treatment-related toxicities prior to administration of the first dose of eryaspase or chemotherapy.
7. Bone as the only site of metastatic disease from pancreatic cancer (bone-only disease).
8. History of recent clinical pancreatitis, according to revised Atlanta criteria, within 3 months of randomization.

   **NOTE:** The revised Atlanta classification [1] requires that two or more of the following criteria be met for the diagnosis of acute pancreatitis: (a) abdominal pain suggestive of pancreatitis, (b) serum amylase or lipase level ≥3 x ULN, or (c) characteristic imaging findings using CT or MRI.
9. Neurosensory neuropathy > Grade 2 at baseline.
10. Pregnancy or breastfeeding.
11. History of infection with human immunodeficiency virus (HIV) and/or active infection with hepatitis B or hepatitis C.

    **NOTE:** Patients with unknown status of hepatitis B or C must be tested and declared negative before randomization.

12. Hypersensitivity to any of the components of the chemotherapy or ASNase.

    **NOTE:** Patients known to be homozygous for UGT1A1*28 who are assigned to an irinotecan-containing regimen must have the initial irinotecan dose reduced unless they have previously tolerated full doses of irinotecan. Subjects whose UGT1A1 status is not known but are being considered for irinotecan-based chemotherapy must be screened for UGT1A1*28 allele unless they have previously tolerated full doses of irinotecan before enrollment into the trial and must have the initial irinotecan dose reduced if demonstrated to be homozygous for the UGT1A1*28 allele.

    **NOTE:** Patients assigned to the irinotecan/5-FU arms in the study should not have dihydropyridine dehydrogenase deficiency (DPD). Patients whose DPD status is unknown at time of screening should be tested before enrollment in the irinotecan/5-FU arm unless they have previously tolerated full doses of 5-FU.

13. Patients who have received live or live attenuated vaccines within 3 weeks of randomization.
14. History of other malignancies

    **NOTE:** Adequately treated non-melanoma skin cancer or curatively treated in-situ cancer of the cervix may be eligible.

    **NOTE:** Patients successfully treated for other malignancies and are disease-free for at least 5 years may be eligible.

15. Any other severe acute or chronic condition/treatments that may increase the risk of study participation including:

    a. History of abdominal fistula, gastrointestinal perforation, peptic ulcer, or intra-abdominal abscess within 6 months prior to randomization.
    b. Current or history within 6 months prior to randomization of medically significant cardiovascular disease including symptomatic congestive heart failure >New York Heart Association (NYHA) Class II, unstable angina pectoris, clinically significant cardiac arrhythmia.
    c. Patients with pre-existing coagulopathy (e.g. hemophilia).
    d. Psychiatric illness/social situations or any other serious uncontrolled medical disorders in the opinion of the Investigator that would limit compliance with study requirements.

## 4.3 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, in order to meet the Consolidated Standards of Reporting Trials (CONSORT) publication requirements and to respond to queries from regulatory authorities.

This minimal information includes demography and reason for screen failure.

Patients who do not meet the criteria for participation in this study because of abnormal laboratory findings at screening may be rescreened. Rescreened patients should be assigned the same patient number as for the initial screening.

# 5 STUDY TREATMENTS

## 5.1 DESCRIPTION OF STUDY DRUGS

The study drugs include all chemotherapy agents used in both treatment arms, as well as the investigational drug which is eryaspase (Investigational Medicinal Product).

The chemotherapy agents used in this study (gemcitabine, Abraxane, irinotecan, and 5-FU/leucovorin) are commercially available and are being used in accordance with approved labeling.

### 5.1.1 Eryaspase

Eryaspase is a dispersion for infusion of allogeneic RBCs encapsulating recombinant *E. coli* L-ASNase, 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.

Please refer to the IB for information regarding properties of the drug substance and drug product.

### 5.1.2 Gemcitabine and Abraxane

Gemcitabine is an antineoplastic agent. It is commercially available as a lyophilized powder for solution for IV use. Gemcitabine will be reconstituted/used as per the manufacturer's suggestions and will be administered as per institutional procedure.

Abraxane (protein-bound paclitaxel) is a microtubule inhibitor. It is commercially available as a lyophilized powder in a single-use vial for reconstitution for IV use. Abraxane will be reconstituted/used as per the manufacturer's suggestions and will be administered as per institutional procedure.

Gemcitabine and Abraxane will be sourced locally. Investigators are responsible for ensuring that patients receive supplies of gemcitabine and Abraxane for the entire duration of the study treatment, except in countries where regulatory authorities mandate that the Sponsor must supply all medications required for study participation.

### 5.1.3 Irinotecan and 5-FU/Leucovorin

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.

Onivyde (liposomal irinotecan) is a topoisomerase I inhibitor. It is commercially available as an opaque liposomal dispersion in a single-dose vial for IV infusion. Onivyde will be reconstituted/used as per the manufacturer's suggestions and will be administered as per institutional procedure.

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 or Onivyde and 5-FU/leucovorin will be sourced locally. investigators are responsible for ensuring that patients receive supplies for the entire duration of the study treatment, except in countries where regulatory authorities mandate that the Sponsor must supply all medications required for study participation.

## 5.2 DOSAGE AND ADMINISTRATION

### 5.2.1 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 is 100 U/Kg, to be administered at Days 1 and 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

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 and noted in the patient's electronic Case Report Form (eCRF).

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

### 5.2.2 Gemcitabine and Abraxane

Gemcitabine and Abraxane are to be administered on Days 1, 8, and 15 of each 4-week cycle as follows:

- Abraxane: 125 mg/m$^2$ IV over 30-40 minutes, followed by
- Gemcitabine: 1000 mg/m$^2$ IV over 30 minutes.

### 5.2.3 Irinotecan and 5-FU/Leucovorin

**Onivyde (irinotecan nanoliposomal) + 5-FU/leucovorin** are to be administered on Days 1 and 15 of each 4-week cycle as follows:

- Onivyde 70 mg/m$^2$ IV over 90 minutes (recommended starting dose of Onivyde in patients homozygous for UGT1A1*28 is 50 mg/m$^2$),

  **NOTE:** The approved dose of Onivyde is based on the NAPOLI-1[36] trial, in which Onivyde was given at a dose of 80 mg/m$^2$ (i.e. equivalent of 70 mg/m$^2$ of irinotecan free base).

- Leucovorin 400 mg/m$^2$ IV over 30 minutes, and
  **NOTE**: Modifications to the leucovorin dose per sites standard administration protocol may be allowed in the study following approval from the medical monitor.
- 5-FU 2400 mg/m$^2$ over 46 hours.

**FOLFIRI (irinotecan, 5-FU, and leucovorin)** is to be administered every 2 weeks on Day 1 and Day 15 of each 4-week cycle as follows:

- Irinotecan 180 mg/m$^2$ IV infusion over 90 minutes (recommended starting dose of irinotecan in patients homozygous for UGT1A1*28 is 150 mg/m$^2$)
- Leucovorin 400 mg/m$^2$ IV infusion over 2 hours
  **NOTE**: Modifications to the leucovorin dose per sites standard administration protocol may be allowed in the study following approval from the medical monitor.
- 5-FU 400 mg/m$^2$ IV bolus injection over 2-4 minutes, immediately following leucovorin infusion, and
- 5-FU 2400 mg/m$^2$ IV continuous infusion over 46 hours, immediately following bolus 5-FU.

### 5.2.4 Guidelines for Treatment Discontinuation and Dose Modification

Patients will be treated until disease progression, unacceptable toxicity as determined by the Investigator, or withdrawal of consent. Each patient will be evaluated for drug-related toxicity. If a patient experiences unacceptable toxicity for more than two weeks, then such patients should be withdrawn from study treatment. Unacceptable toxicity will be determined at the investigator's discretion; however, as a guidance, unacceptable toxicity could consist of prolonged Grade 3 or 4 toxicity not resolving within two weeks. The medical monitor must be consulted if any patient requires further treatment delays or dose modifications.

Throughout the study, the following toxicity criteria will be used to guide treatment modifications and treatment delays. However, standard practice at sites may also be referred to, particularly for any of the chemotherapy components.

Appropriate supportive care will be provided for the management of drug-related toxicities.

In the instance of adverse events that require course changes, then the general guidance is delaying dose as opposed to skipping a dose. This could mean that a cycle could be longer than 4 weeks.

#### 5.2.4.1 DOSE MODIFICATION FOR ERYASPASE

One 25% dose reduction of eryaspase is permitted at the first occurrence of an eryaspase-related toxicity. Additional dose reduction to 50% is allowed on second instance. If further dose reductions are necessary, then eryaspase should be discontinued.

Table 6 presents guidelines for carrying out eryaspase dose reductions when deemed appropriate. Dose reduction approach will depend on whether the drug is at site and ready for infusion (during a cycle) or is planned for a subsequent cycle. Dose reduction during a cycle will follow an empirical estimation of the volume in the eryaspase bag. Dose reduction in subsequent cycles will be reflected in the prescription form and will therefore be carried out by reducing the dose level per unit of body weight to be used in manufacturing the drug for the next cycle(s).

**Table 6 Pre-Specified Dose Reductions for Adverse Events Related to Eryaspase**

| Dose level | After manufacturing (during cycle) | Before manufacturing (subsequent cycle) |
|---|---|---|
| 0 | 100 U/Kg (full bag) | 100 U/Kg |
| -1 | 75% of the bag volume | 75 U/Kg |
| -2 | 50% of the bag volume | 50 U/Kg |

After a dose reduction, the dose of eryaspase may be re-escalated to the previous higher dose level, provided that toxicity resolves to at Grade 1 (or 2 where specified).

Treatment with eryaspase may be delayed for up to 2 weeks at the first instance of an eryaspase-related toxicity to allow for resolution of toxicity, defined as a return to ≤Grade 2, where indicated. The sponsor's Medical Monitor must be consulted if any patient requires further treatment delays or dose modifications. If eryaspase-related adverse events do not resolve after a period of 2 weeks, the patient should discontinue eryaspase and should then complete the EOT visit and Follow-up visits per the Schedule of Events (Table 1).

#### 5.2.4.2 DOSE MODIFICATIONS FOR CHEMOTHERAPY (WITH OR WITHOUT ERYASPASE)

The product labeling information and local institutional practice should be referred to regarding hematological and non-hematological AEs attributable to the individual chemotherapy agents used in this study. In addition, it is recommended that patients receive pre-medication according to respective product labeling information. In case of Abraxane and Onivyde, pre-medication standard doses of dexamethasone (or an equivalent corticosteroid) together with a 5-hydroxytryptamine 3 (5-HT3) antagonist (or other antiemetic) at least 30 minutes prior to start of chemotherapy infusion.

##### 5.2.4.2.1 DOSE MODIFICATIONS FOR GEMCITABINE AND ABRAXANE

Table 7 presents a summary of dose modifications for gemcitabine, Abraxane, and eryaspase. Patients who experience adverse events will be re-evaluated weekly, or more often according to the Investigator's discretion. Dose delays or reduction for gemcitabine or Abraxane follow the respective prescribing information, and are provided in the table below for ensuring consistency

across sites. If toxicities do not resolve within two weeks, then the patient will discontinue the study treatment, but will continue to be followed for 90 days or until start of new anti-cancer treatment, whichever is first, for adverse events and serious adverse events. Thereafter, the patient will be followed for radiological disease assessment and survival until withdrawal from study or death.

**Table 7 Dose Modifications for Gemcitabine, Abraxane, and Eryaspase**

| | Abraxane | Gemcitabine | Eryaspase |
|---|---|---|---|
| **Hypersensitivity Reactions:** | | | |
| **Grade 1:** transient flushing/rash, intervention not indicated | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 2**: intervention/ infusion interruption indicated; responds promptly to symptomatic treatment | Maintain original dose level | Maintain original dose level | During cycle→ interrupt for transient period and then resume(1)<br>Subsequent cycles → Maintain dose level |
| **Grade 3:** Prolonged recurrence of symptoms ± clinical sequelae, or anaphylaxis (symptomatic bronchospasm, edema/angioedema, hypotension, parenteral intervention required) infusion interruption indicated; responds promptly to symptomatic treatment | During cycle → delay dose until resolved to ≤Grade 2, then full dose | During cycle → delay dose until resolved to ≤Grade 2, then full dose | During cycle → delay until resolved ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| **Grade 4:** Systemic allergic reaction or anaphylaxis | Discontinue | Discontinue | Discontinue |
| **Pancreatitis:** | | | |
| **Grade 2:** enzyme (lipase/amylase) elevation >3.0 ULN, or Radiological findings only | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 3:** Symptomatic pancreatitis [Severe pain, vomiting; Lipase /amylase elevation | During cycle → delay dose until resolved to ≤Grade 2, then full dose | During cycle → delay dose until resolved to ≤Grade 2, then full dose | During cycle → Delay until resolved to ≤Grade 2, then ↓ to 75% of dose |

**Table 7 Dose Modifications for Gemcitabine, Abraxane, and Eryaspase**

| | Abraxane | Gemcitabine | Eryaspase |
|---|---|---|---|
| >3.0 ULN for >3 days; Medical intervention needed | | | Subsequent cycles → 75 U/Kg |
| **Grade 4:** Symptomatic pancreatitis, life-threatening | Discontinue | Discontinue | Discontinue |
| **Hepatic toxicity:** | | | |
| *No Hepatic metastasis* | | | |
| **Grade 1:** ALT/AST >3.0 x ULN, and total bilirubin ≤1.5 x ULN | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 2:** ALT/AST ≤5.0 x ULN and total bilirubin ≤1.5 x ULN | Maintain original dose level | Maintain original dose level | During cycle → ↓ to 75% of dose<br>Subsequent cycles → 100 U/Kg |
| **Grade 3:** ALT/AST >5.0 x ULN, and total bilirubin >2 x ULN | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 100 mg/m$^2$<br>Subsequent cycles → 100 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 800 mg/m$^2$<br>Subsequent cycles → 800 mg/m$^2$ | During cycle → Delay until resolved to ≤Grade 2, then ↓ to 75% of dose<br>Subsequent cycles → 75 U/Kg |
| **Grade 4:** ALT/AST >20.0 x ULN, or total bilirubin >2 x ULN | Discontinue | Discontinue | Discontinue |
| **Hepatic metastasis** | | | |
| ALT/AST >5.0 x ULN - ≤10.0 x ULN<br>and total bilirubin ≤1.5 x ULN | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| ALT/AST >10.0 - 20.0 x ULN, and total bilirubin ≤1.5 x ULN | During cycle → delay until resolved to ≤10.0, then ↓ to 100 mg/m$^2$<br>Subsequent cycles → 100 mg/m$^2$ | During cycle → delay dose until resolved to ALT/AST <10.0 x ULN, then ↓ to 800 mg/m$^2$<br>Subsequent cycles → 800 mg/m$^2$ | During cycle → delay until resolved to ≤10.0, then ↓ to 50% of dose<br>Subsequent cycles → 50 U/Kg |
| ALT/AST >20.0 x ULN and total bilirubin ≤1.5 x ULN | Discontinue | Discontinue | Discontinue |
| Total bilirubin >2.0 x ULN | Discontinue | Discontinue | Discontinue |

**Table 7 Dose Modifications for Gemcitabine, Abraxane, and Eryaspase**

| | Abraxane | Gemcitabine | Eryaspase |
|---|---|---|---|
| **Motor or Sensory Neuropathy** | | | |
| **Grade 1 or Grade 2** | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 3 or Grade 4** | During cycle → delay until resolved to ≤Grade 2, then ↓ to 100 mg/m$^2$<br>Subsequent cycles → 100 mg/m$^2$ | During cycle → delay until resolved to ≤Grade 2, then ↓ to 800 mg/m$^2$<br>Subsequent cycles → 800 mg/m$^2$ | Maintain original dose level |
| **Hematological Toxicity – Neutropenia (Absolute Neutrophil Count [ANC]):** | | | |
| **Grade 1:** <lower limit of normal (LLN) to 1.5 x 10$^9$/L | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 2:** <1.5 x 10$^9$/L - ≥1 x 10$^9$/L | During cycle → delay until resolved to ≤Grade 1 then ↓ to 100 mg/m$^2$<br>Subsequent cycles → 100 mg/m$^2$ | During cycle → delay until resolved to ≤Grade 1 then then ↓ to 800 mg/m$^2$<br>Subsequent cycles → 800 mg/m$^2$ | Maintain original dose level |
| **Grade 3:** <1.0 x 10$^9$/L - ≥0.5 x 10$^9$/L | Day 1 → delay until resolved<br>Day 8 → ↓ to 100 mg/m$^2$<br>Day 15 → ↓ to 75 mg/m$^2$ | Day 1 → delay until resolved<br>Day 8 → ↓ to 800 mg/m$^2$<br>Day 15 → ↓ to 600 mg/m$^2$ | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| **Grade 4:** <0.5 x 10$^9$/L<br>or<br>Febrile neutropenia | Day 1 → delay until resolved<br>Day 8 → delay dose<br>Day 15 → delay dose | Day 1 → delay until resolved<br>Day 8 → delay dose<br>Day 15 → delay dose | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| **Other hematological toxicities (anemia and thrombocytopenia) follow same guidelines as recommended for neutropenia** | | | |
| **Other laboratory investigations** | | | |
| Any **Grade 1** or **Grade 2** | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| Any **Grade 3** or **Grade 4** – not clinically significant | During cycle → delay dose until resolved to ≤Grade 2, then full dose | During cycle → delay dose until resolved to ≤Grade 2, then full dose | During cycle → Delay until resolved to ≤Grade 2, then full dose |

**Table 7 Dose Modifications for Gemcitabine, Abraxane, and Eryaspase**

| | **Abraxane** | **Gemcitabine** | **Eryaspase** |
|---|---|---|---|
| | Subsequent cycles → Maintain original dose level | Subsequent cycles → Maintain original dose level | Subsequent cycles → Maintain original dose level |
| Any **Grade 3** or **Grade 4** – clinically significant | During cycle → delay until resolved to ≤Grade 2, then ↓ to 100 mg/m$^2$<br>Subsequent cycles → 100 mg/m$^2$ | During cycle → delay until resolved to ≤Grade 2, then ↓ to 800 mg/m$^2$<br>Subsequent cycles → 800 mg/m$^2$ | During cycle → Delay until resolved to ≤Grade 2, then ↓ to 75% of dose<br>Subsequent cycles→ 75 U/Kg |
| **Other non-Hematological Adverse Event:** | | | |
| Any **Grade 1** toxicity | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| Any other **Grade 2** toxicity | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| Any other **Grade 3** toxicity | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → full original dose | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → full original dose | During cycle → delay until resolved ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| Upper gastro-intestinal (GI) peptic ulcer **Grades 2** or **3** | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → full original dose | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → full original dose | During cycle → delay until resolved to ≤Grade 1, then use next lower dose level<br>Subsequent cycles → next lower dose level |
| Any other **Grade 4** toxicity | During cycle→ delay until resolved to ≤Grade 2, then ↓ to 100 mg/m$^2$<br>Subsequent cycles → 100 mg/m$^2$ | During cycle→ delay until resolved to ≤Grade 2, then ↓ to 800 mg/m$^2$<br>Subsequent cycles → 800 mg/m$^2$ | During cycle→ delay until resolved ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| Upper gastro-intestinal (GI) peptic ulcer **Grade 4**, and/or **life-threatening GI bleeding** | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → full original dose | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → full original dose | Withdraw |
| **IMP Incompatibility:** | | | |

**Table 7 Dose Modifications for Gemcitabine, Abraxane, and Eryaspase**

| | Abraxane | Gemcitabine | Eryaspase |
|---|---|---|---|
| Positive serologic cross-match test result | No actions for the chemotherapy. Repeat eryaspase manufacturing. If persists, discontinue. | | |

(1) Infusion may be resumed at a lower infusion rate, provided that it is within shelf-life and the infusion is completed within the 6-hour window of bringing eryaspase to room temperature.

#### 5.2.4.2.2 DOSE MODIFICATIONS FOR IRINOTECAN AND 5-FU/LEUCOVORIN

Table 8 presents a summary of dose modifications for irinotecan, Onivyde, and eryaspase. Patients who experience adverse events will be re-evaluated weekly, or more often according to the Investigator's discretion. Dose delays or reductions for irinotecan or Onivyde follow the respective prescribing information, and are provided in the table below for consistency across sites. If toxicities do not resolve to ≤Grade 2 within two weeks, then the patient will discontinue the study treatment, but will continue to be followed for 90 days or until start of new anti-cancer treatment, whichever is first, for adverse events and serious adverse events. The patient will be followed for radiological disease assessment and must complete an EOT visit and Follow-up visits per the Schedule of Events (Table 1).

Following 5-FU treatment, mucositis, stomatitis, hand-foot syndrome, and diarrhea occur most commonly. Leukopenia is the usual dose-limiting toxicity after IV bolus administration. Patients with dihydropyrimidine dehydrogenase deficiency (DPD) are at risk of severe life-threatening toxicity with 5-FU. While severe deficiency is rare, 3-4% of the population has some degree of DPD deficiency. Patients with DPD deficiency cannot be enrolled in the 5-FU arm unless they have tolerated full doses of 5-FU previously. In general, dose modifications and delays follow a similar approach to that used with irinotecan. However, in case of mucositis or stomatitis, only 5-FU (and not irinotecan or eryaspase) should be withheld during the cycle, and resumed at full dose in subsequent cycles.

**Table 8 Dose Modifications for Irinotecan, Onivyde, and Eryaspase**

| | Irinotecan(1) | Onivyde(2,3) | Eryaspase |
|---|---|---|---|
| **Hypersensitivity Reactions:** | | | |
| **Grade 1:** transient flushing/rash, intervention not indicated | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 2:** intervention/ infusion interruption indicated; responds promptly to symptomatic treatment | Maintain original dose level | Maintain original dose level | During cycle → interrupt for transient period and then resume(4)<br>Subsequent cycles → Maintain original dose level |

**Table 8 Dose Modifications for Irinotecan, Onivyde, and Eryaspase**

| | **Irinotecan**[1] | **Onivyde**[2,3] | **Eryaspase** |
|---|---|---|---|
| **Grade 3:** Prolonged recurrence of symptoms ± clinical sequelae, or anaphylaxis (symptomatic bronchospasm, edema/angioedema, hypotension, parenteral intervention required) | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 150 mg/m$^2$<br>Subsequent cycles → 180 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$ | During cycle → delay until resolved ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| **Grade 4:** Systemic allergic reaction or anaphylaxis | Discontinue | Discontinue | Discontinue |
| **Pancreatitis:** | | | |
| **Grade 2:** enzyme (lipase/amylase) elevation >3.0 x ULN, or Radiological findings only | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 3:** Symptomatic pancreatitis [Severe pain, vomiting; Lipase or amylase elevation >3.0 x ULN for >3 days; and Medical intervention needed | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 150 mg/m$^2$<br>Subsequent cycles → 150 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$ | During cycle → Delay until resolved to ≤Grade 2, then ↓ to 75% of dose<br>Subsequent cycles → 75 U/Kg |
| **Grade 4:** Symptomatic pancreatitis, life-threatening | Discontinue | Discontinue | Discontinue |
| **Hepatic toxicity:** | | | |
| *No Hepatic metastasis* | | | |
| **Grade 1:** ALT/AST >3.0 x ULN, and total bilirubin ≤1.5 x ULN | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 2:** ALT/AST ≤5.0 x ULN and total bilirubin ≤1.5 x ULN | During cycle → ↓ to 150 mg/m$^2$<br>Subsequent cycles → Maintain original dose level | Maintain original dose level | During cycle → ↓ to 75% of dose<br>Subsequent cycles → Maintain original dose level |
| **Grade 3:** ALT/AST >5.0 x ULN, and total bilirubin >2 x ULN | Discontinue | Discontinue | During cycle → Delay until resolved to ≤Grade 2, then ↓ to 75% of dose |

**Table 8 Dose Modifications for Irinotecan, Onivyde, and Eryaspase**

| | **Irinotecan**[1] | **Onivyde**[2,3] | **Eryaspase** |
|---|---|---|---|
| | | | Subsequent cycles → 75 U/Kg |
| **Grade 4:** ALT/AST >20.0 x ULN, or total bilirubin >2 x ULN | Discontinue | Discontinue | Discontinue |
| *Hepatic metastasis* | | | |
| ALT/AST >5.0 x ULN - ≤10.0 x ULN and total bilirubin ≤1.5 x ULN | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| ALT/AST >10.0 - 20.0 x ULN, and total bilirubin ≤1.5 x ULN | During cycle → delay dose until resolved to ALT/AST <5.0 x ULN, then ↓ to 120 mg/m$^2$<br>Subsequent cycles → 120 mg/m$^2$ | During cycle → delay dose until resolved to ALT/AST <5.0 x ULN, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$<br>Third occurrence → Discontinue | During cycle → delay until resolved to ≤10.0, then ↓ to 50% of dose<br>Subsequent cycles → 50 U/Kg |
| ALT/AST >20.0 x ULN and total bilirubin ≤1.5 x ULN | Discontinue | Discontinue | Discontinue |
| Total bilirubin >2.0 x ULN | Discontinue | Discontinue | Discontinue |
| **Diarrhea** | | | |
| **Grade 1:** (2-3 stools/day >pretreatment | During cycle → delay until resolved, then full dose<br>Subsequent cycles → Maintain original dose level | During cycle → delay until resolved, then full dose<br>Subsequent cycles → Maintain original dose level | Maintain original dose level |
| **Grade 2:** (4-6 stools/day >pretreatment) | During cycle → delay dose until resolved, then ↓ to 150 mg/m$^2$<br>Subsequent cycles → 180 mg/m$^2$ | During cycle → delay dose until resolved, then full dose<br>Subsequent cycles → 70 mg/m$^2$ | Maintain original dose level |
| **Grade 3:** (7-9 stools/day >pretreatment) | During cycle → delay dose until resolved, then ↓ to 150 mg/m$^2$<br>Subsequent cycles → 150 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Subsequent cycles → 43 mg/m$^2$ | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |

**Table 8 Dose Modifications for Irinotecan, Onivyde, and Eryaspase**

| | **Irinotecan**[1] | **Onivyde**[2,3] | **Eryaspase** |
|---|---|---|---|
| **Grade 4:** (≥10 stools/day >pretreatment) | During cycle → delay dose until resolved, then ↓ to 120 mg/m$^2$<br>Subsequent cycles → 120 mg/m$^2$ | During cycle→delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$<br>Third occurrence → Discontinue | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| **Hematological Toxicity – Neutropenia (Absolute Neutrophil Count [ANC]):** | | | |
| **Grade 1:** <LLN to 1.5 x 10$^9$/L | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| **Grade 2:** <1.5 x 10$^9$/L - ≥1 x 10$^9$/L | During cycle → ↓ to 150 mg/m$^2$<br>Subsequent cycles → Maintain original dose level | During cycle → delay dose until resolved, then full dose<br>Subsequent cycles → 70 mg/m$^2$ | Maintain original dose level |
| **Grade 3:** <1.0 x 10$^9$/L - ≥0.5 x 10$^9$/L | During cycle → delay dose until resolved to ≤Grade 2, then ↓ 150 mg/m$^2$<br>Subsequent cycles→ 150 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$<br>Third occurrence → Discontinue | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| **Grade 4:** <0.5 x 10$^9$/L or Febrile neutropenia | During cycle → delay dose until resolved to ≤Grade 2, then ↓ 120 mg/m$^2$<br>Subsequent cycles → 120 mg/m$^2$ | During cycle →delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$<br>Third occurrence → Discontinue | During cycle → delay until resolved to ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| **Other hematological toxicities (anemia and thrombocytopenia): follow same guidelines as recommended for neutropenia** | | | |
| **Other laboratory investigations** | | | |
| Any **Grade 1** or **Grade 2** | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| Any **Grade 3** or **Grade 4** – not clinically significant | During cycle → delay dose until resolved to ≤Grade 2, then ↓ 150 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then full original dose | During cycle → Delay until resolved to ≤Grade 2, then full original dose |

**Table 8 Dose Modifications for Irinotecan, Onivyde, and Eryaspase**

| | **Irinotecan**[1] | **Onivyde**[2,3] | **Eryaspase** |
|---|---|---|---|
| | Subsequent cycles → 150 mg/m$^2$ | Subsequent cycles → 50 mg/m$^2$ | Subsequent cycles → Maintain dose level |
| Any **Grade 3** or **Grade 4** – clinically significant | During cycle → delay dose until resolved to ≤Grade 2, then ↓ 120 mg/m$^2$<br>Subsequent cycles → 120 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$<br>Third occurrence → Discontinue | During cycle → Delay until resolved to ≤Grade 2, then then ↓ to 75% dose<br>Subsequent cycles → 75 U/Kg |
| **Other non-Hematological Adverse Event:** | | | |
| Any **Grade 1** toxicity | Maintain original dose level | Maintain original dose level | Maintain original dose level |
| Any other **Grade 2** toxicity | During cycle → delay dose until resolved to ≤Grade 1, then ↓ to 150 mg/m$^2$<br>Subsequent cycles → 180 mg/m$^2$ | Maintain original dose level | Maintain original dose level |
| Any other **Grade 3** toxicity | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 150 mg/m$^2$<br>Subsequent cycles → 150 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$<br>Third occurrence → Discontinue | During cycle → delay until resolved ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| Any other **Grade 4** toxicity[5] | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 120 mg/m$^2$<br>Subsequent cycles → 120 mg/m$^2$ | During cycle → delay dose until resolved to ≤Grade 2, then ↓ to 50 mg/m$^2$<br>Second occurrence → 43 mg/m$^2$<br>Third occurrence → Discontinue | During cycle → delay until resolved ≤Grade 2, then full dose<br>Subsequent cycles → Maintain original dose level |
| Upper gastro-intestinal (GI) peptic ulcer **Grades 2 or 3** | During cycle → delay until resolved to ≤Grade 1, then use next lower dose level.<br>Subsequent cycles → next lower dose level | During cycle → delay until resolved to ≤Grade 1, then use next lower dose level<br>Subsequent cycles → next lower dose level | During cycle → delay until resolved to ≤Grade 1, then use next lower dose level<br>Subsequent cycles → next lower dose level |

**Table 8 Dose Modifications for Irinotecan, Onivyde, and Eryaspase**

| | Irinotecan(1) | Onivyde(2,3) | Eryaspase |
|---|---|---|---|
| Upper gastro-intestinal (GI) peptic ulcer Grade 4, and/or life-threatening GI bleeding | Withdraw | Withdraw | Withdraw |
| **IMP Incompatibility:** | | | |
| Positive serologic cross-match test result | No actions for the chemotherapy. Repeat eryaspase manufacturing. If persists, discontinue. | | |

(1) For patients starting irinotecan at a reduced dose of 150 mg/m$^2$ due to the presence of UGT1A1*28 homozygous allele, dose should be reduced to 120 mg/m$^2$ at first occurrence and an additional decrease of about 20% at the second occurrence of toxicity.
(2) Onivyde dose reductions are presented based on a starting dose of 70 mg/m$^2$ irinotecan free base (equivalent to 80 mg/m$^2$ of Onivyde).
(3) For patients starting Onivyde at a reduced dose of 50 mg/m$^2$ irinotecan free base due to the presence of UGT1A1*28 homozygous allele, dose should be reduced to 43 mg/m$^2$ at first occurrence and to 35 mg/m$^2$ at the second occurrence.
(4) Treatment with eryaspase can be resumed, provided that it is within shelf-life and the infusion is completed within the 6-hour window of bringing eryaspase to room temperature.
(5) For mucositis or stomatitis, decrease only 5-FU, not irinotecan and not eryaspase.

### 5.2.5 Management of Events of special Interest

Hypersensitivity reactions have been reported with Abraxane, irinotecan, Onivyde, and eryaspase. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists as per institutional protocols.

Eryaspase is an ASNase encapsulated into RBCs; therefore, the risk of allergic reactions is potentially attributed to one or more of the following causes: a) antibody-mediated clinical hypersensitivity reactions; b) non-antibody-mediated infusion reactions attributed to ASNase; and/or c) the RBC component in eryaspase.

#### 5.2.5.1 MANAGEMENT OF HYPERSENSITIVITY REACTIONS WITH ERYASPASE OR OTHER AGENTS

Generally, eryaspase does not require premedication for hypersensitivity reactions. However, eryaspase contains *E. coli*-derived ASNase, which has been associated with hypersensitivity reactions. These reactions range from local rash or flushing to severe systemic reactions with features such as urticaria, bronchospasm, angioedema, and severe anaphylactic shock. In the eryaspase program, there had been 15 (4.8%) Grade 3 or 4 allergic reactions as of 28 Feb 2017.

The following is guidance for the treatment of hypersensitivity reactions. Treatment should be based on clinical presentation and is at the Investigator's discretion. Institution-specific pre-medication and/or treatment plans may also be followed if appropriate.

**Grade 2 Symptoms:**

- Stop administration.

- Administer IV dexamethasone 10 mg and diphenhydramine hydrochloride (HCL) 25 to 50 mg.
- After recovery of symptoms, treatment may be resumed once the patient is stable, if the product is not expired and the bag has been out of the cold box for less than 6 hours.
- Use premedication for subsequent infusions of eryaspase.

**Grade 3 and 4 Symptoms (such as hypotension, angioedema, or respiratory distress):**

- Stop administration.
- Administer IV dexamethasone 10 mg and diphenhydramine HCL 25 to 50 mg.
- Add adrenaline or bronchodilators as indicated.
- For Grade 4 toxicity, the treatment should be discontinued.

**Example of Infusion Premedication Regimen:**

- Dexamethasone 12 mg PO and diphenhydramine HCL 25-50 mg PO approximately 6 to 12 hours prior to the next dose of eryaspase.

#### 5.2.5.2 MANAGEMENT OF INFUSION/TRANSFUSION REACTIONS

Allogeneic blood transfusions are associated with immune-related effects in the form of alloimmunization due to the exposure to alloantigens, cytokines, or other cellular components. Transfusion reactions are typically classified into the following entities [38]: i) transfusion-related lung injury (TRALI); ii) volume overload in susceptible patients with cardiovascular problems ; iii) bacterial contamination; iv) acute hemolytic reactions, either immune-related with ABO incompatibility or non-immune related (for example, concomitant medications causing RBC hemolysis, incorrect storage of RBCs, or non-validated administration systems); v) non-hemolytic febrile reactions due to cytokines and other allo-proteins; and vi) allergic reactions, mostly related to unidentified allergens in the donor blood.

Overall, eryaspase-related transfusion/infusion events have been reported in 25 (8.1%) patients enrolled in the combined clinical development program. None of these events were Grade 4 or fatal. Eryaspase utilizes leuko-depleted packed RBCs; its manufacturing process additionally helps to wash away any remaining leukocytes. Alloimmunization (switch from negative to positive anti-erythrocyte irregular antibodies) has been observed in 14.6% of patients (45 out of 307) as of 28 Feb 2017.

Management of transfusion/infusion reactions follows well-known published guidelines, as summarized in these publications [39-41]. It is recommended that Investigators follow institutional and local practice guidelines. Table 9 provides a summary of patient management for transfusion reactions.

**Table 9 General Guidelines for Managing Transfusion Reactions**

| Reaction | Symptoms | Interventions |
|---|---|---|
| Increase in Temperature | | |
| **Increase in Temperature** | | |

**Table 9 General Guidelines for Managing Transfusion Reactions**

| Reaction | Symptoms | Interventions |
|---|---|---|
| Possible febrile non-hemolytic reaction | Incremental increase <1°C above baseline and no other new symptoms | • Close observation, frequent vital signs measurement.<br>• If stable and no other new symptoms, then continue with eryaspase. |
| Possible bacterial contamination | Incremental increase ≥1°C above baseline, or incremental increase <1°C with any other new symptoms (chills or rigors, hypotension, nausea, or vomiting) | • Stop eryaspase; keep IV line open, assess patient, check patient ID and unit ID and compatibility.<br>• Administer antipyretic drug. Strongly consider culturing blood product if ≥2°C increase in temperature or if high clinical suspicion of sepsis. |
| Possible hemolysis | For consistently febrile patient due to underlying disease or treatment with chemotherapy agents, when possible:<br>Delay eryaspase if patient's temperature is increasing.<br>Treat fever with antipyretic drug before starting transfusion. | |
| **Respiratory Symptoms** | | |
| Possible anaphylaxis, transfusion-associated circulatory overload, septic transfusion reaction, or transfusion-related acute lung injury | Bronchospasm, dyspnea, tachypnea and hypoxemia, copious frothy pink-tinged fluid (from endotracheal tube) | • Stop eryaspase; keep IV line open, assess patient, check patient ID and unit ID and patient compatibility.<br>• Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support, diuretics; fluid, blood pressure, and renal support).<br>• Chest radiograph for presence of bilateral interstitial infiltrate, if suggestive of transfusion-related acute lung injury (TRALI).<br>• Blood cultures (patient and product) if high clinical suspicion of sepsis.<br>• Do not resume eryaspase.<br>• Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quarantined. |
| **All Other Symptoms** | | |

**Table 9 General Guidelines for Managing Transfusion Reactions**

| Reaction | Symptoms | Interventions |
|---|---|---|
| Possible anaphylaxis, hemolytic transfusion reaction, fluid overload, or transfusion-related acute lung injury | Chills, rigors, hypotension, nausea or vomiting, feeling of impending doom, back or chest pain, intravenous site pain, cough, dyspnea, hypoxia | • Stop eryaspase; keep IV line open, assess unit, check patient ID and unit ID and patient compatibility.<br>• Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support; diuretics; fluid, blood pressure, and renal support).<br>• Blood cultures (patient and product) if high clinical suspicion of sepsis.<br>• Do not resume transfusion.<br>• Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quarantined. |

IV: intravenous; ID: identification; TRALI: transfusion-related acute lung injury.

#### 5.2.5.3 MANAGEMENT OF DIARRHEA

Diarrhea is commonly reported with irinotecan and Onivyde, which typically has an onset in ≤24 hours after starting Onivyde (early onset). A late onset (>24 hours) diarrhea has also been reported. When appropriately managed with anti-diarrheal treatment, diarrhea is generally mild to moderate.

These broad general management principles are provided as a guideline to proactively avoid serious complications of diarrhea syndrome. These guidelines do not replace sound clinical judgment.

In the event of diarrhea, patients should take loperamide at initial 4 mg dose, followed by 2 mg doses every 4 hours until 12 hours have lapsed without symptoms. Patients should be advised to increase fluid intake (water, sports drinks, clear juices, decaffeinated tea), and modify diet (banana, rice, apples and toast).

- If mild to moderate diarrhea persists for more than 12 hours, loperamide should be taken at a dose of 2 mg every 2 hours
- If mild to moderate diarrhea persist after 24 hours despite treatment with loperamide, a cocktail of atropine-diphenoxylate (Lomotil) and loperamide may be considered. Loperamide 2 mg may be alternated with one tablet of Lomotil every 3 hours. Loperamide should not be used for more than 48 consecutive hours due to risk of paralytic ileus. Oral antibiotic support (e.g. fluoroquinolone for 7 days) should be also considered. If diarrhea persists for more than 48 hours, loperamide should be stopped, and fluid replacement should be considered.

For Grade 3 or 4 diarrhea or complicated Grade 1 or 2 (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration), IV fluids should be used as appropriate, as well as prophylactic antibiotics.

## 5.3 ERYASPASE PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 5.3.1 Acquisition and Accountability

#### 5.3.1.1 ACQUISITION

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

- **Information to be provided at study start:** RBCs phenotype (including D, C, E, c, e, K and other antigens tested as per site practice), ABO blood group status, and Rhesus factor, all assessed on two separate samples, which can be collected on the same day. In addition, provide historical results of an irregular antibody screening test (IAST), if available. This information is required at least 5 working days before the first infusion.
- **Prior to Cycle 1 Day 1 and each eryaspase dose:** A prescription form indicating patient identifiers and body weight should be provided at the latest 5 working days prior to Cycle 1 Day 1 (for all patients) and each eryaspase infusion (patients in eryaspase arm).
- **Information to be provided during the treatment phase:** Results of IAST performed for previous eryaspase dose to be provided at the latest 5 working days prior to subsequent 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 (from the previous infusion), 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.

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.

#### 5.3.1.2 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.

### 5.3.2 Formulation, Appearance, Packaging, and Labeling

Please refer to the IB for details of eryaspase formulation and appearance.

Eryaspase is packed in medical-grade polyvinyl chloride (PVC) blood bags according to GMP requirements and place in a photoprotective pocket. 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 RBCs, phenotype, patient identification number, etc.) to allow verification of the patient's identity and blood group before administration.

### 5.3.3 Preparation

Prior to eryaspase administration, an IAST and a complete compatibility test (cross-match test) between the patient's blood and eryaspase, using the removable segment tubes, must be performed to confirm compatibility. In case a patient receives multiple bags of eryaspase to achieve the intended prescribed dose, separate cross-match tests 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.

## 5.4 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

### 5.4.1 Blinding

The study is an open-label pivotal trial. Investigators and patients will be unblinded to the treatment due to the nature of the investigational therapy.

### 5.4.2 Randomization

Patients will be randomized to receive either chemotherapy in combination with eryaspase or chemotherapy alone in a 1:1 ratio, using an IWRS. At screening, the IWRS system will assign a unique patient number that will remain constant over the duration of the study. If a patient is rescreened after initial screen failure, the IWRS will allocate the same number. Treatment arm will be automatically determined by the IWRS system. Detailed instructions will be provided in the IWRS manual.

Randomization will be stratified by these factors:

- ECOG PS score (0 or 1),
- Chemotherapy regimen (gemcitabine plus Abraxane or irinotecan-based therapy [FOLFIRI or Onivyde, 5-FU, and leucovorin]), and
- Time interval since diagnosis of advanced disease to date of randomization in the study (<6 months or ≥6 months).

## 5.5 COMPLIANCE WITH STUDY TREATMENT

Eryaspase will be administered by IV infusion under the supervision of study personnel. Compliance with the treatment dose and schedule will be documented in the source documents and recorded in the eCRF.

## 5.6 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. All prescription medications, over-the-counter medications, and supplements used concomitantly or within 14 days prior to Cycle 1 Day 1 must be reported in the eCRF.

### 5.6.1 Prior Medications

All treatments received within 14 days prior to Cycle 1 Day 1 will be recorded in the eCRF, including the name of the drug, route, indication, start date, and stop date (if applicable). In addition, *any and all* prior therapies for the treatment of pancreatic cancer (or cancer-related events such as bone pain) will also be recorded in the eCRF.

### 5.6.2 Permitted Medications

Patients may receive supportive care for disease-related symptoms and for toxicity associated with study treatment. The date of supportive medication administration as well as the name and dosage regimen of each medication must be recorded in the eCRF.

The following treatments are permitted during the study:

- **Transfusion of blood products.**

  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.

- **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.

- **Palliative radiotherapy (e.g., for painful bone metastases).**
- **Prophylactic granulocyte colony-stimulating factor (GCSF) in case of neutropenia.**

  Details and indications for use of GCSF should follow American Society for Cooperative Oncology (ASCO) guidelines [42].

### 5.6.3 Prohibited Medications

During the treatment phase, the following treatments are prohibited:

- **Concomitant vaccination with live vaccines**, due to increased risk of serious infection. Immunization with live or live-attenuated vaccines should take place no earlier than 3 months after completion of eryaspase treatment.
- **Other L-ASNase products.**
- **Highly hemolytic agents** that may lead to RBC hemolysis: acetanilide, antipyrine (phenazone), and chloroquine and derivatives.
- **Prophylactic phenytoin.**

# 6 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

## 6.1 DISCONTINUATION OF STUDY TREATMENT

Discontinuation from eryaspase and/or chemotherapy treatment does not imply discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol.

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine whether any change in patient management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

A patient may be **withdrawn from treatment** for any of the following reasons:

- Unacceptable toxicity.
- Objective disease progression following radiological assessment as determined by the investigator (per modified RECIST 1.1 criteria).
- Patient's withdrawal of consent for treatment.
- Pregnancy
- Investigator's decision for other reasons, **with documentation of reason(s) if not included in any of the above categories.**
  **NOTE:** Clinical progression must be confirmed radiologically before treatment discontinuation and patient withdrawal.
- Sponsor's decision, including discontinuation of the study, with documentation of reason(s) in the eCRF.

The reason for withdrawal will be recorded in the eCRF.

The EOT visit must be performed and documented within 30 days after the last dose of eryaspase or chemotherapy. AEs/SAEs and concomitant medications must be collected up to 90 days after the last dose of study treatment or until start of new anti-cancer treatment, whichever is first. For details of the assessments to be performed, refer to the Schedule of Events (SOE), Table 1.

## 6.2 PARTICIPANT WITHDRAWAL FROM THE STUDY

A patient may be **withdrawn from the study** for the following reasons:

- Patient's withdrawal of consent for the study.
- Loss to follow-up.
- Death.
- Sponsor's decision, including discontinuation of the study.

The reason for withdrawal will be recorded in the eCRF.

If a patient withdraws from the study during treatment, it is recommended that the EOT visit be performed and documented within 30 days if possible. For details of the assessments to be performed, refer to the SOE, Table 1.

**If a patient withdraws from the study, the Investigator must make every effort to follow safety events to resolution, until the events stabilize, or until the patient's death.**

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples that have been taken but not yet tested, and the Investigator must document this request in the site's study records and inform the Sponsor within 5 working days.

## 6.3 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he or she fails to return for scheduled visits and cannot be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the patient and reschedule the missed visit within one week, will counsel the patient on the importance of maintaining the assigned visit schedule, and will ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter [or local equivalent] to the patient's last known mailing address). These contact attempts should be documented in the patient's medical record or study file.
- Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of loss to follow-up.

## 6.4 STUDY TERMINATION

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason. If the study is terminated, the Sponsor will notify the Investigators in writing. If the study is prematurely terminated or suspended, the Investigator will promptly inform study participants and the relevant IEC/IRB, and the Sponsor will provide the reason(s) for the termination or suspension to competent regulatory authorities. Study participants will be contacted as appropriate and will be informed of any changes to the study visit schedule.

The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the sponsor's procedures, or Good Clinical Practice (GCP) guidelines.

- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further drug development.

The Investigator will be responsible for completing all study close-out procedures as required by the Sponsor and/or local regulatory authorities if a site is closed or the study is terminated early.

# 7 STUDY ASSESSMENTS AND PROCEDURES

Screening and study procedures and their timings are summarized in the Schedule of Events (SOE) in Table 1.

Adherence to the study requirements, including those specified in the SOE, is essential and required for study conduct. Protocol waivers or exemptions are not allowed (with the exception of those in response to immediate safety concerns).

All screening evaluations must be completed within 3 weeks prior to randomization, with confirmation that the patient continues to meet eligibility criteria prior to dosing on Cycle 1 Day 1. The Investigator will maintain a screening and enrollment log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

The COVID-19 pandemic has impacted the conduct of this study, including travel restrictions and confinements of the trial participants and trial staff to perform study assessments. Several measures have been implemented by ERYTECH, and are reflected on trial assessments as described further below in the respective sections.

## 7.1 SCREENING ASSESSMENTS AND PROCEDURES

All patients must sign and date an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) prior to any screening assessments. However, an evaluation conducted as part of the patient's routine clinical management (e.g., blood counts, disease evaluation) that is performed before signature of the ICF may be utilized for screening or baseline purposes provided that the procedure met the protocol-specified criteria and was performed within the time frame defined in the SOE (Table 1). Separate informed consent for the optional PGx assessment will be requested at the same time.

For further information on the informed consent process, please refer to Section 9.1.1.

Eligibility criteria are to be evaluated within 3 weeks prior to randomization, with confirmation that the patient continues to meet eligibility pre-dose on Cycle 1 Day 1.

**NOTE:** Screening period longer than 3 weeks may be allowed due to COVID-19 related restrictions

**Screening Assessments to Be Completed within 3 Weeks prior to Randomization**

- Demography, including gender and date of birth.
- Medical history, including cancer history and prior anticancer therapies.
- Complete physical exam, including height and weight (height to be collected at screening only).
- Vital signs: temperature, heart rate, and blood pressure.
- ECOG PS, and KPS if ECOG PS is 1 (see **APPENDIX 2** and **APPENDIX 3**).
- Laboratory assessments (to be completed within 14 days of randomization): hematology, clinical chemistry, and coagulation panels will be completed at the local laboratory for the parameters defined in Table 10 below. All laboratory results must be documented in the eCRF. Additionally, reference ranges must be provided to the sponsor or its designee.

NOTE: Please see Table 12 in Section 7.8.3 for Minimum Safety Labs required during COVID-19.

- Serum pregnancy test (for patients of childbearing potential): a negative human chorionic gonadotropin test is required before the patient may receive any chemotherapy agent or eryaspase.
- **NOTE:** A woman is considered of childbearing potential unless post-menopausal or permanently sterile by one of following methods: hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A woman is considered postmenopausal in she has not had menses for 12 months without an alternative medical cause.
- Collection of a paraffin-embedded tumor tissue block, or a minimum of 10 unstained slides, obtained from an archived or newly obtained tumor tissue sample for biomarker analysis.
- Whole blood sample for PGx assessment (optional)
- 12-lead ECG.
- Baseline disease assessments:
  - Radiological imaging studies:
    - Chest CT scans.
    - Abdomen CT scans.
    - Brain MRI is indicated in patients with known/suspected brain metastasis at study entry. Brain scans will be repeated during the study at 12-week intervals if clinically indicated.
    - Bone scan is indicated in patients with known/suspected bone metastasis at study entry. Bone scans will be repeated during the study at 12-week intervals if clinically indicated.
- Additional imaging as clinically indicated.
  - In general, CT scans are the preferred method of radiological assessment of the chest and abdomen; however, other techniques may be used (i.e., MRI).
    - **The same imaging technique must be used for a given patient throughout the study.**
    - **Radiological images must be collected in a de-identified manner, quality controlled, stored, and available for future review and reading as necessary.**
- Prior and concomitant medications: record all medications the patient has received from 14 days prior to randomization, as well as *any and all* prior therapies for the treatment of pancreatic cancer (or cancer-related events such as bone pain), and any currently ongoing medications.
- Collection of AEs and SAEs from the date of informed consent.

**Table 10 List of Laboratory Assessments**

| Category | Parameter |
|---|---|
| **Hematology:** | Hematocrit<br>Hemoglobin<br>Platelet count |

**Table 10 List of Laboratory Assessments**

| Category | Parameter |
|---|---|
| | RBC count<br>White blood cell (WBC) count with differential<br>Neutrophils<br>Lymphocytes<br>Eosinophils<br>Monocytes<br>Basophils |
| **Coagulation:** | Fibrinogen<br>Antithrombin III (AT III) |
| **Serum Chemistry and Tumor Markers:** | Albumin<br>Alkaline phosphatase<br>Alanine aminotransferase (ALT)<br>Ammonia<br>Amylase<br>Aspartate aminotransferase (AST)<br>Bicarbonate<br>Calcium<br>Chloride<br>Creatinine<br>Gamma-glutamyl transferase (GGT)<br>Glucose<br>Lactate dehydrogenase (LDH)<br>Lipase<br>Potassium<br>Sodium<br>Total bilirubin<br>Total cholesterol<br>Triglycerides<br>Urea<br>Uric acid<br>CA19-9 |
| **Other Laboratory Tests:** | Blood phenotype, Rh factor, and ABO blood group, all done on two separate samples<br>Irregular antibody screening test (IAST)<br><br>Pregnancy test for women of childbearing potential (serum at screening and at End of |

**Table 10 List of Laboratory Assessments**

| Category | Parameter |
|---|---|
| | Treatment; urine on Cycle 1 Day 1 before treatment and as indicated during treatment for females of child-bearing potential) |

## 7.2 RANDOMIZATION

Patients who are found to be eligible for the study will be randomized to study treatment within 3 days prior to Cycle 1 Day 1. Randomization will be done through the IWRS as described in Section 5.4.2.

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

- RBC phenotype (including D, C, E, c, e, K and other antigens as per site practice), ABO blood group status, and Rhesus factor, all assessed on 2 separate samples, which can be collected on the same day. This information is required at least 5 working days before the first eryaspase infusion.

A prescription form indicating patient identifiers and body weight, the recipient of the product (Investigator or designee), and the place and time of the delivery must be sent as soon as possible once the first infusion is scheduled (at the latest 5 working days before planned administration ).

## 7.3 TREATMENT PHASE ASSESSMENTS AND PROCEDURES

### 7.3.1 Assessments prior to Initiation of Treatment on Cycle 1 Day 1

The following assessments will be performed on Cycle 1 Day 1 prior to initiation of study treatment. Screening laboratory tests and procedures may be substituted for those on Cycle 1 Day 1 if performed within 5 days prior to Cycle 1 Day 1.

- Symptom-directed physical examination, including body weight.
- Vital signs: temperature, heart rate, and blood pressure.
- ECOG PS, and KPS if ECOG PS is 1 (see **APPENDIX 2** and **APPENDIX 3**).
- EORTC QLQ-C30.
- Hematology, clinical chemistry, and coagulation panels and CA19-9, Table 10.
- Urine pregnancy test for patients of childbearing potential. A negative test is required before administration of any chemotherapy agent or eryaspase.
- Baseline blood and plasma samples for pharmacokinetic and pharmacodynamic analysis (for patients in the eryaspase arm).
- Baseline blood samples for immunogenicity (for patients in the eryaspase arm).
- Baseline blood and plasma samples for biomarker analysis (both arms), such as ctDNA, proteomics, and transcriptomics.

Prior to administration of the first infusion of eryaspase, (and each subsequent infusion during the treatment period), an IAST and complete compatibility (cross-match) test between the

patient's blood and eryaspase should be performed using the removable segment tubes to confirm compatibility. In case a patient receives multiple bags of eryaspase to achieve the intended prescribed dose, a separate cross-match test must be performed with each eryaspase bag to confirm compatibility. In case of incompatibility, an additional blood sample may be required for further investigations. Details of collection and shipment are provided in the IMP Manual.

### 7.3.2 Efficacy Assessments During the Treatment Phase

#### 7.3.2.1 RADIOLOGICAL DISEASE ASSESSMENTS

CT/MRI of the chest and abdomen will be performed every 8 weeks (±3 days) calculated from the date of randomization until disease progression, patient's withdrawal from study, or death. **Every effort should be made to adhere to the assessment schedule, irrespective of any treatment delays or modifications. The same imaging technique must be utilized for a given patient throughout the study.**

Bone and/or brain scans are to be repeated every 12 weeks if clinically indicated.

#### 7.3.2.2 HEALTH OUTCOMES

Patient-reported outcomes will be measured using a standardized instrument, the EORTC QLQ-C30. The self-administered questionnaires will be completed every 4 weeks during the treatment phase.

#### 7.3.2.3 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

For patients in the eryaspase arm, blood/plasma samples for pharmacokinetic and pharmacodynamic assessment will be collected, where possible, at the following time points of Cycles 1 and 3:

- Day 1 prior to eryaspase administration,
- Day 1 at 5-10 minutes post- eryaspase infusion,
- At 5-8 days post-infusion (at the Investigator's discretion), and
- At Day 15 pre-dose.

Samples will be analyzed for whole blood and plasma concentrations of ASNase and amino acids. The sparse PK data will be combined with previous data as part of a Population PK (POP PK) analysis. To this effect, sample collection for PK and pharmacodynamics may be stopped based on the outcome of the evaluation of sample results during the course of the trial.

The date and clock time for collection of each blood sample and for sample processing (e.g., time placed on ice, time of centrifugation, etc.) will be documented. Further details will be provided in the lab manual.

#### 7.3.2.4 IMMUNOGENICITY

For patients in the eryaspase arm, samples for assessment of anti-ASNase antibodies and neutralizing antibodies will be collected pre-dose at Cycle 1 Day 1, and Day 15 and at Day 1 of every second cycle thereafter (i.e., at Cycle 3 Day 1, Cycle 5 Day 1, and so on), and upon determination of disease progression, and EOT, whichever is sooner.

#### 7.3.2.5 BIOMARKER ASSESSMENTS

**Plasma Samples**

Plasma samples for biomarker analysis will be collected pre-dose on Cycle 1 Day 1 and Day 15 and at Day 1 of every second cycle thereafter (i.e., at Cycle 3 Day 1, Cycle 5 Day 1, and so on), upon determination of disease progression, and EOT, whichever is sooner.

**Pharmacogenetic Sample**

An optional blood sample for pharmacogenetic (PGx) analysis will be obtained once during the study, preferably during the screening phase. A separate informed consent must be signed before the sample is obtained.

### 7.3.3 Safety Assessments during the Treatment Phase

The following safety assessments will be performed pre-dose for all patients on Day 1, and Day 15, unless otherwise specified.

- Hematology, clinical chemistry, and coagulation panels and CA19-9.
- For patients under eryaspase arm, in addition to regular evaluation of liver function tests before treatment administration, patients will be monitored on weekly basis in the event of occurrence of ≥Grade 2 elevation of liver enzymes and bilirubin levels.
- For women of childbearing potential, additional pregnancy testing should be performed in case of delayed menstrual period and is recommended to be performed monthly and until the end of treatment exposure extended by 30 days, in case of sexual activity.
- Vital signs: temperature, heart rate, and blood pressure.
- Symptom-directed physical examination, including body weight.
- ECOG PS (see **APPENDIX 2**).
- 12-lead ECG: as clinically indicated.
- Collection of AEs: from time of informed consent until 90 days after the last study treatment or start of new anti-cancer treatment, whichever is sooner.
- Review/recording of all concomitant medications added and/or changed from 14 days prior to randomization until 90 days after the last study treatment or start of new anti-cancer treatment, whichever is sooner.

## 7.4 END OF TREATMENT VISIT

The End of Treatment (EOT) visit should be conducted as soon as possible (but no later than 30 days) after the patient's discontinuation of the study drug, and will include the following assessments:

- Hematology, clinical chemistry, and coagulation panels and CA19-9.
- Serum pregnancy test for patients of childbearing potential.
- Vital signs: temperature, heart rate, and BP.
- Symptom-directed physical exam, including body weight.
- ECOG PS (see **APPENDIX 2**).
- EORTC QLQ-C30.
- Review of AEs and concomitant medications.

- Samples for immunogenicity (for patients in the eryaspase arm) and biomarker analysis (both arms).

## 7.5 FOLLOW-UP PHASE ASSESSMENTS AND PROCEDURES

During the follow-up phase, the extent of efficacy evaluation will depend on the disease status:

- In the absence of disease progression or starting new anti-cancer therapy
  – Radiological imaging of Tumor lesions to be carried out every 8 weeks until disease progression,
  – And then OS follow up every 8 weeks until death, lost for follow up or withdrawal from study
- In the presence of objective disease progression or start of anticancer therapy
  – OS follow up every 8 weeks until death, lost for follow up or withdrawal from study.

Collection and follow-up of AEs and SAEs will occur until 90 days after discontinuation of the study drug, beginning of a new cancer treatment, or death, whichever occurs first. SAEs will be followed until resolution.

For all patients who discontinue study treatment, the EORTC QLQ-C30 questionnaire will be completed every 8 weeks during the follow-up phase until withdrawal from the study or death.

### 7.5.1 Post-Study Subsequent Cancer Therapy

Information will be collected about any subsequent cancer therapy given after discontinuation of study drug (s), including both medications and procedures.

### 7.5.2 Survival Follow-Up

Survival information will be collected by phone, follow-up visit, or from medical records approximately every 8 weeks from the date of the EOT visit until the patient's death, until the patient is lost to follow-up, or until study closure. Survival follow-up will include collection of information about any subsequent anticancer therapy received after discontinuation of study drug.

If a patient fails to return for scheduled visits or is unreachable for survival follow-up, the following efforts should be made to contact him/her: 3 phone attempts, including the date and time, should be documented in the patient's chart. If there is no response to the phone calls, a certified letter or local equivalent should be sent. After these efforts have been exhausted with no response, a patient should be considered as lost to follow-up.

## 7.6 EFFICACY ASSESSMENTS

### 7.6.1 Radiological Disease Assessment and Evaluation of Response

CT/MRI scans of the chest and abdomen will be performed every 8 weeks, calculated from the date of randomization, until disease progression, or until withdrawal from the study, or death.

**Every effort should be made to adhere to the assessment schedule. The same imaging technique must be utilized for a given patient throughout the study.**

Tumor response and disease progression will be evaluated in this study using a modified version of the criteria proposed by the RECIST Committee, version 1.1 (RECIST 1.1). The modifications to RECIST 1.1 will be used to more accurately and consistently assess responses in specific cases that are not addressed in RECIST 1.1. **These modifications are indicated below in *italics*.**

#### 7.6.1.1 KEY DEFINITIONS

##### 7.6.1.1.1 MEASURABLE DISEASE

- **Measurable non-nodal lesions:** those that can be accurately measured in at least 1 dimension, longest diameter (LD) to be recorded as ≥10 mm by CT scan (CT slice thickness no greater than 5 mm).
- **Malignant lymph nodes:** to be considered pathologically enlarged and measurable, a lymph node must measure ≥15 mm in the short axis (SA) when assessed by CT scan (CT slice thickness recommended to be no greater than 5 mm).
- It is recommended that slice gaps not be utilized for the image acquisition procedures.
- All radiographic measurements should be taken and recorded in millimeters utilizing an electronic measurement method based on lesion boundary definition.
- ***Lesions on chest X-ray will not be considered measurable.***

##### 7.6.1.1.2 NON-MEASURABLE DISEASE

- All other lesions (or sites of disease), including small lesions (LD <10 mm or pathological lymph nodes ≥10 mm to <15 mm in the SA) as well as truly non-measurable lesions, are considered non-measurable disease. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, and masses or abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques.

##### 7.6.1.1.3 TARGET LESIONS

- Target lesions must be measurable lesions.
- ***All lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, will be identified as target lesions, recorded and measured at baseline, and followed consistently throughout the study.***
- Target lesions should be selected on the basis of their size (based on LD for non-nodal lesions or SA for lymph nodes), their suitability for accurate repeated measurements, and on their being most representative of the patient's tumor burden.
- A sum of the diameters for all target lesions will be calculated and reported for each time point. The baseline sum of diameters will be used as a reference according to which the objective tumor response will be characterized.

#### 7.6.1.1.4 NON-TARGET LESIONS

- All other lesions (or sites of disease, including any measurable lesions that were not selected as target lesions) will be identified as non-target lesions and indicated as present at baseline.
- It is possible to record multiple non-target lesions involving the same organ as a single item (e.g., multiple enlarged pelvic lymph nodes or multiple liver metastases).
- Measurements of these non-target lesions will not be performed, but the presence, absence, or unequivocal progression of these lesions should be noted for subsequent assessments.

#### 7.6.1.1.5 NEW LESIONS

- A separate assessment category of "new lesions" is defined as part of the independent reading.
- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality, etc.).
- If a new lesion is equivocal (i.e., because of its small size), and follow-up imaging confirms that it is definitely a new lesion, then the lesion will be considered to have appeared on the date of the initial scan, indicating disease progression as of that date.
- A lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.
- ***A lesion that reappears at follow-up after a response of PR or stable disease is not considered new. The lesion's LD (or SA for lymph nodes) is added back into the sum of diameters.***
- ***A lesion that reappears at follow-up after a CR is automatically considered PD.***

#### 7.6.1.1.6 LYMPH NODES

- At baseline, lymph nodes with tumor burden will be considered target lesions if the SA is ≥15 mm.
- At baseline, lymph nodes will be considered non-target lesions if the SA is ≥10 mm and <15 mm.
- At baseline, lymph nodes will be considered normal if the SA is <10 mm.
- At subsequent assessments, a lymph node must measure ≥10 mm along the SA to be considered a new lesion.
- ***A lymph node that was identified as a target lesion at baseline that falls below the measurable threshold at subsequent assessment and then gets larger is not considered new if it follows a PR or SD. The lymph node SA measurement is added back into the sum of diameters.***
- ***A lymph node that was identified as a target lesion at baseline that falls below the measurable threshold at subsequent assessment and then gets larger following a CR is automatically considered PD.***

#### 7.6.1.2 OTHER CONSIDERATIONS

##### 7.6.1.2.1 IRRADIATED LESIONS

Previously irradiated lesions cannot be selected as target lesions. These lesions can be monitored to assess progression as non-target lesions.

##### 7.6.1.2.2 HANDLING OF LESIONS THAT SPLIT

When non-nodal and nodal lesions split or fragment, the individual diameters of the fragmented portions should be added together to calculate the target lesion sum.

##### 7.6.1.2.3 HANDLING OF LESIONS THAT MERGE

As lesions merge, a boundary between the lesions should be drawn so the LD or SA of each individual lesion can continue to be measured. If the lesions have merged in such a way that they can no longer be separated by this boundary, the LD or SA of the merged lesion should be measured.

#### 7.6.1.3 MEASUREMENT OF SMALL LESIONS ON FOLLOW-UP SCANS

##### 7.6.1.3.1 NON-NODAL LESIONS

A non-nodal target lesion that is present but too small to measure accurately at evaluations after baseline (<5 mm but greater than 0 mm in unilateral dimension) will be classified as Too small to measure and will be assigned a value of 5 mm for the purposes of determining the sum of diameters. All other lesions (i.e., ≥5 mm) will have actual size recorded.

##### 7.6.1.3.2 LYMPH NODES

A target lymph node should always have the actual SA measurement recorded, even if the lymph node regresses to <10 mm on study. This means that when lymph nodes are included as target lesions, the sum of diameters may not be zero even if CR criteria are met, since a normal lymph node is defined as having an SA of <10 mm.

#### 7.6.1.4 RESPONSE CRITERIA

##### 7.6.1.4.1 TARGET LESION RESPONSE CRITERIA

- Complete response (CR): Disappearance (or normalization) of all target lesions.
  - Any pathological lymph nodes (whether target or non-target) must have reduction in SA to <10 mm.
- Partial response (PR): At least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- Non-evaluable (NE): Patient time points that have inadequate or missing images, ***including the inability to visualize >25% of target disease***.

#### 7.6.1.4.2 NON-TARGET LESION RESPONSE CRITERIA

- CR: Disappearance (or normalization) of all non-target lesions.
- All lymph nodes must be non-pathological in size (<10 mm SA).
- Non-complete response, non-progressive disease (Non-CR/Non-PD): Persistence of 1 or more non-target lesion(s).
- PD: Unequivocal progression of existing non-target lesions.
- NE: Patient time points that have inadequate or missing images, ***including the inability to visualize >50% of non-target disease***.
- ***No disease (ND): No non-target disease noted. The absence of non-target lesions at follow-up time points is designated as ND and not SD when there is no non-target disease noted at baseline.***

#### 7.6.1.4.3 NEW LESION RESPONSE CRITERIA

A separate assessment of the appearance of one or more new lesions will be provided in the read. If at least one new lesion is present, the patient is considered to have progressive disease overall.

#### 7.6.1.4.4 RESPONSE ASSESSMENT IN CASE OF MISSING OR TECHNICALLY INADEQUATE SCANS

If no lesions were identified at baseline in a specific body region (e.g., chest or abdomen) and the scan of that body region is unavailable at follow-up, then the response assessment will be based on the scans of the other regions.

### 7.6.1.5 DETERMINATION OF RADIOLOGICAL BEST OVERALL RESPONSE

Best overall response (BOR) is the best response recorded from the start of treatment until the end of treatment (taking as reference for PD the smallest measurement recorded since the start of treatment).

## 7.6.2 Health Outcomes

Patient-reported outcomes will be measured using a standardized instrument, the EORTC QLQ-C30, at the following time points:

- Cycle 1 Day 1 before treatment.
- Every 4 weeks during the treatment phase, Day 1 of each cycle before treatment.
- At the End of Treatment visit.
- Every 8 weeks during the follow-up phase until end of study.

The following scores will be calculated: 5 functional scales, 3 symptom scales, a global health status/quality of life (QoL) scale, and 6 single items (Table 11).

**Table 11 EORTC QLQ-30 Scales and Items [43]**

| | Scale | Number of Items | Item Range* | Version 3.0 Item Numbers | Function Scales |
|---|---|---|---|---|---|
| **Global health status/QoL** | QL2 | 2 | 6 | 29, 30 | |
| **Functional scales** | | | | | |
| Physical functioning (revised)† | PF2 | 5 | 3 | 1 to 5 | F |
| Role functioning (revised)† | RF2 | 2 | 3 | 6, 7 | F |
| Emotional functioning | EF | 4 | 3 | 21 to 24 | F |
| Cognitive functioning | CF | 2 | 3 | 20, 25 | F |
| Social functioning | SF | 2 | 3 | 26, 27 | F |
| **Symptom scales/items** | | | | | |
| Fatigue | FA | 3 | 3 | 10, 12, 18 | |
| Nausea and vomiting | NV | 2 | 3 | 14, 15 | |
| Pain | PA | 2 | 3 | 9, 19 | |
| Dyspnoea | DY | 1 | 3 | 8 | |
| Insomnia | SL | 1 | 3 | 11 | |
| Appetite loss | AP | 1 | 3 | 13 | |
| Constipation | CO | 1 | 3 | 16 | |
| Diarrhoea | DI | 1 | 3 | 17 | |
| Financial difficulties | FI | 1 | 3 | 28 | |

**Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
†(revised) scales are those that have been changed since version 1.0, and their short names are indicated by a suffix "2" – for example, PF2.

### 7.6.3 Pharmacokinetic and Pharmacodynamic Assessments

Eryaspase pharmacokinetics will be evaluated using sparse sampling, where possible. Whole blood and plasma concentrations of ASNase from these samples will be combined with previous data as part of a POP-PK analysis. The pharmacodynamic effect of eryaspase on amino acid levels will also be evaluated.

For all patients who provide samples, PK and pharmacodynamics of eryaspase will be assessed at each measurement in terms of:

- Total ASNase activity (U/L),
- Plasma ASNase activity (U/L),
- Plasma concentrations of asparagine (µmol/L), and

- Plasma concentrations of glutamine (µmol/L).

See Section 7.8.5 for information related to the discontinuation of PD sample collection due to COVID-19

### 7.6.4 Immunogenicity

The development of anti-ASNase antibodies and neutralizing antibodies will be determined for patients in the eryaspase arm.

### 7.6.5 Biomarker Assessments

This study will collect samples for biomarker assessments in all patients. Sample types collected include tumor samples, whole blood samples and plasma samples. Biomarkers will be tested prospectively and summarized at baseline and, where applicable, at subsequent assessments. These assays will be performed at central laboratories. In addition, biomarkers identified in other clinical studies may also be assessed in the biomarker samples collected from patients enrolled in this study. Detailed instructions for processing, storage, and shipping of samples will be provided in the Laboratory Manual

#### 7.6.5.1 ANALYSIS OF TUMOR TISSUES

A paraffin-embedded tissue block (FFPE), or a minimum of 10 unstained slides, obtained from an archived or newly obtained tumor tissue sample (primary tumor or metastatic lesion) will be required.

All tumor samples may be used to assess the effects of eryaspase and tumor-relevant pathway dysregulation (such as mutations, amplifications) that may be important in the development of progression of cancer as well as for the potential use in diagnostic development. Assays to evaluate biomarkers that may correlate with clinical outcome may be performed at central laboratories, such as:

- Mutational analyses and detection of gene amplification of relevant oncogenes (e.g., KRAS, MYC, PI3KCA, and FGFR) and genes involved in activated pathways of survival and proliferation (e.g., Erk1/2, STAT3, AKT, and MAPK).
- Expression profiling may be done by analysis of ribonucleic acid (RNA) extracted from tissue.
- Depending on tissue availability, additional assays including immunohistochemistry (IHC), gene expression profiling, or protein activation may be performed.
- If applicable, mechanisms of resistance to eryaspase treatment will be evaluated.

#### 7.6.5.2 ANALYSIS OF PLASMA SAMPLES

Plasma samples will be collected for the following biomarker analyses:

- Circulating tumor DNA (ctDNA) may be analyzed in plasma samples to identify plasma-borne somatic mutations as predictors of clinical outcome with eryaspase.
- Proteomic and transcriptomic analyses of biomarker samples may be conducted to identify profiles that can be related to treatment response. Examination of pre- and

post-treatment protein and transcript profiles may uncover novel blood-borne candidate biomarkers/profiles that could be used to predict response to eryaspase.

- Markers of immunological response may be evaluated for correlation with response.

#### 7.6.5.3 PHARMACOGENETIC ANALYSIS

Pharmacogenetic analysis is the study of the variability in drug response due to hereditary factors. Individual genetic composition (genotype) may have an impact on the PK and the pharmacodynamic effects of the drug. Examples of pharmacogenetic analyses include genotyping of metabolizing enzymes such as uridine 5'-diphosphate glucuronosyltransferases (UGTs) and transports, evaluation of a whole-genome single nucleotide polymorphism (SNP), or other genetic marker sets. The information obtained is solely used to further characterize drug effects and does not have clinical, diagnostic, or therapeutic implications for the individual patients. This PGx research is not designed to determine whether other members of the patient's family are at risk of developing pancreatic cancer. The Sponsor will be blinded as to the subject's identity and since the analysis is done for research purposes only, individual results will not be shared with the Investigator and/or subject or the subject's relatives. Any information obtained is not intended for inclusion in the medical record. This research will not change the care the subject receives in this study.

A whole blood sample (5 mL) will be drawn using a tube containing ethylenediaminetetraacetic acid (EDTA) from patients who provide separate written informed consent for this optional procedure. Patient participation in the PGx analysis is voluntary, and refusal of consent will not disqualify the patient from participating in the study. Furthermore, a patient can withdraw consent for the PGx analysis at any time during the study.

#### 7.6.5.4 SAMPLE COLLECTION, STORAGE, AND SHIPPING

Detailed procedures for collection, processing, handling, storage, and shipment of samples for central laboratory analysis (PK, pharmacodynamics, immunogenicity, biomarkers, and PGx) will be provided in the Laboratory Manual.

#### 7.6.5.5 BIOANALYSIS

Samples will be analyzed using validated, where applicable, analytical methods. A description of the assays and validation data will be provided in separate analytical reports.

#### 7.6.5.6 STORAGE OF BIOLOGICAL SAMPLES FOR POTENTIAL FUTURE ANALYSIS

After the end of the study, biological samples or derivatives (such as DNA, RNA, and protein) will be stored at a central repository for the maximum number of years defined per local regulatory requirements to allow scientific research to be conducted in the future as new discoveries are made.

## 7.7 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The Investigator is required to report to the Sponsor or its representative all AEs occurring during the clinical study (Title 21 Code of Federal Regulations [CFR] Part 312.64[b] and International Council for Harmonization [ICH] E6 [R2]).

### 7.7.1 Definition of Adverse Events

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

### 7.7.2 Definition of Serious Adverse Events

A **serious adverse event (SAE)** is any untoward medical occurrence that at any dose:

1. Results in death,
2. Is life-threatening,
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect, or
6. Is otherwise medically significant (any event not meeting the above criteria that, based upon medical judgment, jeopardizes the patient, and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of an SAE).

**NOTE:** If the standard of care or institutional practice requires hospitalization of patients for the sole purpose of conducting study procedures or delivering study therapy, then such hospital admission will not be considered or reported as meeting SAE criteria. However, should an SAE develop during such a hospitalization, it will be considered serious and reported as such.

**NOTE:** Disease progression should not be reported as an SAE for the purposes of this study.

**NOTE**: in instances, where an adverse event changes to serious event; this date should be the onset date of the SAE.

### 7.7.3 Classification of Adverse Events

#### 7.7.3.1 SEVERITY GRADING

The severity of AEs is to be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. For AEs not listed in the CTCAE scale, the following definitions should be used:

- **Mild (Grade 1):** The AE is noticeable to the patient but does not disrupt normal daily activities; it does not require discontinuation of the study drug, but may require additional therapy.

- **Moderate (Grade 2):** The AE is moderately uncomfortable and interferes with the patient's daily activities; it does not require discontinuation of the study drug but may require additional therapy.
- **Severe (Grade 3):** The AE is intolerable and disrupts normal daily activities, and may require additional therapy or hospitalization and/or discontinuation of the study drug.
- **Life-threatening (Grade 4):** The AE exposes the patient to risk of death at the time of the event; this does not refer to an event that might have caused death if it had been more severe. Any event which is considered life-threatening is considered to be serious, and must be reported as described in Section 7.7.6.
- **Death related to AE (Grade 5):** An event that results in death is considered a Grade 5 AE, and by definition, is an SAE. Any event with a fatal outcome must be reported as described in Section 7.7.6.

#### 7.7.3.2 CAUSALITY ASSESSMENT

An Investigator who is qualified in medicine must assess the causal relationship between eryaspase, chemotherapy, or both and each occurrence of each AE/SAE. The Investigator should decide whether, in his/her medical judgment, there is a "reasonable possibility" that the event may have been caused by the study drug (IMP and non-IMP background treatment).

- If no valid reason exists for suggesting a causal relationship between the study drug (IMP or non-IMP background treatment) and the occurrence of the AE, then the AE should be classified as "unrelated."
- If there is any valid reason for suspecting a possible causal relationship between the study drug (IMP and non-IMP background treatment) and the occurrence of the AE, then the AE should be considered "related."

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, should be considered and investigated. The Investigator should also consult the IB in making his/her assessment.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is critical that the Investigator provide an assessment of causal relationship for every event before the initial transmission of the SAE report to the Sponsor, as it is one of the criteria used when determining regulatory reporting requirements.

The Investigator may change his/her opinion of causality in light of follow-up information; in this case an SAE follow-up report should be sent with the updated causal relationship assessment.

Definitions of the causal relationship of an AE to the use of the study medication are as follows:

- **Related:** There is a reasonable possibility of a causal relationship between the administration of the study drug (IMP and non-IMP background treatment) and the adverse event emergence. "Reasonable possibility" means there is evidence to suggest a causal relationship, e.g. temporal relationship, biological plausibility, between study intervention and the AE.

- **Not Related:** There is no reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and the event onset, or an alternate etiology has been established.

#### 7.7.3.3 EXPECTEDNESS

The drug safety group will be responsible for determining whether an AE is expected or unexpected, based on available reference safety information in the IB. An AE will be considered unexpected if its nature, severity, or frequency is not consistent with the reference safety information described for eryaspase in the IB.

### 7.7.4 Time Period and Frequency for Adverse Event Assessment and Follow-Up

All AEs that are reported by a patient or observed by study personnel from the date of patient informed consent until 90 days after the last study treatment or start of new anti-cancer treatment, whichever is sooner, will be reported.

Any medical condition that is present at the time that the patient is screened will be considered as a baseline condition and not reported as an AE.

All AEs must be followed until they resolve, return to baseline, or are determined to be permanent at the EOT visit.

### 7.7.5 Recording Adverse Events and Serious Adverse Events

All AEs, whether serious or non-serious, must be recorded in the source documents and in the eCRF using standard medical terminology. For each event, the Investigator will evaluate and report the onset date, resolution date, severity, causality, action taken, seriousness, outcome (if applicable), and whether or not it caused any change in study drug administration (dose delay, dose reduction, or study treatment discontinuation). Changes in the severity of an AE must be documented to allow the duration of the event at each level of severity to be assessed. AEs characterized as intermittent require documentation of the onset and duration of each episode.

Whenever possible, diagnoses should be provided when signs and symptoms represent a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). A specific disease or syndrome, rather than individual associated signs and symptoms, should be identified whenever possible. Where there is no link between different clinical symptoms occurring at the same time, each sign should be recorded as a separate AE. All reported information must be in English.

When an AE occurs, it is the Investigator’s responsibility to review all documentation related to the event (e.g., hospital progress notes, laboratory and diagnostics reports). The Investigator will then record all relevant AE information in the eCRF. It is not acceptable for the Investigator to send photocopies of the patient’s medical records to the Sponsor in lieu of completion of the eCRF AE pages.

In some instances, the Sponsor may request copies of medical records for certain patients. Should this occur, all patient identifiers, with the exception of the patient’s study identification number, will be redacted on the copies of the medical records before submission to the Sponsor.

### 7.7.6 Serious Adverse Event Reporting

#### 7.7.6.1 INVESTIGATOR REPORTING RESPONSIBILITIES FOR SERIOUS ADVERSE EVENTS

If an AE meets the definition of "serious," the Investigator must report it immediately (within a maximum of 24 hours from knowledge of the event), regardless of its presumed relationship to the IMP. To do so, the Investigator must complete the SAE Form, and forward it to PrimeVigilance, mandated by ERYTECH Pharma, at:

**Email: erytechpv@primevigilance.com**

**eFax (US): +1(0) 8006470631**

**eFax (EU): +44(0) 8000669250**

All reported information must be submitted in English. It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the SAE form.

If necessary, the Investigator will be asked for additional information which may include hospital records, laboratory reports, or other test results.

SAEs must be followed until they resolve, or are determined to be permanent at the EOT visit, or until the patient dies or is lost to follow-up. The Investigator must forward any relevant follow-up information for SAEs (including outcome and diagnosis) in the same manner as the initial report within 24 hours of obtaining the information.

#### 7.7.6.2 EXPEDITED REPORTING AND INVESTIGATOR SAFETY REPORTS

The Sponsor is responsible for submitting all suspected unexpected serious adverse reactions (SUSARs) related to the IMP to Competent Authorities (and IECs/IRBs as required) and to Investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable.

It is the Investigator's responsibility to notify the local IEC/IRB of all suspected unexpected serious adverse reactions or other specific safety information (e.g., summary or listing of SAEs) involving risk to human subjects as appropriate according to local requirements.

The Investigator will acknowledge and file all safety updates received from the sponsor along with the IB in the Investigator's Site File.

### 7.7.7 Events of Special Interest

The following events are considered events of special interest:

- Venous thrombotic events,
- Hepatic toxicity,
- Pancreatitis, and
- Transfusion-related events.

### 7.7.8 Reporting of Pregnancy

If a female patient or the partner of a male patient becomes pregnant, the patient must inform the Investigator immediately. The Investigator must immediately report any pregnancy occurring during the trial to ERYTECH Pharma by completing the "Exposure during pregnancy case report form" and forward it to PrimeVigilance, mandated by ERYTECH Pharma, at:

**Email: erytechpv@primevigilance.com**

**eFax (US): +1(0) 8006470631**

**eFax (EU): +44(0) 8000669250**

Patients will give consent upon enrollment for this reporting of any pregnancy during the trial as well as information about the delivery and about the baby's health until the age of 6 month. Pregnancy complications must be recorded as AEs. If the infant has a congenital anomaly/birth defect, this must be reported and followed as an SAE.

## 7.8 CHANGES IN PROTOCOL DUE TO COVID-19

### 7.8.1 BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.

The COVID-19 worldwide pandemic has the potential to impact the conduct of clinical trials and challenges may arise due to issues such as quarantines, site closures, travel limitations, or interruptions to the supply chain of investigational products. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or the use of investigational products or adhering to protocol-mandated visits and laboratory/diagnostic testing.

Regulatory authorities in the EU and the US have provided guidance on how to handle the potential impacts of the COVID-19 pandemic when conducting clinical studies. In the US, the Food and Drug Administration (FDA) published "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency", and in the EU, the European Medicines Agency (EMA) published "Guidance on the Management of Clinical Trials during the COVID-19 (coronavirus) pandemic".

Erytech followed the guidance in these documents and conducted a Risk Assessment of the COVID-19 pandemic on the conduct of Trybeca-1 to ensure the safety of subjects seen during the COVID-19 pandemic and maintain data quality and integrity.

### 7.8.2 MODIFIED PROTOCOL REQUIRED PROCEDURES

Erytech recognizes that subjects may encounter difficulties having all protocol required laboratory assessments completed due to possible local laboratory closures or shortages of lab personnel. Please refer to Table 12 for a list of COVID-19 Minimum Safety Assessments that are to be completed.

Inclusion criteria number 7 (requirement for archival or fresh tumor tissue) will be waived if archive tissue is not available and an elective biopsy cannot be scheduled due to COVID.

### 7.8.3 MINIMUM SAFETY ASSESSMENTS

**Table 12 Minimum Safety Assessments**

| Category | Parameter | Must Be Performed |
|---|---|---|
| **Hematology: (no waivers)** | Hematocrit | X |
| | Hemoglobin | X |
| | Platelet count | X |
| | RBC count | X |
| | White blood cell (WBC) count with differential | X |
| | Neutrophils | X |
| | Lymphocytes | X |
| | Eosinophils | X |
| | Monocytes | X |
| | Basophils | X |
| | | X |
| **Coagulation:** | Fibrinogen | X |
| | Antithrombin III (AT III) | X |
| **Serum Chemistry and Tumor Markers:** | Albumin | X |
| | Alkaline phosphatase | waived |
| | Alanine aminotransferase (ALT) | X |
| | Ammonia | waived |
| | Amylase | X |
| | Aspartate aminotransferase (AST) | X |
| | Bicarbonate | waived |
| | Calcium | X |

**Table 12 Minimum Safety Assessments**

| Category | Parameter | Must Be Performed |
|---|---|---|
| | Chloride | X |
| | Creatinine | X |
| | Gamma-glutamyl transferase (GGT) | X |
| | Glucose | X |
| | Lactate dehydrogenase (LDH) | waived |
| | Lipase | X |
| | Potassium | X |
| | Sodium | X |
| | Total bilirubin | X |
| | Total cholesterol | waived |
| | Triglycerides | waived |
| | Urea | waived |
| | Uric acid | waived |
| | CA19-9 | waived |
| **Other Laboratory Tests: (no waivers)** | Blood phenotype, Rh factor, and ABO blood group, all done on two separate samples | X |
| | Irregular antibody screening test (IAST) | X |
| | Pregnancy test for women of childbearing potential (serum at screening and at End of Treatment; urine on Cycle 1 Day 1 before treatment and as indicated during treatment for females of child-bearing potential) | X<br>X |

### 7.8.4 ON-SITE VISIT SCHEDULES

Investigators should make every attempt to maintain patient's treatment administration as planned for each treatment arm per protocol and patient assessments as outlined in the Schedule of Events. Given the need to quarantine, travel restrictions and site closures, patients may be evaluated outside of the protocol parameters, including having laboratory or radiological assessments performed at another location.

Disease assessments, particularly CT/MRI scans should be performed every 8 weeks [+ 3 days] from randomization per protocol, when possible. Local imaging centers should be used if possible.

### 7.8.5 PHARMACODYNAMIC SAMPLES

The laboratory that supplied the sulphosalicylic acid (SSA) vacutainer tubes for collecting pharmacodynamic (PD) samples was closed due to COVID-19. All remaining SSA tubes were supplied to active sites. A determination was made that no further PD samples would be obtained after SSA vacutainer supplies were exhausted.

### 7.8.6 PROTOCOL DEVIATIONS

Investigators will apply due diligence to avoid protocol deviations if possible. All protocol deviations due to delayed or missed visits and protocol required assessments or treatments related to COVID-19 will be collected on the COVID-19 Related Deviation Log (**APPENDIX 4**). This log will serve as source documentation for entry into the COVID-19 eCRF form within the electronic data capture system.

### 7.8.7 CLINICAL MONITORING

On-site monitoring visits may be converted to remote monitoring visits according to the Monitoring Plan if on-site visits cannot be conducted due to COVID-19 restrictions on site closures, limited access to study staff and travel restrictions. Access to source documents (medical records) may be provided electronically or other secure method to comply with applicable privacy and security laws for the use and disclosure of information related to the research set forth in this protocol if authorized by national competent authorities.

Remote monitoring visits will be converted back to on-site visits upon a site's availability to reopen safety.

# 8 STATISTICAL CONSIDERATIONS

## 8.1 STATISTICAL HYPOTHESES

The primary efficacy endpoint is Overall Survival (OS) and the study is designed to test the superiority of eryaspase plus chemotherapy over chemotherapy alone. The primary analysis will test the following hypotheses:

- Null Hypothesis: The hazard ratio for OS between eryaspase plus chemotherapy and chemotherapy alone is equal to one
- Alternative Hypothesis: The hazard ratio for OS between eryaspase plus chemotherapy and chemotherapy alone is less than one

The key secondary efficacy endpoints are Progression-free Survival (PFS), Objective Response, Duration of Response (DoR) and Disease Control Rate (DCR).

The null and alternative hypotheses for PFS will be as for OS

The primary analyses of the endpoints objective response and disease control will test the following hypotheses:

- Null Hypothesis: The Objective Response Rate (ORR)/Disease Control Rate (DCR) in the eryaspase plus chemotherapy group is equal to the Objective Response Rate (ORR)/Disease Control Rate (DCR) in the chemotherapy alone group
- Alternative Hypothesis: The Objective Response Rate (ORR)/Disease Control Rate (DCR) is greater in the eryaspase plus chemotherapy group versus the chemotherapy alone group

There will be no formal statistical testing for DoR as this is not a randomized comparison and these data will be evaluated through the presentation of descriptive statistics

All statistical testing will be undertaken based on a one-sided 2½% significance level subject to adjustments for interim analysis.

## 8.2 SAMPLE SIZE DETERMINATION

With a power of 88.4% and an overall one-sided type I error of 2.5%, and including one interim analysis for efficacy with an O'Brien-Fleming type stopping rule, a total of 390 deaths are required to detect a treatment effect hazard ratio of 0.725 for eryaspase plus chemotherapy versus chemotherapy alone. The hazard ratio in the Phase 2 study for eryaspase was 0.63 (95% CI: 0.39 to 1.10), and 0.725 represents a conservative estimate based on these data that is viewed as being highly clinically relevant.

The interim analysis for efficacy will take place once 261 (67%) events have been observed.

Assuming a recruitment period of 26 months, a median overall survival in the control group of 6.0 months, a 10% probability of dropping out during the course of the study, and a minimum follow-up of 9 months, the study size will be based on the recruitment of 482 patients.

## 8.3 ANALYSIS POPULATIONS

**Intent to Treat population (ITT):** All patients randomized, irrespective of whether they received study medication.

**Safety population (SP):** All randomized patients who receive at least one dose of study medication (eryaspase or chemotherapy).

**Per Protocol population (PP):** The PP population is a subset of the ITT population, and consists of all randomized patients who meet the major inclusion criteria and none of the major exclusion criteria and who receive at least one cycle of treatment. The major inclusion/exclusion criteria that are to be considered here will be defined in the Statistical Analysis Plan (SAP).

## 8.4 STATISTICAL ANALYSES

### 8.4.1 Analysis of the Primary Efficacy Endpoint

The primary endpoint is OS which is measured from the date of randomization to the date of death from any cause. Patients who are not known to have died will be censored at the date of last contact, and this will apply as of the date of data cut-off for any particular analysis.

The primary analysis will be the comparison of OS between the two treatment arms in the ITT population using the one-sided stratified log-rank test, with stratification factors as used in the randomization. Data will be summarized in Kaplan-Meier curves together with medians and 95% confidence intervals for those medians. The Cox Proportional Hazards model, stratified for the randomization factors, will be used to obtain a hazard ratio together with its 95% confidence interval.

### 8.4.2 Analysis of the Secondary Endpoints

PFS will be compared between the two treatment arms using the same methods of analysis as for OS.

The following efficacy analysis will also be performed in the ITT population:

- ORR, defined as the proportion of patients who achieve objective tumor response (CR or PR) per RECIST 1.1. Each patient's BOR will be summarized (CR, PR, SD, PD, or unknown). This comparison will be based on the Cochran-Mantel-Haenszel test, with stratification factors as for the analysis of OS and PFS. Results will be reported in terms of an odds ratio and associated 95% confidence interval.
- DCR (disease control rate), defined as the proportion of patients who achieve CR, PR and SD,
- DoR will be evaluated in patients who achieve CR/PR. It will be measured from the time CR/PR (whichever is first recorded) is first met until the first date that recurrence or PD is objectively documented. Kaplan-Meier curves will be provided in association with this analysis; however, there will be no p-value calculations, as this is not a randomized comparison.

- Extensive evaluation of the consistency of treatment effect for OS and PFS across the population as a whole will be undertaken by providing analyses in subgroups, with displays in forest plots and p-values for treatment by interactions.

### 8.4.3 Other Aspects of the Efficacy Analyses

Additional disease control endpoints will be evaluated as exploratory analyses, namely DCR8, DCR12, and DCR16 defined as the disease control rates when SD is required to last for at least 8 weeks, at least 12 weeks, and at least 16 weeks respectively. These analyses will follow the methodology for DCR outlined in Section 8.4.2.

All primary and secondary efficacy analyses will be repeated in the PP population.

Confirmatory testing for the primary and secondary efficacy endpoints will be performed hierarchically (OS followed by PFS followed by ORR followed by DCR) in order to account for multiplicity. Any statistically significant findings occurring below a non-significant result in the hierarchy will be considered as exploratory findings.

### 8.4.4 Planned Interim Analyses

This study will have an event-driven interim analysis for OS, based on O'Brien-Fleming boundaries. The interim analysis for OS will take place following 261 deaths. The number of deaths required to trigger the final analysis will be 390.

### 8.4.5 Subgroup Analyses

Hazard ratios and 95% confidence intervals will be calculated for OS within subgroups using the unadjusted Cox proportional hazards model in order to evaluate the consistency of treatment effect. These subgroups will include those defined by the stratification factors. Other subgroups may also be considered, with a full list being set down in the SAP.

Subgroup analyses of PFS will be performed in a similar way. ORR and DCR will also be evaluated within these same subgroups, based on the calculation of unadjusted odds ratios and corresponding 95% confidence intervals.

### 8.4.6 Independent Data Monitoring Committee (IDMC)

An IDMC, composed of at least two oncologists (at least one of whom specializes in pancreatic cancer) and a statistician, will be set up to review the safety of eryaspase during the study and to review the interim analysis for efficacy. The IDMC will develop and follow an IDMC plan and charter.

The IDMC will review the safety of eryaspase in combination with irinotecan-based therapy or gemcitabine/Abraxane regimen after 10 or more patients have been enrolled per regimen and have received at least one cycle of study therapy. Thereafter, and at a frequency to be defined in the IDMC Charter, the IDMC will be provided with reports of baseline demographics, medical history, concomitant medications, AEs, SAEs, and other safety data for regular review and recommendations.

In addition, at the interim analysis, the IDMC will be provided with a report containing the results of the efficacy analyses. The IDMC will review these reports and will provide a recommendation to ERYTECH for the continuation, termination, or modification of the study.

# 9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

### 9.1.1 Informed Consent Process

Participation in the study is voluntary; each patient must indicate his/her agreement and willingness to participate by signing and dating the approved ICF prior to the initiation of any study-related procedures.

The Sponsor or designee will provide an Informed Consent Form to Investigators in a separate document. The consent forms that are used, including the separate consent form for PGx, must be approved both by the Sponsor and by the reviewing IECs/IRBs.

The ICF should be in accordance with the principles originating in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Prior to the start of any protocol-specific evaluations or screening procedures, the Investigator (or designated staff) will explain the nature of the study and its risks and benefits to the patient. Each patient will receive a copy of the ICF, which includes patient information. Patients should be given ample time to read the information and the opportunity to ask questions. One copy of the signed ICF will be given to the patient, and another will be retained with the study records by the Investigator. The process of obtaining informed consent should be documented in the patient's medical file.

### 9.1.2 Independent Ethics Committees and Regulatory Authorities

This clinical study will be conducted in accordance with the current ICH GCP Guidelines, as well as the ethical principles founded in the Declaration of Helsinki and applicable local laws and regulations (including European Directive 2001/20/EC, EU Regulation No. 536/2014, and US Code of Federal Regulations (CFR) 21).

Before the start of the study, the Sponsor or the Sponsor's designee will submit the clinical study protocol, ICF, and any other appropriate documents to regulatory authorities in accordance with local legal requirements. All required documents will also be submitted to the relevant IECs/IRBs by the Sponsor, the Sponsor's designee, or the investigative sites, as applicable. As required by local regulations or by the IECs/IRBs, the Sponsor or Investigator will also submit the financial arrangements for the study and/or other financial interests of the Investigator or applicable site staff in the investigational drug or the Sponsor company.

The study will only be conducted at sites where IEC/IRB and regulatory authority approval has been obtained as required.

All substantial amendments to the study protocol will also be submitted to the IECs/IRBs and authorities in accordance with local legal requirements. Amendments must be evaluated to determine whether the ICF should also be revised. Protocol amendments must not be implemented without prior IEC/IRB and regulatory approval, except where necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the study (e.g., change in Sponsor contacts or telephone numbers).

The Investigator must keep a record of all communication with the IECs/IRBs and if applicable, between a national coordinating investigator and the IECs/IRBs. This also applies to any communication between the investigator (or sub-investigator, if applicable) and regulatory authorities.

### 9.1.3 Study Completion or Discontinuation and Closure

The study will be considered completed with completion of the last visit of the last patient participating in the study.

It is expected that each Investigator will complete the last study visit for the last patient at his/her site and submit all eCRFs to the Sponsor (or designee) in satisfactory compliance with the protocol within the time frame specified in the Clinical Trial Agreement.

This study may be prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Investigator will promptly inform study participants and the relevant IEC/IRB, and the Sponsor will provide the reason(s) for the termination or suspension to competent regulatory authorities. Study participants will be contacted as appropriate, and will be informed of any changes to the study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants,
- Demonstration of efficacy that would warrant stopping,
- Determination that the primary endpoint has been met,
- Determination of futility, and
- Sponsor decision to stop development of the IMP.

The study may resume once concerns about safety, protocol compliance, and data quality have been addressed to the satisfaction of the Sponsor, IEC/IRB, and/or the applicable regulatory agency.

Following study completion or termination, the Investigator will provide the Sponsor, the IEC/IRB, and the applicable regulatory agency with final reports and summaries as required by local regulations (e.g., for Investigational New Drug (IND) studies, the Investigator must submit a written report to the Sponsor and the Ethics Committee within 3 months after the completion or termination of the study).

### 9.1.4 Protocol Adherence

This protocol defines the study objectives, the study procedures, and the data to be collected on study patients. Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research-related purpose.

Investigators will apply due diligence to avoid protocol deviations.

All protocol deviations identified via monitoring and data review will be tracked, and all significant protocol deviations (i.e., major deviations that would exclude a patient from the PP population; to be defined in the SAP) will be reported in the Clinical Study Report (CSR).

See Section 7.8.6 on collection protocol deviations related to COVID-19.

### 9.1.5 Definition of Source Data

Source data are defined as data contained in original documents or certified copies of original records in the patient's medical file (source documents), including but not limited to hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy records, recorded data from automated instruments, X-rays, consultant letters and correspondence, and nurse's notes.

**NOTE:** Each patient's involvement in the study should be clearly documented in his/her medical file; details should include the study protocol number, the patient's study identification number, the patient's consent to take part in the study (with the date of consent), and the dates of all study visits. Such essential documents must be retained by the Investigator in accordance with local regulations.

### 9.1.6 Access to Source Data

By signing the ICF, the patient agrees that Investigators, monitors, and all mandated staff including the sponsor or its representatives and regulatory inspectors will have access to his/her personal data during and after the study to ensure the quality of data recorded for study purposes.

By agreeing to participate in this clinical trial, the Investigator agrees to give full and direct access to all records (including electronic records) for patients enrolled in the study to the Sponsor or its representatives at the time of each monitoring visit or audit. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of regulatory authorities (FDA, *Agence nationale de sécurité du médicament et des produits de santé* [ANSM], EMA, and others) and IECs/IRBs.

The Investigator will comply with applicable privacy and security laws for the use and disclosure of information related to the research set forth in this protocol.

### 9.1.7 Confidentiality and Privacy

To maintain patient confidentiality and to comply with applicable data protection and privacy laws and regulations, all eCRFs, study reports, and communications relating to the study will identify patients by their assigned patient identification numbers and by dates of birth, if this is permitted by local laws and regulations. Access to patient names linked to such numbers shall be limited to the site and the Investigator, and shall not be disclosed to the Sponsor.

In accordance with legal requirements, anyone having direct access to source data must respect data confidentiality and must ensure patient anonymity on documents that could be forwarded to the Sponsor.

### 9.1.8 Data Quality Control

Steps taken by the Sponsor to ensure the accuracy and reliability of study data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and appropriate personnel before the study, training related to study conduct, periodic monitoring visits by the Sponsor or its designee, and when applicable, direct transmission of clinical laboratory data from the central laboratory to the Sponsor's database.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled patient will be entered into an eCRF by study site personnel using a secure, validated web-based electronic data capture (EDC) application. All users will be required to complete EDC training before they are given access to the system.

Instances of missing, discrepant, or uninterpretable data will be queried to the Investigator for resolution, via auto-queries generated by programmed edit checks or via manual queries raised by site monitors and/or data managers. Any changes to the study data will be made in the eCRF; the EDC system will document these changes in an audit trail, which will be maintained within the clinical database.

### 9.1.9 eCRF Completion using Electronic Data Capture

Guidelines for eCRF completion will be provided and will be reviewed with study personnel before the start of the study, and as needed during the study.

It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF. All data entered in the eCRFs must be supported by source data. The Investigator or designee must complete eCRFs within 5 days after data are collected.

The Sponsor or designee will review eCRF data for accuracy and completeness during on-site monitoring visits and after transmission of data to the Sponsor or designee; any discrepancies will be resolved with the Investigator or designee, as appropriate. After the data are uploaded into the clinical study database, they will be verified for accuracy. The Investigator must answer all queries as soon as possible.

The Investigator will provide formal approval of all information in the eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for patients for whom he or she is responsible.

A copy of the final archival eCRF in the form of a compact disc (CD) or PDF will be provided to the Investigator for filing in his/her study file. The Sponsor will retain the eCRF data.

### 9.1.10 Key Roles and Study Governance

The worldwide Sponsor of this clinical trial is ERYTECH Pharma. The Sponsor will enlist the support of a contract research organization (CRO), imaging management vendors, central labs, and statistical firms to perform the operational aspects of the trial. The Sponsor will supervise and practice oversight on all outsourced activities. All structures and associated procedures will be described in the Oversight Plan, which will include information about IMP, quality assurance, and vendor management.

The Sponsor Medical Monitors will support the Investigators during the conduct of the study, and the Sponsor site monitor will support the site personnel and will provide the necessary protocol training, RECIST 1.1 training, and any additional training required for the successful conduct of this trial.

### 9.1.11 Safety Oversight

The Sponsor's Global Drug Safety department or its designated representative will oversee, monitor and report AEs and SAEs to all relevant parties as required by the regulations and applicable laws. Continuous safety monitoring will be performed by Investigators and site clinicians. An IDMC will be appointed and will meet in regular intervals to monitor the safety of the study participants and provide recommendations to the Sponsor.

### 9.1.12 Clinical Monitoring

In order to comply with GCP guidelines, the study sites must follow monitoring procedures developed by the Contract Research Organization (CRO) and approved by the Sponsor.

The Sponsor or its designee will perform on-site monitoring visits as frequently as necessary and according to the Monitoring Plan developed for the study to ensure that the investigation is conducted according to the protocol design and regulatory requirements. The monitor will cross-check the data entered into the eCRFs and SAE Forms with the hospital or clinic records (source documents) for completeness and clarity. Data queries will be raised in the EDC system, findings from this review of eCRFs and source documents will be discussed with the investigational staff, and administrative matters will be clarified.

At site initiation visits, the nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and investigational staff and are accessible for verification by the Sponsor site monitor. If electronic records are maintained at the investigational site, access to these records and methods of verification must be discussed with the investigational staff.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the data in the eCRF are consistent with the original source data. It is expected that during monitoring visits the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitors will meet with the Investigator on a regular basis during the study to provide feedback on study conduct.

See Section 7.8.7 for further information regarding Clinical Monitoring related to COVID-19.

### 9.1.13 Site Audits and Inspections

The Sponsor is responsible for implementing and maintaining quality assurance (QA) and quality control (QC) systems, and for performing systematic and independent auditing of study conduct, data generation, documentation, analysis, and reporting to determine whether the evaluated activities are being performed in compliance with the protocol, the Sponsor's standard operating procedures, GCP, and applicable local regulatory requirements.

Representatives of the Sponsor's clinical QA department or designee may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. Similar auditing procedures may also be conducted by agents of any IRB/IEC or regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The

Investigator should immediately notify the Sponsor if he or she is contacted by a regulatory agency concerning an upcoming inspection.

The Investigator/institution will ensure direct access to all source data/documents and reports (including but not limited to written, electronic, magnetic, and optical records) for the purpose of monitoring, auditing, and inspection by the IRB/IEC or regulatory authorities. All parties will take reasonable precautions to maintain patient privacy. The Investigator and staff are also responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its designees or during inspections by regulatory authorities.

### 9.1.14 Data Handling and Record Keeping

#### 9.1.14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Patient data will be collected by the Investigator or designee using the eCRF provided by ERYTECH.

It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the eCRFs.

All data entered in the eCRFs must be supported by and consistent with source data, and any discrepancies must be explained.

The Investigator or designee will complete eCRFs within 5 days after data are collected.

The Investigator will provide formal approval of all information in the eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for patients for whom the Investigator is responsible.

Patient data necessary for analysis and reporting will be entered into a validated database system. Clinical data management will be performed in accordance with ERYTECH standards and data cleaning procedures.

#### 9.1.14.2 STUDY RECORD RETENTION

In compliance with the ICH GCP guidelines, the Investigator/institution will maintain all eCRFs (provided at the end of the study on electronic media for site records), source documents that support the data collected from each patient, and other study documents as specified in ICH GCP Section 8 (Essential Documents for the Conduct of a Clinical Trial) and applicable regulatory requirements. The Investigator/institution will take measures to prevent accidental or premature destruction of these documents.

All documents must be retained by the Investigator for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. At the end of the two -year period, the Sponsor or its designee must be consulted prior to the destruction of study documents. These documents will be retained per country regulations. It is the Sponsor's responsibility to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such documents.

### 9.1.15 Publication and Data Sharing Policy

Any and all scientific, commercial, and technical information disclosed by the Sponsor in relation to this trial will be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party without the Sponsor's permission except to Investigator's employees and staff who have been made aware that the information is confidential and who are bound to treat it as such.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and that it therefore may be disclosed as required to other clinical Investigators, business partners and associates, and government agencies. The Investigator understands that to allow use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

The Sponsor or designee will list this study on the public databases of clinical studies, www.clinicaltrials.gov and www.clinicaltrialsregister.eu. A clinical study report of the study will be made available after the conclusion of the study. The final report may be submitted to relevant regulatory authorities to support a request for product registration. It is the intention of the Sponsor to publish the results of this study in a peer-reviewed journal.

No publication or disclosure of study results will be permitted except under the terms and conditions defined in a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

## 9.2 PROTOCOL AMENDMENT HISTORY

| Version | Date | Description |
|---|---|---|
| 0 | 05th March 2018 | GRASPANC 2018-01 Study Protocol (Original) |
| 1.0 | 05th September 2019 | GRASPANC 2018-01 Study Protocol 1.0 (Global Amendment) |
| 2.0 | 14th December 2020 | GRASPANC 2018-01 Study Protocol 2.0 (Global Amendment) |

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# 10 REFERENCES

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2012;**62**(1):102

2. GLOBOCAN. Mortality Tables by Population. Available from: http://globocan.iarc.fr/Default.aspx Accessed: 04 January 2018 2018

3. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;**136**(5):E359-86 doi: 10.1002/ijc.29210[published Online First: Epub Date]|.

4. Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? Therap Adv Gastroenterol 2013;**6**(4):321-37 doi: 10.1177/1756283X13478680[published Online First: Epub Date]|.

5. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;**26 Suppl 5**:v56-68 doi: 10.1093/annonc/mdv295[published Online First: Epub Date]|.

6. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;**15**(6):2403-13 doi: 10.1200/JCO.1997.15.6.2403[published Online First: Epub Date]|.

7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;**364**(19):1817-25 doi: 10.1056/NEJMoa1011923[published Online First: Epub Date]|.

8. NCCN. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. Available from: https://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf Accessed: 16 January 2018 2017

9. ESMO. Guidelines Committee eUpdate Published 20 June 2017 Available from: http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas/eUpdate-Treatment-Recommendations. Accessed 03 January 2018 2017

10. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;**387**(10018):545-57 doi: 10.1016/S0140-6736(15)00986-1[published Online First: Epub Date]|.

11. Sarabi M, Mais L, Oussaid N, Desseigne F, Guibert P, De La Fouchardiere C. Use of gemcitabine as a second-line treatment following chemotherapy with folfirinox for metastatic pancreatic adenocarcinoma. Oncol Lett 2017;**13**(6):4917-24 doi: 10.3892/ol.2017.6061[published Online First: Epub Date]|.

12. Perera RM, Bardeesy N. Pancreatic Cancer Metabolism: Breaking It Down to Build It Back Up. Cancer Discov 2015;**5**(12):1247-61 doi: 10.1158/2159-8290.CD-15-0671[published Online First: Epub Date]|.

13. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 2008;**321**(5897):1801-6 doi: 10.1126/science.1164368[published Online First: Epub Date]|.

14. Ji Z, Mei FC, Xie J, Cheng X. Oncogenic KRAS activates hedgehog signaling pathway in pancreatic cancer cells. J Biol Chem 2007;**282**(19):14048-55 doi: 10.1074/jbc.M611089200[published Online First: Epub Date]|.

15. Collins MA, Bednar F, Zhang Y, et al. Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. J Clin Invest 2012;**122**(2):639-53 doi: 10.1172/JCI59227[published Online First: Epub Date]|.

16. Son J, Lyssiotis CA, Ying H, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 2013;**496**(7443):101-5 doi: 10.1038/nature12040[published Online First: Epub Date]|.

17. Gaglio D, Metallo CM, Gameiro PA, et al. Oncogenic K-Ras decouples glucose and glutamine metabolism to support cancer cell growth. Mol Syst Biol 2011;**7**:523 doi: 10.1038/msb.2011.56[published Online First: Epub Date]|.

18. Hosios AM, Hecht VC, Danai LV, et al. Amino Acids Rather than Glucose Account for the Majority of Cell Mass in Proliferating Mammalian Cells. Dev Cell 2016;**36**(5):540-9 doi: 10.1016/j.devcel.2016.02.012[published Online First: Epub Date]|.

19. Commisso C, Davidson SM, Soydaner-Azeloglu RG, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature 2013;**497**(7451):633-7 doi: 10.1038/nature12138[published Online First: Epub Date]|.

20. Shrivastava A, Khan AA, Khurshid M, Kalam MA, Jain SK, Singhal PK. Recent developments in L-asparaginase discovery and its potential as anticancer agent. Crit Rev Oncol Hematol 2016;**100**:1-10 doi: 10.1016/j.critrevonc.2015.01.002[published Online First: Epub Date]|.

21. Cui H, Darmanin S, Natsuisaka M, et al. Enhanced expression of asparagine synthetase under glucose-deprived conditions protects pancreatic cancer cells from apoptosis induced by glucose deprivation and cisplatin. Cancer Res 2007;**67**(7):3345-55 doi: 10.1158/0008-5472.CAN-06-2519[published Online First: Epub Date]|.

22. Gwinn DM, Lee AG, Briones-Martin-Del-Campo M, et al. Oncogenic KRAS Regulates Amino Acid Homeostasis and Asparagine Biosynthesis via ATF4 and Alters Sensitivity to L-Asparaginase. Cancer Cell 2018;**33**(1):91-107 e6 doi: 10.1016/j.ccell.2017.12.003[published Online First: Epub Date]|.

23. Ueno T, Ohtawa K, Mitsui K, et al. Cell cycle arrest and apoptosis of leukemia cells induced by L-asparaginase. Leukemia 1997;**11**(11):1858-61

24. Miller HK, Balis ME. Glutaminase activity of L-asparagine amidohydrolase. Biochem Pharmacol 1969;**18**(9):2225-32

25. Iiboshi Y, Papst PJ, Hunger SP, Terada N. L-Asparaginase inhibits the rapamycin-targeted signaling pathway. Biochem Biophys Res Commun 1999;**260**(2):534-9 doi: 10.1006/bbrc.1999.0920[published Online First: Epub Date]|.

26. Wu MC, Arimura GK, Yunis AA. Mechanism of sensitivity of cultured pancreatic carcinoma to asparaginase. Int J Cancer 1978;**22**(6):728-33

27. Dufour E, Gay F, Aguera K, et al. Pancreatic tumor sensitivity to plasma L-asparagine starvation. Pancreas 2012;**41**(6):940-8 doi: 10.1097/MPA.0b013e318247d903[published Online First: Epub Date]|.

28. Lessner HE, Valenstein S, Kaplan R, DeSimone P, Yunis A. Phase II study of L-asparaginase in the treatment of pancreatic carcinoma. Cancer Treat Rep 1980;**64**(12):1359-61

29. Hays JL, Kim G, Walker A, et al. A phase II clinical trial of polyethylene glycol-conjugated L-asparaginase in patients with advanced ovarian cancer: Early closure for safety. Mol Clin Oncol 2013;**1**(3):565-69 doi: 10.3892/mco.2013.99[published Online First: Epub Date]|.

30. Agrawal NR, Bukowski RM, Rybicki LA, Kurtzberg J, Cohen LJ, Hussein MA. A Phase I-II trial of polyethylene glycol-conjugated L-asparaginase in patients with multiple myeloma. Cancer 2003;**98**(1):94-9 doi: 10.1002/cncr.11480[published Online First: Epub Date]|.

31. Borad MJ, Babiker HM, Anthony S, et al. A multicenter, open-label, phase 1 study evaluating the safety and tolerability of pegaspargase in combination with gemcitabine in advanced metastatic solid tumors and lymphoma. Cancer Invest 2015;**33**(5):172-9 doi: 10.3109/07357907.2015.1019677[published Online First: Epub Date]|.

32. Domenech C, Thomas X, Chabaud S, et al. l-asparaginase loaded red blood cells in refractory or relapsing acute lymphoblastic leukaemia in children and adults: results of the GRASPALL 2005-01 randomized trial. Br J Haematol 2011;**153**(1):58-65 doi: 10.1111/j.1365-2141.2011.08588.x[published Online First: Epub Date]|.

33. Ataullakhanov FI, Vitvitskii VM, Zhabotinskii AM, Pichugin AV. [Permeability of human erythrocytes to asparagine]. Biokhimiia 1985;**50**(10):1733-7

34. Bachet JB, Gay F, Marechal R, et al. Asparagine Synthetase Expression and Phase I Study With L-Asparaginase Encapsulated in Red Blood Cells in Patients With Pancreatic Adenocarcinoma. Pancreas 2015;**44**(7):1141-7 doi: 10.1097/mpa.0000000000000394[published Online First: Epub Date]|.

35. Hunault-Berger M, Leguay T, Huguet F, et al. A Phase 2 study of L-asparaginase encapsulated in erythrocytes in elderly patients with Philadelphia chromosome negative acute lymphoblastic leukemia: The GRASPALL/GRAALL-SA2-2008 study. Am J Hematol 2015;**90**(9):811-8 doi: 10.1002/ajh.24093[published Online First: Epub Date]|.

36. Wang-Gillam A, CP L, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): A global, randomised, open-label, phase 3 trial. Lancet Journal Translated Name The Lancet 2016;**387**(10018):545-57 doi: http://dx.doi.org/10.1016/S0140-6736%2815%2900986-1[published Online First: Epub Date]|.

37. Godfrin Y, Liens D, Andre T, Adenis A, Joly F. L-asparaginase loaded red blood cells (RBC) in pancreatic cancer: A phase i clinical study. Pancreas 2011;**40**(8):1323 doi: http://dx.doi.org/10.1097/MPA.0b013e318232ea83[published Online First: Epub Date]|.

38. Delaney M, Taune-Wikman A, Van De Watering LM, et al. Red blood cell transfusion antigen matching influence on gestational outcomes (AMIGO) study. Transfusion 2015;**55**:25A

39. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. The Lancet 2016;**388**(10061):2825-36 doi: http://dx.doi.org/10.1016/S0140-6736(15)01313-6[published Online First: Epub Date]|.

40. Roselló S, Blasco I, García Fabregat L, Cervantes A, Jordan K. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines†. Annals of Oncology 2017;**28**(suppl_4):iv100-iv18 doi: 10.1093/annonc/mdx216[published Online First: Epub Date]|.

41. Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. The World Allergy Organization Journal 2011;**4**(2):13-37 doi: 10.1097/WOX.0b013e318211496c[published Online First: Epub Date]|.

42. 2006 Update of ASCO Practice Guideline Recommendations for the Use of White Blood Cell Growth Factors: Guideline Summary. J. Oncol. Pract. Journal Translated Name Journal of Oncology Practice 2006;**2**(4):196-201 doi: 10.1200/jop.2006.2.4.196[published Online First: Epub Date]|.

43. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;**85**(5):365-76

44. Lan KKG, Demets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70:659--663.

# 11 APPENDICES

## APPENDIX 1 TNM CLASSIFICATION

American Joint Committee on Cancer

### Pancreas Cancer Staging* 7th EDITION

#### Definitions

**Primary Tumor (T)**

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ1**
- **T1** Tumor limited to the pancreas, 2 cm or less in greatest dimension
- **T2** Tumor limited to the pancreas, more than 2 cm in greatest dimension
- **T3** Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- **T4** Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

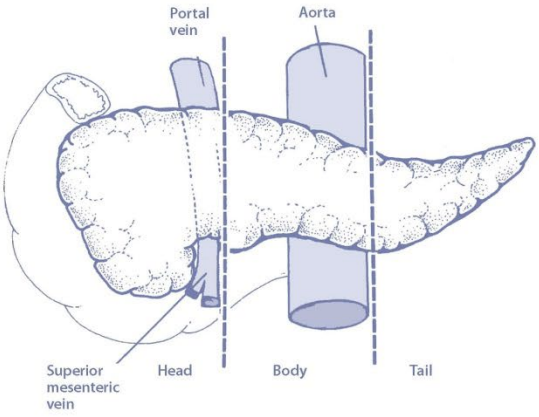
**Regional Lymph Nodes (N)**

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Regional lymph node metastasis

**Distant Metastasis (M)**

- **M0** No distant metastasis
- **M1** Distant metastasis

| ANATOMIC STAGE/PROGNOSTIC GROUPS | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage III | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |




Tumors of the head of the pancreas are those arising to the right of the superior mesenteric-portal vein confluence.

**Notes**

* Endocrine AND exocrine tumors are now staged by a single pancreatic staging system.

** Also includes the "PanIntIII" classification.



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## APPENDIX 2 PERFORMANCE STATUS (ECOG GRADING 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 house work, 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 |
| **5** | Dead |

*ECOG, Robert Comis, MD, Group Chair.
Reference: Oken MM, Creech RH, Tormey DC et-al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 1983;5 (6): 649-55.

## APPENDIX 3 KARNOFSKY PERFORMANCE STATUS

| Definition | Rating | Description |
|---|---|---|
| Able to carry on normal activity and to work; no special care needed. | 100 | Normal; no complaints; no evidence of disease. |
| | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| | 80 | Normal activity with effort; some signs or symptoms of disease. |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | 70 | Cares for self; unable to carry on normal activity or to do active work. |
| | 60 | Requires occasional assistance, but is able to care for most of his personal needs. |
| | 50 | Requires considerable assistance and frequent medical care. |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | 40 | Disabled; requires special care and assistance. |
| | 30 | Severely disabled; hospital admission is indicated although death not imminent. |
| | 20 | Very sick; hospital admission necessary; active supportive treatment necessary. |
| | 10 | Moribund; fatal processes progressing rapidly. |
| | 0 | Dead. |

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

## APPENDIX 4 COVID-19 RELATED PROTOCOL DEVIATION LOG

Subject Number: |_____|-|_____|
(Site) (Number)

Eryaspase
Protocol: GRASPANC 2018-01
TRYbeCA-1 – TRial of erYaspase in pancreatic Cancer

### COVID-19 Related Protocol Deviation Log

Completed by: |_____| Date:|_____|
(Name/Signature) (dd-MMM-yyyy)

| | |
|---|---|
| ***Visit (select one):**<br>☐Cycle: |_____/Day: |_____|<br>☐End of Treatment<br>☐Survival Follow-up |_____| (Week)<br>☐End of Trial<br>☐Unscheduled | **Select one:**<br>*☐**Specify assessment:** |_____| Or ☐ **All assessments at visit**<br>**Assessment source**<br>If visit or assessment performed at alternate location, please specify (Site/Clinic/Provider Name & Address): |
| **Date of Assessment** (if performed)<br>|_____|-|_____|-|_____|<br>(DD) (MMM) (YYYY)<br>**Deviation type**<br>☐Missed ☐Delayed | ***Reason visit and/or assessment missed or delayed (select one):**<br>☐Patient acquired COVID-19 ☐Investigative site closed due to COVID-19 ☐ Unable to obtain study treatment<br>☐Patient discretion due to COVID-19 ☐Travel restrictions due to COVID-19 ☐Site staff unavailable for study visits due to COVID-19 ☐ Other<br>**Other, specify and/or additional information:** |

Completed by: |_____| Date:|_____|
(Name/Signature) (dd-MMM-yyyy)

| | |
|---|---|
| ***Visit (select one):**<br>☐Cycle: |_____/Day: |_____|<br>☐End of Treatment<br>☐Survival Follow-up |_____| (Week)<br>☐End of Trial<br>☐Unscheduled | **Select one:**<br>*☐**Specify assessment:** |_____| Or ☐ **All assessments at visit**<br>**Assessment source**<br>If visit or assessment performed at alternate location, please specify (Site/Clinic/Provider Name & Address): |
| **Date of Assessment** (if performed)<br>|_____|-|_____|-|_____|<br>(DD) (MMM) (YYYY)<br>**Deviation Type**<br>☐Missed ☐Delayed | ***Reason visit and/or assessment missed or delayed (select one):**<br>☐Patient acquired COVID-19 ☐Investigative site closed due to COVID-19 ☐ Unable to obtain study treatment<br>☐Patient discretion due to COVID-19 ☐Travel restrictions due to COVID-19 ☐Site staff unavailable for study visits due to COVID-19 ☐ Other<br>**Other, specify and/or additional information:** |

***Response required**

Page |____| of |____| **Please complete in blue or black ink.** **V6.0 17Apr2020**