STATISTICAL ANALYSIS PLAN
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

Protocol Number: **(Version Date)**	GRASPANC 2018-01 05Sep2019 (Protocol Amendment version 1.0)
Name of Test Drug:	Eryaspase (L-Asparaginase Encapsulated in Red Blood Cells)
Phase:	3
Methodology:	Open-Label, Randomized Trial
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SIGNATURE PAGE

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
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Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:
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Date:_____

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Richard Kay, PhD
Statistician

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Date:_____

REVISION HISTORY

Date	Version number	Reason for change	Authored by
09Dec2020	1.0	Signed	Iman Elhariry David Bushnell
11Jan2021	1.1	Minor Clarifications	
07 Oct 2021	2	Removed mITT per client request. Clarifications on date conventions and endpoint definitions. Some patient history, safety and exposure analysis added. Specified the intention of releasing final topline results and final outputs Changed ATC for Concomitant medications from ATC level 3 to ATC level 2 Provided details on adverse event retrieval terms for events of special interest	David Bushnell
18 Oct 2021	2.1	Added Appendix 2 to clarify protocol deviations	Iman Elhariry

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ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ASNase	Asparaginase
ASN	Asparagine
AST	Aspartate aminotransferase
AT III	Antithrombin III
ATC	Anatomic Therapeutic Class
BP	Blood pressure
BMI	Body Mass Index
BOR	Best overall response
CA19-9	Cancer antigen 19-9
CBC	Complete blood count
CFB	Change from baseline
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
ctDNA	Circulating tumor DNA
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	European Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDR	Early discrepancy rate
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
FOLFIRI	FOLinic acid-Fluorouracil-IRInotecan regimen
FOLFIRINOX	FOLinic acid-Fluorouracil-IRInotecan-Oxaliplatin regimen
mFOLFOX6	Modified FOLinic acid-Fluorouracil-Oxaliplatin-6 regimen
5FU	5 Fluorouracil
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLN	Glutamine

HCL	Hydrochloride
HR	Hazard ratio
IAST	Irregular antibody screening test
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IR	Independent radiological review
ITT	Intent to Treat
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
KPS	Karnofsky Performance Status
LDH	Lactate dehydrogenase
LDR	Late discrepancy rate
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
NALIRI	NAnoliposomal irinotecan, folinic acid-fluorouracil-IRInotecan regimen
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-evaluable
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PAC	Pancreatic adenocarcinoma
PFS	Progression-free survival
PGx	Pharmacogenetics
PH	Proportional Hazards
PK	Pharmacokinetic
POP PK	Population pharmacokinetic
PP	Per Protocol
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PTT	Partial thromboplastin time
QoL	Quality of life
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors

RMST	Restricted mean survival time
RS	Raw score
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ class
SOE	Schedule of Events
SP	Safety population
TEAE	Treatment emergent adverse events
TLFs	Tables, listings and figures
TNM	Tumor, Node, Metastasis staging system
TRYbeCA	TRial of erYaspase in pancreatic CAncer
U	Units
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures and listings. It describes the planned analyses of the data collected during the study, including the safety and efficacy variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol, for the purpose of submission to the relevant authorities and for publication as appropriate. The results of all analyses in this SAP will be included in the Clinical Study Report (CSR).

This SAP is based on the following study documents:

- Protocol Amendment Version 1.0 dated 05SEP2019
- Electronic Case Report Form (eCRF) for the study.

The statistical analyses will be performed in accordance with International Conference on Harmonisation (ICH) E9 guidelines. This SAP conforms to the Cytel standard operating procedure STAT C002 Timing and Content of Statistical Analysis Plans using SAP template STAT C002 TP01 Version 2, dated 19FEB2016.

The SAP should be validated and signed before study database extract for interim analysis.

The CSR deliverables: (shells for tables, figures and listings) and further programming specifications are described in SAP documents “Table, Listings and Figures (TLFs) Shells” and “Programming Dataset Specifications”, respectively.

2. STUDY OBJECTIVES

The study objectives and corresponding endpoints as specified in the protocol are provided in Table 2-1.

Table 2-1 Study objectives

Objective	Endpoint	Analysis
Primary		Refer to section
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	OS in the Intent to Treat (ITT) population	Section 6.1

adenocarcinoma compared to chemotherapy alone		
Key Secondary		**Refer to Section**
To compare progression-free survival (PFS) between the 2 treatment arms	PFS based on local investigator's assessment using modified RECIST 1.1 – ITT population The declaration of PD will be based on the investigator assessment as per modified RECIST 1.1	Section 6.2
To compare the disease control rate (DCR) between the 2 treatment arms.	DCR – ITT population	Section 6.2.3
To compare the objective response rate (ORR) and duration of response (DoR) between the 2 treatment arms.	ORR and DoR- ITT population	Section 6.2.2
Other Secondary		
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 (QLQ-C30).	Patient reported outcome (PRO) – PRO population Change from baseline (CFB) in the global health status scale score of the EORTC QLQ-C30	Section 6.3.4
To determine the pharmacokinetics of eryaspase. To assess the immunogenicity of eryaspase: the induction of anti-asparaginase antibodies and neutralizing antibodies.	Summary statistics for PK: Asparaginase activity, asparagine and glutamine concentration, and individual PK parameters based on population PK model– PK population Anti-asparaginase antibody induction – PK population	Section 6.3.1
To evaluate the safety and tolerability of eryaspase in combination with	Type, frequency and severity of TEAE per CTCAE v5 – Safety population	Section 8

chemotherapy versus chemotherapy alone	Type, frequency and severity of laboratory toxicities per CTCAE v5 – Safety population	
To evaluate the relationship of clinical outcome with relevant biomarkers and genetic changes present in tumor tissues and blood and/or serum samples.	Separate document	NA
To investigate the predictive relationship between genetic variants in select candidate genes in the patient's somatic (blood) cell deoxyribonucleic acid (DNA) and their response to combination treatment in terms of safety and tolerability (pharmacogenetics [PGx]).	Separate document	NA

3. STUDY DESIGN

3.1. Overall Design

This is an open-label, multicenter, randomized Phase 3 study in patients with ductal 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, Figure 3-1:

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

- Arm B (control arm): gemcitabine/abraxane, or irinotecan-based therapy (FOLFIRI or Onivyde/5-fluorouracil/leucovorin).

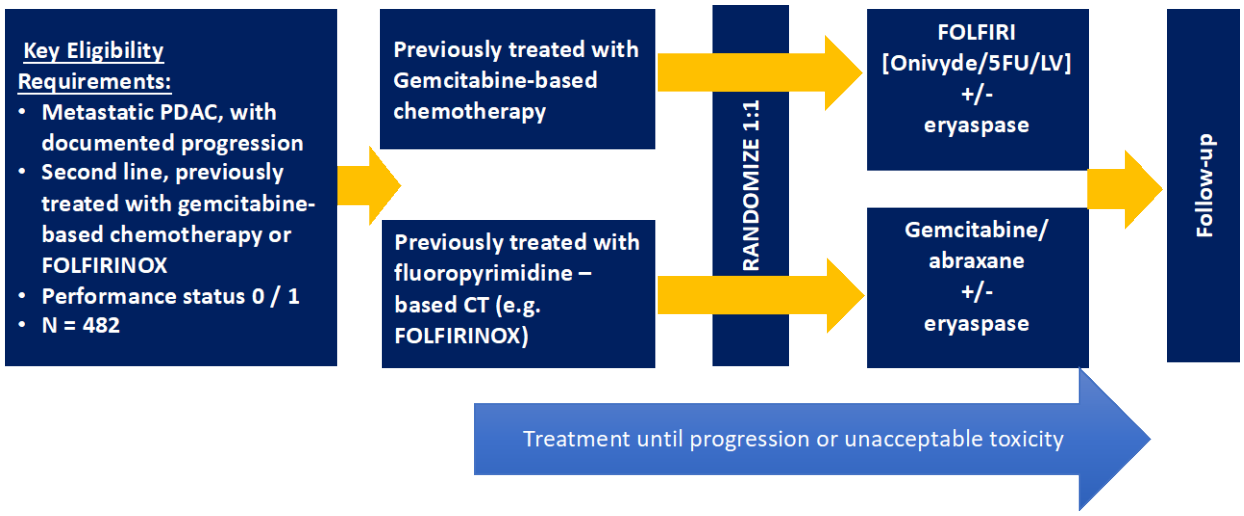


Figure 3-1 Study Schema

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 defined as 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 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.

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

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

Assessments and timing of data collection are detailed in the Schedule of Events in Table 3-1.

Clinical and laboratory parameters will be assessed in all patients to evaluate disease status and toxicity. Patients will have safety assessments (e.g. laboratory tests, physical exams, vital signs including temperature, heart rate, and blood pressure, electrocardiograms [ECGs as needed], 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 for at least 30 days (90 days in Amendment 1) after the last dose of study treatment or until start of a new anti-cancer treatment, whichever is sooner.

Tumor assessments utilizing computed tomography (CT)/magnetic resonance imaging (MRI) scans will be repeated every 8 weeks (±3 days), 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 should 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 objective disease progression. All radiological images must be collected in a de-identified manner, quality controlled, stored, and available for future review.

Survival information will be collected by phone, follow-up visit, or medical records review every 8 weeks (±3 days) from the last dose of study treatment 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.

Patient reported outcomes (PRO) using quality of life (QoL) assessment (EORTC QLQ-C30) will be performed on Day 1 of each cycle, 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.

Blood/plasma samples for pharmacokinetic (PK) and pharmacodynamic assessments will be collected at the following time points on Days 1 of Cycles 1 and 3 of study treatment: prior to eryaspase administration, at 5-10 minutes post-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 asparaginase (ASNase) and amino acids (asparagine (ASN) and glutamine (GLN)). The sparse PK data will be combined with previous data as part of a Population PK (POP PK) analysis.

Samples for assessment of anti-asparaginase 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.

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.

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.

3.2. Eligible Patients

Refer to study protocol for the inclusion/exclusion criteria.

3.3. Number of Sites and Patients

Approximately 100 study centers will participate in the study.

The target sample size is approximately 482 patients.

3.4. 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.

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 3-1.

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

3.6. Randomization Methodology

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. Patient will be randomized only once. Detailed instructions will be provided in the IWRS manual. APPENDIX 1 provides a brief summary of the randomization specifications.

Randomization will be stratified by the following 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).

If stratification factors are missing from the randomization form, they will be imputed either by derived baseline value (ECOG and time interval since diagnosis) or actual treatment (chemotherapy regimen).

3.7. Stopping Rules

An interim analysis for efficacy is planned to take place once 261 (67%) events have been observed. There will be no stopping rule for futility built in at the interim. The study could be stopped early for efficacy considerations.

3.8. 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.

Consequently, it is not possible to completely blind everyone at the Sponsor and the contract research organization (CRO)/vendors involved with the study with respect to treatment assignment. In addition, as eryaspase is an off-shelf investigational agent, the manufacturing team will need to have access to information about individual patients.

The operational, biostatistics and medical teams in Erytech, PPD (CRO) and Cytel will be blinded until the study is completed for the primary analysis.

A separate, unblinded biostatistics team working in a restricted server directory will provide data and tables/listings/figures (TLFs) to the IDMC.

3.9. Study Procedures

The schedule of event, as outlined in the study protocol, is provided in Table 3-1.

Table 3-1. 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	D8	D15	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[1]	X		X		X		X	X	
12-Lead ECG[2]	X		X						
Radiological assessments (CT or MRI)[3]	X		X (every 8 weeks [±3 days] from time of randomization until disease progression, or death)						
Randomization[4]		X							
QoL assessment (EORTC QLQ-C30)			X					X	X[5]
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)								
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									

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	D8	D15	D21	D28 End of Cycle Evaluation (or D1 subsequent cycle)		
Blood phenotype[6]	X[6]								
Prescription with current weight			X[7]		X[7]				
Irregular antibody screening test (IAST)			X[8]		X[8]				
IAST historical result if available	X								
Pre-eryaspase dose complete compatibility test			X[9]		X[9]				
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[10]	X[10,11]		X	X[16]	X	X[16]	X	X	
Pregnancy test, for patients of childbearing potential[12]	X		X					X	
Tumor tissue (for biomarker analysis, mandatory)	X								
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[17]		X[13]			X	
Pharmacokinetic (ASNase activity) and pharmacodynamic (amino acid) sample (eryaspase arm only)			X[14]		X[14]				

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	D8	D15	D21	D28 End of Cycle Evaluation (or D1 subsequent cycle)		
Immunogenicity sample for anti-ASNase antibodies and neutralizing antibodies (eryaspase arm only)			X[17]		X[13]			X	
Survival follow-up									X[15]
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. Per Eastern Cooperative Oncology Group (ECOG)/Karnofsky scales.
2. Performed during screening, pre-dose Cycle 2 Day 1 and then as clinically indicated.
3. Radiological assessment to be completed within 3 weeks of randomization and then every 8 weeks (±3 days) from time of randomization until disease progression 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.
4. Randomization performed via interactive web response system (IWRS) within 3 days of 1st chemotherapy dose.
5. During follow-up, questionnaire is to be completed every 8 weeks.
6. A complete RBC phenotype (including D, C, E, c, e, and K antigens), 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.
7. 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.

8. 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.
9. In case of incompatibility, collection of an additional blood sample will be required for further investigation.
10. 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 – international normalized ratio (INR), Partial thromboplastin time, fibrinogen, antithrombin III.
    Tumor marker: CA19-9
11. Baseline labs to be collected within 14 days of randomization.
12. 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.
13. Pre-dose Day 15 sample to be collected only during Cycle 1.
14. 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.
15. Survival follow to be conducted by phone, visit, or medical records review every 8 weeks (±3 days) from last treatment visit until patient's death, loss to follow up, or study closure. Subsequent therapy should be collected during this follow-up.
16. 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.
17. 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.

4. GENERAL STATISTICAL CONSIDERATIONS AND DATA HANDLING

4.1. Sample Size Determination

The primary objective of this study is to compare eryaspase in combination with chemotherapy versus chemotherapy alone in terms of OS. 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 a Phase 2 study for eryaspase was HR=0.60 (95% CI: 0.41 to 0.87) [1], and 0.725 represents a conservative estimate based on these data that is viewed as being clinically relevant. This translates to an approximate 2.28 months increase from an assumed median overall survival of 6 months in the control arm. The choice of 6 months in the control arm is based on reported OS in Napoli-1 study [2], and the average OS improvement (2.3-10.2 months) in several randomized trials in second line setting [3].

The interim analysis for efficacy will take place once 261 (67%) events have been observed. As of October 2021, the interim analysis for efficacy was conducted on 04 Feb 2021. The IDMC recommended that the study would continue to completion. The Sponsor continues to be blinded to any aggregate tables and figures.

Assuming a recruitment period of 26 months, a median overall survival in the control group of 6 months, a 10% drop-out rate, and a minimum follow-up of 9 months, the study size will be based on the recruitment of approximately 482 patients. Database lock was planned for 30 Jun 2021 having observed the required number of events. Based on the time taken to clean the database this date was pushed back to 30 Aug 2021 and at this time the number of events was 420. The final analyses will be based on this number of events in order to maximize the power to detect treatment differences.

4.2. General Methods

The primary statistical analyses will be performed using cleaned eCRF data obtained until a clinical cut-off date, which will be determined based on the reaching the pre-defined number of events. A further analysis will be undertaken once all patients have completed the study.

All outputs will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic, PRO and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Time to event data will be summarized using Kaplan-Meier

methodology: median time-to-event, survival rates and rate differences between treatment at specified timepoints, and restricted mean survival time, all presented with associated 2-sided 95% confidence intervals. Event types and censoring reasons will be summarized.

All tumor measurement-related variables (PFS, ORR, DCR) will be based on both Investigator assessment and independent radiological reviews (IR).

All efficacy analyses will use the intent-to-treat (ITT) principle (analysis of data by the groups to which patients were randomized). Safety analyses will be based on the actual treatment received.

All statistical testing will be undertaken based on a one-sided 2.5% significance level (or equivalently a two-sided 5% significance level) subject to adjustments for interim. Summary statistics will be presented, as well as confidence intervals (CIs) which will be provided at a 2-sided 95% level, unless otherwise stated.

4.3. General Date Conventions

The general data handling conventions used in the derivation of variables used in data summaries and analysis are summarized in Table 4-1.

Table 4-1 General data handling conventions

Term	Definition/Rule
Date of diagnosis of pancreatic cancer	Date of initial pathological or radiological diagnosis. If both are available, then the date of pathological diagnosis will be used.
Date of first administration of study treatment	This is derived as the first date when a non-zero dose of any component of study treatment is administered. The first date of first administration is also referred as the start date of study treatment.
Date of last administration of study treatment	This is derived as the last date when a non-zero dose of any component of study treatment is administered.
Study Day	Study Day describes the day of the event or the assessment date, relative to the reference start date, which is either the randomization date or the start date of study treatment The reference start date is designated as the Study Day 1. Day-1 is the day that precedes Day 1. The study day will be calculated as follows: - If the event is on or after the reference start date, then: the date of the event = (Visit date, onset date of an event, assessment date, etc.) – reference start date + 1).

	- If the event precedes the reference start date, then: the date of the event = (Visit date, onset date of an event, assessment date, etc.) – reference start date). The reference start date for ***all safety assessments***, QoL assessment (EORTC QLQ-C30) and PK data will be the start date of study treatment. The reference start date for ***all efficacy assessments*** (tumor assessment, death, ECOG,) will be the randomization date. The reference start date for ***any non-safety screening assessment or events*** (baseline characteristics, medical history, cancer history, etc) will be the randomization date.
Cycle	Start date: Date of first study drug dose at each cycle. End date: The day before the start date of the following cycle. For the last cycle, the end date will be the start date of the cycle + planned cycle length (4 weeks), or the death, or discontinuation date, whichever is earlier.
Weeks	Study days divided by 7 and rounding to one decimal place.
Months	Study days divided by 30.4375 days and rounding to one decimal place.
Years	Study days divided by 365.25 days and rounding to one decimal place.
Baseline	Baseline is defined as the period from the date of signing any informed consent document to the date of randomization or the start date of study treatment. For efficacy assessments (tumor assessment, death, ECOG), the latest non-missing value generated on or before the date of randomization will be used as the baseline value/assessment. For safety assessments (including QoL assessment (EORTC QLQ-C30)), the last available assessment on or before the start date of study treatment (likely Cycle 1 Day 1) is considered as the "baseline" value or assessment. In the case of patients who are randomized but not yet treated, randomization date will be used to select baseline

	value/assessment; for demographic or baseline data summarized by ITT or PP population. If a patient has 2 "baseline" ECOG (or PRO) values at the same date, then the worst ECOG PS value will be taken as the "baseline". Assessments specified to be collected post-dose on the first date of treatment are not considered as baseline values. If patients have no value as defined above then the baseline value will be missing.
Post-baseline	Any non-missing measurement after the first dose of study drug.
Time to Event (i.e., PFS or OS)	(date of the event) – (randomization date) + 1
Age	(date of informed consent – date of birth)/365.25 rounded down In case of partial birth date, impute missing day as 15th of the month; impute the missing month as June 30th; if year is missing, set age as missing.
Total duration of treatment (weeks)	(date of last dose) – (date of first dose) + 1) /7
Last contact date	Derived for patients not known to have died at the analysis cut-off date, defined as the latest complete date from the following list, or the last contact date, whichever comes first: - Assessments dates (e.g. laboratory, vital signs, ECOG, PRO, ECG, tumor scans, PK, etc) - Medication and procedures dates (e.g. concomitant medications, medical or surgical procedures, new anticancer therapy) - Adverse events start and end dates - "last date patient alive" in the "survival" eCRF page - Study treatment start/end date - Randomization date The cut-off date will not be used for the last contact date, unless the patient is contacted on that date. Further, completely imputed dates (eg the analysis cut-off date imputed by the SAS program to replace the missing end date) will not be used to derive the last contact date.

4.4. Computing Environment

All statistical analyses will be performed using Statistical Analysis Systems (SAS®) release 9.4 or higher, unless indicated otherwise.

Medical History and adverse events will be coding using MedDRA version 21.0. The intensity of AEs will be graded according to the NCI-CTCAE (version 5.0).

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary, version B3 June 2018. The dictionaries will remain static throughout the life of the project. However, an update to the most recent version will be performed before final database lock.

4.5. Methods of Pooling Data

Not applicable to the present study.

4.6. Efficacy, PK, Pharmacodynamic and Safety Variables

4.6.1. Efficacy Variables

4.6.1.1. Primary efficacy variable

The primary endpoint is Overall Survival (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 prior to data cut-off will be censored at the date of last contact or the date of data cutoff, whichever is earlier.

4.6.1.2. Secondary efficacy variables

Secondary efficacy variables include:

- Progression-free Survival (PFS) is defined as the time interval from randomization to first disease progression (PD) per modified RECIST 1.1 based on the investigator review or death from any cause in the absence of PD, whichever occurs first.
- The Objective Response Rate (ORR) is the proportion of patients who achieve tumor response (CR or PR) per modified RECIST 1.1.
- Duration of Response (DoR) is defined as the time from first response of CR or PR until disease progression, as determined by modified RECIST 1.1.
- Disease Control Rate (DCR) is defined as the proportion of patients who have CR, PR, or SD as determined by modified RECIST 1.1 criteria.
- Emergence of new metastatic lesions, defined as the proportion of patients with radiological progression that included new metastatic lesions will be presented.

- Patient reported outcomes (PRO) using QoL endpoints include variables from various scales from the standardized instrument, EORTC QLQ-C30, at the following time points.

4.6.2. PK, Pharmacodynamic and Immunogenicity Variables

Eryaspase pharmacokinetics will be evaluated using sparse sampling. Whole blood 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 asparaginase activity (U/L)
- Plasma asparaginase activity (U/L)
- Plasma concentrations of asparagine (µmol/L)
- Plasma concentrations of glutamine (µmol/L)

Immunogenicity variables include the presence of anti-asparaginase antibodies and neutralizing antibodies over time.

4.6.3. Safety Variables

Safety assessments performed during the study included measurement of vital signs, physical examination, ECOG performance status, clinical laboratory evaluations including standard blood chemistry, hematology, coagulation, and serum electrolytes, and monitoring of AEs.

4.6.4. Other Variables

This study will collect samples for biomarker assessments in all patients. Sample types include tumor tissue samples (archival or fresh), whole blood samples for pharmacogenetics and plasma samples for circulating tumor DNA (ctDNA). All biomarker analyses will be performed at central laboratories.

4.7. Analysis Populations

The primary population for analysis is the ITT population. All primary and secondary analyses will be repeated on the PP population and this will serve as sensitivity analysis.

Intent to treat population (ITT):

All patients randomized to study treatment (eryaspase, gemcitabine, abraxane, irinotecan and 5FU). According to the ITT principle, patients will be analyzed according to the treatment and

strata they have been assigned to during the randomization procedure. The ITT population will be the primary population for the efficacy analyses.

Safety population (SP):

All randomized patients who receive at least one dose of study drug(s). Patients will be analyzed according to the actual study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment, or the first treatment received if the randomized treatment was never received.

Per Protocol population (PP):

The PP population is a subset of the ITT population consisting of patients who are sufficiently compliant with the protocol, with no protocol deviations that could confound the interpretation of the primary analysis conducted on the ITT population. Patients included in the PP population should meet the following criteria:

- Received at least one dose of study drug to which they were randomized
- No major protocol deviation in inclusion/exclusion criteria

Patient inclusion in the PP population and the reasons for exclusion will be summarized. The reasons for exclusion will be determined during the data review meeting and documented prior to the performance of the primary OS analysis.

Pharmacokinetic analysis population

The pharmacokinetic analysis set will include all randomized patients who received at least one dose of eryaspase and who have at least one post-baseline PK assessment. Patients will be evaluated by the treatment actually received.

PRO analysis Population

The PRO population will consist of all patients who receive at least one dose of the study treatment and provide answers to at least some items of the EORTC QLQ-C30 at Cycle 1 Day 1 (i.e, baseline) and a time point after the date of first dose of study treatment.

4.8. Adjustment for Covariates

Primary and secondary efficacy analyses include stratification factors (as defined by the IWRS) as covariates, together with gender and time since first diagnosis of pancreatic cancer to randomization as detailed below:

- 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]).
- Time interval since initial diagnosis of advanced disease to date of randomization in the study (<6 months or ≥6 months).
- Gender.
- Time since first diagnosis of pancreatic cancer to randomization ((<12 months or ≥12 months).

4.9. Multiple Comparisons/Multiplicity

All statistical testing will be undertaken based on a one-sided 2.5% significance level (or equivalently a two-sided 5% significance level) subject to adjustments for interim.

Confirmatory testing for the primary and secondary efficacy endpoints will be performed hierarchically (OS followed by PFS followed by DCR followed by ORR (investigator assessment)) 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.

4.10. Subgroup Analyses

OS and PFS hazard ratios will be calculated for the following subgroups of patients and displayed in Forest Plots. In each case hazard ratios will be obtained from the Cox proportional hazards regression model including the stratification factors as covariates. For subgroups associated with those stratification factors the model will not include that factor.

- Gender (Male, Female).
- Age Group (< 65 years, >= 65 years).
- Chemotherapy regimen (gemcitabine plus abraxane, irinotecan-based therapy FOLFIRI or onivyde, 5-FU, and leucovorin).
- Eastern Cooperative Oncology Group (ECOG) performance status (0, >=1).
- Time since diagnosis of advanced disease to date of randomization in the study (<6 months or ≥6 months).
- Time since first diagnosis of pancreatic cancer to date of randomization in the study : (<12 months or ≥12 months).
- Geographical region (US or EU), which will be determined by the IWRS system based on site number.
- Stage at study entry: III and IV.
- CA19-9 at baseline (normal or elevated; < median nadir or >= median nadir).
- Prior systemic adjuvant/neoadjuvant therapies: (Yes or No).
- Prior systemic therapy (1 or 2 or 3).
- Response to prior therapy in advanced setting: (CR+ PR+SD), progressive disease (PD).

- Hepatic metastasis (Yes/No).

4.11. Withdrawals, Dropouts, and Loss to Follow-up

Randomized patients who discontinue the study early for any reason will not be replaced and are not permitted to re-enter the study. Best efforts will be made to follow these patients for survival.

4.12. Missing, Unused, and Spurious Data

4.12.1. Missing dates for study drug administration

When using dates from drug administration pages for the purposes of deriving treatment exposure, the following conventions will apply:

- If the start date is missing, the date of randomization will be used to replace all first administration missing dates.
- If the last administration date is missing, the date will be imputed with the date taken from one of the following eCRF pages, whichever is earlier:
    - The "Status of the Patient at the End of the Treatment" eCRF page.
    - Last known administration date
    - Last contact date for alive patients
    - Date of death for dead patients

4.12.2. Missing dates for adverse events

For missing or partial missing onset dates for adverse events, the following conventions will apply:

- If the start date of an event is completely missing, then the event is assumed to be treatment-emergent (TE). Treatment-emergent adverse event (TEAE) is an event that started on or after the first dose of study medication or that worsened after the first dose of study medication and with an onset date occurring during the treatment period.
- If the start date has the month and year but day is missing, the event will be considered treatment-emergent if the month and year of the start date of the event are equal to, or greater than, the month and year of the date of first dose of study drug.
- If the start date has the year, but day and month are missing, the event will be considered treatment-emergent if the year of the start date of the event is to the same as, or later than, the year of the date of the first dose of study drug.

- If the stop date is not missing, and the imputed start date is after the stop date, the imputed start date is equal to the stop date. If the imputed stop date is before the start date, the imputed stop date is equal to the start date.

4.12.3. Missing dates for other variables

When deriving all other variables that use dates, for dates that include missing values, the following conventions will be used.

Value	Imputation
Missing day, month, and year	Not imputed
Missing day and month	Day imputed to June 30th
Missing day	Day imputed to the 15th

If the stop date is not missing, and the imputed start date is after the stop date, the imputed start date is equal to the stop date. If the imputed stop date is before the start date, the imputed stop date is equal to the start date.

4.13. Visit Windows

Specific visit windows will not be applied to this study given the variable number of courses each patient could have received. Screening assessments were to be completed within 3 weeks prior to randomization.

Disease evaluations per modified RECIST 1.1 criteria will be taken every 8 weeks until disease progression, calculated from the randomization date. Survival follow-up would be conducted every 8 weeks from the last study assessment visit until the patient died, is lost to follow up, or the study closed.

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.

4.14. Protocol Deviations

Protocol deviations will be identified by site monitors, the medical monitors and by the checks of the clinical database. Important deviations will be summarized for each treatment arm by the type of deviation. All protocol deviations will be listed. Major protocol deviations related to inclusion and exclusion criteria result in removal of a patient from the Per Protocol population, APPENDIX 2.

Major protocol deviations will be defined as departure from the approved protocol that may impact the rights, safety of the patients or the integrity of the data. The sponsor, or designee, will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file or using the RAVE output), in collaboration with Cytel; this file will include a description of the protocol deviation.

Data from patients who were randomized to one treatment and received the other treatment will be provided in a separate listing.

5. PATIENT DISPOSITION AND BASELINE DATA SUMMARIES

5.1. Patient Disposition

Patients who give informed written consent but are not randomized are considered screen failures. Minimal data, such as demographic information and the reason for screen failure, for patients who fail screening will be recorded in the case report forms (CRFs).

A tabulation of patient disposition will be provided, including the number of screen failures, the number of patients enrolled, number of patients in each chemotherapy subgroup, the number in each subset, population for analysis, and the primary reasons for withdrawal from treatment and study. Disposition will also be summarized by study site. Reasons for screen failure will also be summarized.

A CONSORT diagram showing the flow of the participants through each stage of the study will be provided APPENDIX 3. A complete accounting of all patients participating in the study will be provided in overall summary table(s). This will include the final disposition of all study patients including the number of:

- Total number of patients assessed for eligibility.
- Number of patients excluded (screen failures), reasons for exclusion.
- Number of patients provided written consent and randomized and are included in the efficacy analyses.
- Number patients randomized to each treatment group: gemcitabine/abraxane, Gemcitabine/abraxane/eryaspase, NALIRI/FOLFIRI, and NALIRI/FOLFIRI/eryaspase.
- Number of patients receiving at least 1 dose of study drug by treatment group and included in the safety analyses.
- Discontinuation from study treatment by primary reason.
- Discontinuation from study participation by primary reason.

Distribution of patients by investigator with respect to the number of patients enrolled by treatment group and overall will be presented.

A by-patient listing of study completion information, including the reason for premature treatment and study discontinuation, if applicable, will be presented.

5.2. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be listed and summarized by treatment group and overall in each of the ITT and PP populations.

Summaries will also be generated by treatment subsets in each arm (Gemcitabine/Abraxane, Irinotecan-based).

5.2.1. Demographic Data

Summary statistics (mean, median, standard deviation, minimum, maximum) will be presented for the continuous variables.

- Age (years).
- Age distribution.
  - Number (and %) of patients according to age in categories (<65 years; ≥65 years).
- Race:
  - White (Caucasian/European Heritage, Arabic/North African Heritage).
  - African American.
  - Asian (Japanese or Japanese Descent).
  - Asian (Others).
  - American Indian or Alaska Native.
  - Native Hawaiian or Other Pacific Islander.
  - Others
- Gender: (Male/Female). Number (and %) of patients.
- Geographic region: Europe, USA.
- Physical Examination at Baseline: Frequency table of patients with at least one abnormal finding.

Blood group, Rhesus system, Phenotype and Irregular Antibody will be summarized by treatment group an listed by patient.

5.2.2. Characteristics of Pancreatic Cancer

Disease history for each patient will be summarized from the "Pancreatic Cancer History" eCRF page and the "Best Response Outcome" eCRF page.

Summary statistics will be displayed by treatment group and overall.

- Stage at Initial Diagnosis (I, II, III, IV, unknown).
- Time from initial diagnosis to randomization in months (date of randomization – date of initial diagnosis +1)/30.4375).

- Stage at study entry (III, IV).
- Time from diagnosis of advanced diagnosis to randomization in months (date of randomization – date of diagnosis of advanced (stage III or IV) disease +1)/30.4375).
- ECOG Performance status: 0, 1, unknown (**NOTE**: ECOG PS should be based on reported status in eCRF at baseline.)
- Number of prior systemic cancer therapies.
- Sites of Metastasis (liver, lung, brain, peritoneal, others, unknown).
- Number of metastatic sites (<3, >=3).
- CA19-9 at baseline (normal vs. elevated), (< median, >= median).

In addition, a separate table and associated listing will present the distribution of the 3 stratification factors (in combination and according to the IWRS system) by treatment groups.

5.2.3. Prior Cancer Therapy

Cancer therapy will be summarized using data recorded in the "Prior Pancreatic Cancer Treatments, Prior Systemic Anti-cancer therapy, Prior Radiotherapy Treatment and Prior surgical treatment for pancreatic cancer" eCRF pages. Summary statistics will be displayed by treatment group and overall. This will include:

- Prior surgery.
- Prior radiotherapy.
- Prior neoadjuvant therapy; and best response to prior neoadjuvant therapy (CR, + PR, SD, PD, unknown).
- Prior adjuvant therapy.
- Prior systemic therapy for advanced disease:
    - Gemcitabine + Abraxane – based chemotherapy
    - FOLFIRINOX and variants
    - Fluoropyrimidine-based, eg FOLFOX
    - Others
- Best objective response to first-line therapy for advanced therapy (CR + PR, SD, PD, unknown).

5.3. Medical and Surgical History

Other medical history, both previous and current conditions, will be summarized by treatment group in the ITT population. Using data from the "Relevant Medical or Surgical History or Current Medical Conditions other than Pancreatic Cancer" eCRF pages. Medical history is coded with MedDRA. Medical history will be displayed in terms of frequency tables: ordered by primary system organ class (SOC) and preferred term (PT) in decreasing frequency order:

- A table with the number of patients having at least one previous medical history will be displayed by treatment group and overall. Previous conditions are medical history that stopped prior to the screening date.
- The same table will be constructed for the number of patients having at least one ongoing medical history. Ongoing conditions are medical history still present at the first infusion date of any of eryaspase or chemotherapy.
- A table with the number of patients having at least one previous cancer history by intervals of time since initial diagnosis of pancreatic cancer.

Medical history will be listed by treatment group and patient number.

In case of a partial or missing end date, medical history will be assumed to be ongoing except if the partial date indicates that the condition stopped prior to the selection visit.

6. STATISTICAL ANALYSIS

6.1. Analysis of Primary Efficacy Endpoint

The primary endpoint is OS which is measured from the date of randomization to the date of death from any cause.

OS (months) = (earliest date of death or censoring – date of randomization + 1)/30.4375

Patients who are not known to have died prior to data cut-off will be censored at the date of last contact or clinical cut-off, whichever comes first. The last contact date will be derived as the latest available date among those detailed in Table 6-1.

Table 6-1 Rules for the last contact date for OS analysis

Source Data	Conditions
Date of randomization	No condition
Last contact date/last date patient known to be alive from Long-Term Follow-Up eCRF	• Use if patient status is reported to be alive • Do not use if patient status is reported unknown
Start/end dates of new anticancer therapy	Non missing chemotherapy term
Start/end dates from drug administration eCRF	Non missing dose.
End of treatment date from the End of Treatment eCRF	No condition

Tumor assessment (RECIST v1.1) date	Evaluation is marked as done.
Laboratory/PK collection dates	Sample collection marked as done.
Vital signs date	At least 1 non missing parameter value
ECOG performance status date	Non missing ECOG performance status
Start/end dates of adverse events	Non missing verbatim term
Physical examination	At least 1 non missing parameter value

For the primary analysis, OS will be summarized by treatment group for the ITT population. Summaries will include the number of patients who had an event during the study, the number of patients who didn't have an event during the study (censored), with the date of censoring equal to the date that the patient was last known to be event-free.

Median time-to-event will be estimated from a Kaplan-Meier analysis, with associated survival curves produced. The p-value for this analysis will be provided from the stratified log-rank test, with stratification factors as used in the randomization. Kaplan-Meir estimates will be given at 6, 8 and 10 months along with the difference in those OS rates at each timepoint. The hazard ratio, its associated 95% CI and p-value will be estimated from a Cox proportional hazards model, including the stratification factors (according to IWRS) as covariates.

Forest plots of the OS hazard ratios and the associated 95% CIs in subgroups will be constructed using the Cox PH model adjusting for the stratification factors as detailed in Section 4.9 (except where the subgroups are defined by a stratification factor, in which case that factor will be excluded) and the other two factors listen in Section 4.7.

6.1.1. Supportive and sensitivity analyses for OS

- A Cox PH model as for the primary analysis for OS but with stratification factors determined according to the baseline characteristics. In addition to the on ITT population, this analysis is repeated for actual treatment assignments (Safety population).
- A Cox PH model will also be performed separately for each stratification factor, Gender and Time since first diagnosis of pancreatic cancer to randomization.
- PP population.
- Restricted mean survival time (RMST) may be computed using the area under the curve from baseline to 6, 12 and 18 months. RMST will be calculated for each treatment arm and the difference with its 95% CI will be displayed.
- Sensitivity analyses to address different censoring rules:
    a) Explore the potential impact of the following
        - Censored at the date of subsequent anticancer therapy

b) Lost to follow-up

- The impact of loss to follow-up on OS will be assessed on the number of patients who are lost to follow-up. If >5% of patients are lost for follow-up for OS in either treatment arm, a sensitivity analysis will be performed for the comparisons between the 2 treatment arms in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

6.1.2. Planned Interim Analyses for Overall Survival

This study will have an event-driven interim analysis for OS, based on O'Brien-Fleming boundaries and the Lan-DeMets alpha-spending function. The interim analysis for OS is planned to take place following 261 deaths.

An independent statistical group will conduct the interim analysis and assist the IDMC in rendering decisions on whether to recommend stopping the trial for efficacy or continuing the study as planned. For the OS interim analysis, if the one-sided p-value from the stratified log-rank test is less than the corresponding significance level, then the study could be stopped for early success on OS, based on the IDMC recommendation. The actual significance levels will be determined based on the exact number of deaths at the time of the interim analysis.

The key secondary endpoints may not be provided to the IDMC at the time of the interim analysis. The primary reason for this is due to the COVID-19 impact. Full data cleaning is increasingly delayed due to travel and sites visit restrictions. Therefore, to avoid undue delay of the interim analysis plan, the IDMC recognizes that these key secondary endpoints will not be available. This will only be performed once those data are fully cleaned and if OS in the ITT analysis set has achieved statistical significance.

6.2. Final Analysis and Topline Results

The final analysis will be conducted following the database lock. Data will be restricted by a cutoff date as close as possible to the date of planned database lock and determined by data cleaning logistics.

Topline results will be generated ahead of full TLFs immediately following database lock. Additional analyses and tables may also be generated in support of topline results, APPENDIX 4

Analyses outside of those listed will be generated subsequently and the sponsor will remain blinded to these analyses and associated endpoints until the requisite tables, figures and listings have been generated.

6.3. Analysis of Secondary Efficacy Endpoints

The key secondary endpoints for this study are the PFS, DCR and ORR. The key secondary endpoints will be evaluated for confirmatory conclusions in this order only if the primary endpoint OS is statistically significant (one-sided $p<0.025$).

6.3.1. Analysis of Progression-Free Survival (PFS)

PFS is defined as the interval time from the date of randomization until objective disease progression per modified RECIST 1.1, or death from any cause in the absence of disease progression, whichever occurs first.

PFS = (earliest date of documented disease progression, death or censoring) – date of randomization) +1

PFS will be compared between the two treatment arms using the same methods of analysis as for OS. In addition, the proportions of patients with PFS events (Total and split by radiological disease progression and death events) and censored PFS events (Total and reasons; no baseline tumor assessment, no progression, treatment discontinuation, new anticancer therapy, missed scans, data cutoff) will be summarized by treatment arm, Table 6-2.

Forest plots of the PFS hazard ratios for the subgroups detailed in Section 4.9 will also be produced for the ITT population. The primary analysis of PFS is based on the investigator's evaluation.

6.3.1.1. Definitions for PFS analysis

The following conventions will be used for the PFS analysis

Definition of progression date: Progression Date is assigned to the first time at which progression can be declared; this will coincide with dates of radiological assessments. If multiple radiological assessments based on the sum of target lesion measurements are done at different times, the progression date is the *earliest* date of the first observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements, or appearance of new lesion.

For sensitivity analysis, the progression date is defined as the date of the protocol-scheduled clinic visit immediately after all radiological assessments (which collectively document progression) have been done.

Definition of adequate tumor assessment.

An adequate tumor assessment includes adequacy of target lesion assessments and adequacy of radiological tests both to evaluate non-target lesions and to search for new lesions.

Partially missing tumor data.

Unless disease progression is evident, partially missing tumor data or indeterminate lesions for a particular tumor assessment will result in an overall response of "unknown" or "not evaluable" and the tumor assessment will not be deemed adequate. If progression is assessed in the subsequent visits, data from partially missing assessments will be ignored.

Completely missing tumor data.

There are several permutations in this situation:

- completely missing adequate tumor assessments followed by death or by assessment visits showing progression.
    - If only a single missing assessment → The assessment will be ignored; use the subsequent assessment (or visit)
    - If 2 or more consequent assessments missed → use the last adequate assessment
- completely missing adequate tumor assessments followed by subsequent assessment shows no progression. → ignore the missing assessment

6.3.1.2. Censoring rules for the primary PFS analysis

Table 6-2 provides the general primary rules for calculating PFS and censoring rules, in line with FDA guidance[4]. If a patient meets the criteria for more than one censoring rule, PFS will be censored at the earliest censoring date.

Table 6-2 Primary PFS analyses and censoring rules.

Situation	Date of Progression or Censoring	Outcome
Documented progression per modified RECIST 1.1	Earliest date on which radiological progression is documented	Progressed
Incomplete or no baseline tumor assessment Change in imaging modality	Randomization date	Censored
Progression documented between scheduled visits (unscheduled scan)*	Earliest** of: ▪ Date of progression assessment showing new lesion; or ▪ Date of last adequate progression assessment	Progressed
No progression	Date of last adequate assessment with no documented progression	Censored
Treatment discontinuation for clinical progression (undocumented progression)	Date of last adequate assessment with no documented[#] progression	Censored
Treatment discontinuation for toxicity or other reasons (eg, withdrawal of consent)	Date of last adequate[$] assessment with no documented progression	Censored
New anticancer treatment started with no claim of adequate progression assessment	Date of last adequate assessment with no documented progression before start of new treatment	Censored
Death before first radiological assessment	Date of death	Progressed
Death between adequate progression assessment visits, or after patient missed one assessment visit	Date of death	Progressed

Death or progression after more than one missed consecutive scans	Date of last adequate assessment with no documented progression	Censored
Death after 8 weeks of treatment discontinuation due to any reason without starting a new anticancer treatment	Date of last adequate assessment with no documented progression	Censored
No progression at the time of final analysis	Date of last adequate assessment with no documented progression	Censored

*An unscheduled scan is defined as a radiological assessment earlier or later than every 8 weeks (+/- 7 days).

** Progression date assigned to the first time at which progression can be declared: For progression based on a new lesion, the Progression Date is the date of the first observation that the new lesion was detected. If multiple assessments based on the sum of target lesion measurements are done at different times, the Progression Date is the date of the first observation or radiological assessment of target lesions that shows a predefined increase in the sum of the target lesion measurements.

documented: evidence of disease progression per modified RECIST 1.1.

$ adequate: progression assessment should be based on appropriate radiological assessments as described in the protocol and schedule of events.

6.3.1.3. Supportive and sensitivity analyses for PFS

These include the following:

- A Cox PH model as for the primary analysis for PFS but with the stratification factors determined according to the baseline characteristics.
- PP population.
- Sensitivity analysis in relation to the investigator declaration of progression based on different definition of progression events and censoring rules, Table 6-3. These analyses will be performed for the ITT population, using the same statistical methods as the primary analysis.
- Sensitivity analyses in relation to the IR based on the original (Table 6-2) and on the different definition of progression events and censoring rules (Table 6-5). These analyses will be performed for the ITT population, using the same statistical methods as the primary analysis.
- Discordance between IR and investigator's assessment using 2 measures, the early discrepancy rate (EDR) and the late discrepancy rate (LDR)[5,6].

6.3.1.3.1. Censoring rules will be used for sensitivity PFS analysis

In the primary PFS analysis, censoring is based on the last adequate tumor assessment, Table 6-2. In case of the sensitivity analysis in relation to progression declared by the investigator, the following situations will be considered progression events, and the progression date will be the patient visit date:

a. Clinical progression
b. Starting new anticancer therapy
c. General deterioration of health and/or performance status

The impact of clinical deterioration, study drug discontinuation, and new anti-cancer therapy sensitivity analyses will be performed as described in Table 6-3.

Table 6-3 Sensitivity PFS analyses and censoring rules

Situation	Date of Progression or Censoring	Outcome
Progression per modified RECIST 1.1	Earliest date on which radiological progression is documented	Progressed
Incomplete or no baseline tumor assessment	Randomization date	Censored
Progression documented between scheduled visits (unscheduled scan)*	Next scheduled visit*	Progressed
No progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for clinical progression (undocumented progression)	Date of discontinuation	Progressed
Treatment discontinuation for toxicity or other reasons (eg, withdrawal of consent)	Date of discontinuation	Progressed
New anticancer treatment started with no claim of adequate progression assessment	Date of start of new anticancer treatment	Progressed
Death before first radiological assessment	Date of death	Progressed
Death between adequate progression assessment visits, or after patient missed one assessment visit	Date of death	Progressed
Death or progression after more than one missed consecutive scans	Date of first missed visit	Progressed
Death after 8 weeks of treatment discontinuation due to any reason without starting a new anticancer treatment	Date of death	Progressed
No progression at the time of final analysis or patient discontinued from the study for any reason other than progression (no survival follow-up)	Date of last visit with adequate assessment with no documented progression	Censored

* this is the date of the protocol-scheduled clinic visit immediately after all radiological assessments (which collectively document progression, or no progression) has been done.

6.3.1.3.2. Independent radiological review (IR)

Analysis of PFS will be performed independent radiological review (IR) per modified RECIST 1.1. The censoring rules in Table 6-2 and Table 6-3will also apply for the IR.

A summary of the concordance between the investigator assessment and the independent radiological evaluation of disease progression will also be provided in Table 6-4.

Table 6-4 Evaluation of the discordance rate between the investigator and the independent review on assessing PFS data

	Independent radiological review	
Investigator assessment	Disease progression	No disease progression
Disease progression	A=A1+A2+A3	B
No disease progression	C	D

A1; number of patients when there is an agreement on timing and occurrence of disease progression
A2; number of patients when investigator declares disease progression later than independent review
A3; number of patients when investigator declares disease progression earlier than independent review
B: number of patients, whose disease declared disease progression by the investigator but not by the independent review
C; number of patients, whose disease declared disease progression by the independent review but not by the investigator

D: number of patients without disease progression as determined by the investigator and the independent review

The early discrepancy rate (EDR) is defined as:

$$EDR = (B + A3) / (A + B)$$

The EDR represents the positive predictive value of investigator assessment and quantifies the frequency with which the investigator declares progression early relative to IR within each arm as a proportion of the total number of investigator's assessed progressions.

The late discrepancy rate (LDR) is defined as:

$$LDR = (C + A2) / (B + C + A2 + A3)$$

The LDR quantifies the frequency that investigator declares progression later than IR as a proportion of the total number of discrepancies within the arm. If the distribution of discrepancies is similar between the arms, then this suggests the absence of evaluation bias favoring a particular arm.

The EDR and LDR can be calculated for each treatment arm and the differential discordance around each measure can be defined as the rate on the experimental arm minus the rate on the control arm [5,6]. A negative differential discordance for the EDR and/or positive differential discordance for the LDR are suggestive of a bias in the investigator favoring the eryaspase arm.

Table 6-5 summarizes all rules and outcomes for both investigator and independent radiological review with censoring rules.

Table 6-5 Summary of all censoring rules for primary and supportive analyses

	PFS = Earliest Date of (Event or Censored) - Randomization Date + 1							
	Primary analysis		**Supportive analysis (1)**		**Supportive analysis (2)**		**Supportive analysis (3)**	
Purpose	Investigator -based		Sensitivity analysis		Independent review		Sensitivity analysis	
Population	ITT		ITT		ITT		ITT	
Situation	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**	**Outcome**	**Date of Outcome**
No Post-baseline	censored	date of rand.	Censored	date of rand.	censored	date of rand.	censored	date of rand.
Documented PD	PD	Date of PD assessment	PD	Date of PD assessment	PD	Date of PD assessment	PD	Date of PD assessment
PD on Unscheduled scan	PD	Date of PD assessment	PD	Next scheduled visit	PD	Date of PD assessment	PD	Next scheduled visit
No progression	censored	last assessment with no PD	Censored	last assessment with no PD	censored	Date of last PD assessment	Censored	last assessment with no PD
Clinical progression	Censored	last assessment with no PD	PD	Date of discontinuation	Censored	last assessment with no PD	Censored	last assessment with no PD
Toxicity	Censored	last assessment with no PD	PD	Date of discontinuation	Censored	last assessment with no PD	Censored	last assessment with no PD
New anticancer therapy + no PD	Censored	last assessment with no PD	PD	Date of anticancer therapy	Censored	last assessment with no PD	Censored	last PD assessment visit with no PD
Death	PD	Date of death	PD	Date of death	PD	Date of death	PD	Date of death

>1 consecutive missing scan	Censored	Date of last assessment with no PD	Censored	Date of last assessment with no PD	Censored	Date of last assessment with no PD	Censored	Date of last assessment with no PD

6.3.2. Analysis of Objective Response Rate (ORR) and Duration of Response (DoR)

ORR, defined as the proportion of patients who achieve objective tumor response (CR or PR) per modified RECIST 1.1.

ORR will be summarized by each treatment group using investigator's assessment. The comparison between the 2 treatment arms will be based on the Cochran-Mantel-Haenszel (CMH) test, with stratification factors as for the primary analyses of OS and PFS. Results will be reported in terms of an odds ratio and associated 95% CI.

In addition, ORR will be summarized by each treatment group using an independent radiological review of tumor response assessment.

Subgroup analysis of ORR and DCR by Chemotherapy regimen will be performed.

Waterfall plots will be used to display the percent change from baseline in the sum of longest diameters by treatment group for the ITT population. Only patients with measurable disease at baseline will be included in the waterfall plots. The following rules will be considered in the construction of the waterfall plots, Table 6-6;

- Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. As a conservative approach, such assessments will be displayed as bars in the graph, and the % change in the sum of diameters of target lesions reflects the non-PD target lesion response, although the overall lesion response is PD. A patient with such assessments will be represented by a special symbol (e.g. *) in the waterfall graph.
- Assessments with "unknown" target lesion response or overall response will be excluded from the waterfall plots

All possible assessment scenarios are described in Table 6-6

Table 6-6 Assessments considered for calculation of best percentage change for waterfall plots

Situation	Target response	Overall lesion response	Calculate % CFB and include in waterfall plot
1	Unknown /non evaluable	Any	No
2	Any	Unknown /non evaluable	No

3	CR/PR/SD	PD	Yes, flag assessment with *
4	PD	PD	Yes
5	CR/PR/SD	CR/PR/SD	yes

6.3.2.1. General rules for assessing objective response

Each patient's best overall response (BOR) will be summarized (CR, PR, SD, PD, non-evaluable or unknown). Patients with "unknown" or "non-evaluable" BOR will be summarized by reason for having unknown or non-evaluable status, such as:

- No valid post-baseline assessment.
- All post-baseline assessments have overall lesion response "unknown".
- New anticancer therapy started before first post-baseline assessment.
- Change in the imaging modality, eg from CT to MRI or vice versa, or contract CT to non- contrast CT. The change in the imaging methodology will result in "unknown status" by default for the BOR assessment.

If multiple radiological assessments based on the sum of target lesion measurements are done at different times, the overall response date is based on the *latest* date of the first radiological assessment of tumor response.

Table 6-7 provides guidance for defining best overall response (BoR) for each tumor assessment.

The best overall response will be determined after all the data for the patient are known. When stable disease (SD) is believed to be best response, it must be based on an assessment at least 5 weeks (35 days) from the baseline scan. If the SD response occurs less than 5 weeks from the baseline, the patient's best response will depend on the subsequent assessments. For example, a patient who had SD at the first assessment, progressive disease (PD) at the second assessment, and did not meet the criteria of SD determined at least 5 weeks from the baseline scan, will have a best response of PD. The same patient lost to follow-up after the first SD assessment will be considered non-evaluable [7].

Table 6-7 Rules for defining best overall response (BoR)

Target	Non-Target	New Lesion	Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD

Target	Non-Target	New Lesion	Response
Not all evaluated	Non-PD	No	non-evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

6.3.2.2. DoR

DoR is measured from the first reporting of CR or PR per modified RECIST 1.1 until the first date of progression, death, or censoring, and will be based on the ITT population. The median DoR will be estimated for each treatment group using the Kaplan-Meier method and the 95% CI will be summarized similar to OS methods. A p-value for this analysis will not be provided. Summaries will include the proportion of patients with subsequent tumor progression after previously objective response and proportion of patients without subsequent tumor progression after previously objective response (censored at last known assessment). If progression has not been documented, a patient's DOR will be censored at the date of last assessment.

DOR (months) = (earliest date of progression, death or censoring – date of first documented objective response + 1)/30.4375

6.3.3. Analysis of Disease Control Rate (DCR)

The DCR for each treatment group, along with 95% CIs will be calculated. The DCRs will be compared using a stratified CMH test with the same strata as for the primary analysis for OS.

6.3.4. Analysis of New Metastatic Lesions

Emergence of new metastatic lesions is evaluated through the proportion of patients with radiological progression that included new metastatic lesions, whether or not new metastatic lesions were also associated with disease progression in existing tumor lesions. In addition, the time to emergence of new metastatic lesions, defined as the time from the baseline scan to the first reporting of radiological PD that included new lesions, will also be evaluated by plotting Kaplan-Meier curves. Patients with no new metastatic lesions will be censored at the time of the most recent radiological assessment; patients that died will be censored to death date. A p-value for this analysis will not be provided.

6.4. Other Secondary Endpoints

6.4.1. PK, Pharmacodynamic and Immunogenicity Summaries

PK, pharmacodynamics and immunogenicity analyses will be performed on the PK population.

For all patients who provided samples, PK and pharmacodynamics of eryaspase will be assessed at each measurement, by describing the following:

- Total asparaginase activity (U/L)
- Plasma asparaginase activity (U/L)
- Plasma concentrations of asparagine (µmol/L).
- Plasma concentrations of glutamine (µmol/L).

Mean and median concentration-time profiles will be generated by cycle using nominal sampling time. Individual listings will be generated by course and include actual date and time, as well as patient demographics (age, gender, body weight). Statistical tabular summaries of concentration data by time point will include mean, SD, median, minimum and maximum.

Box and whisker plots will be generated for whole blood asparaginase concentrations collected at cycle 1 and cycle 3. These results would provide an assessment of trough (nadir) concentration following the first and third infusion of eryaspase.

A spaghetti plot of individual plasma concentration profiles will be generated by time point.

Immunogenicity assessments will include a screening assay, and if positive, a confirmatory binding assay, and if also positive then a neutralizing assay. Individual listings will be generated. An overall summary of baseline and post-baseline assays will be provided. Another summary will tabulate positive screening, confirmatory and neutralizing assays over time.

6.4.2. CA19-9 tumor marker

The CA19-9 levels will be summarized over time and change from baseline will be presented in tables as well as Spaghetti plots. A by-patient listing of these levels will also be summarized.

Kaplan-Meier curves for OS and PFS will also be presented by treatment group and according to normal/elevated CA19-9 value at baseline. In addition, Kaplan-Meier curves for OS and PFS will be presented by treatment group and according to the median nadir levels over the course of the study.

6.4.3. Tumor biomarkers

Tumor biomarkers analysis will be described in a separate statistical analysis plan to be developed after study completion.

6.4.4. Patient-reported outcomes (PRO)

PRO, based on scales from the QLQ-C30 questionnaires, will be summarized at Cycle 1 Day 1 (i.e, baseline) and each time it is measured according the protocol schedule, along with change from baseline (CFB). Box and whisker plots for the changes from baseline over time will also be plotted.

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 6-8.

Table 6-8 EORTC QLQ-30 Scales and Items

	Label	Items (Questions) included	Range of Response for items
Global Health Status / QOL	QL2	29, 30	6
Functional Scales			
Physical functioning	PF2	1 - 5	3
Role functioning	RF2	6, 7	3
Emotional functioning	EF	21 - 24	3
Cognitive functioning	CF	20, 25	3
Social functioning	SF	26, 27	3
Symptom Scales/Items			
Fatigue	FA	10, 12, 18	3
Nausea and vomiting	NV	14, 15	3
Pain	PA	9, 19	3
Dyspnea	DY	8	3
Insomnia	SL	11	3
Appetite loss	AP	13	3
Constipation	CO	16	3
Diarrhea	DI	17	3
Financial difficulties	FI	28	3

All of the scales and single-item measures range in score from 0 to 100. For global health status and functional scales, 100 is associated with a high performance while for symptoms scales, 100 is associated with high burden related to the symptoms. The calculation for each score is derived as follows.

1. A raw score is calculated as the average of the items of the scale
2. A linear transformation is applied to standardize the raw score so that the score ranges from 0 to 100.

For example, the below algorithm demonstrates how various QLQ-C30 scales are computed:

$$\text{Functional scales/items: Score} = \left(1 - \frac{(RS-1)}{\text{Range}}\right) \times 100$$

$$\text{Symptom scales/items: Score} = \left(\frac{(RS-1)}{}\right) \times 100$$

Global health status/QoL: $\text{Score} = \left(\frac{(RS-1)}{\text{Range}} \right) \text{X } 100$

For all scales, the Raw Score, RS, is the mean of the component items.

In case of missing items, the following rules will be applied:

1. If at least half of the items from the scale are not missing, missing items will be ignored
2. If not, the scale will be set to missing. For single item measures, the score is set to missing.

QoL endpoints will be summarized by treatment at baseline and each study visit, along with CFB. Box and whisker plots for the changes from baseline over time will be plotted.

A mixed model repeated measures (MMRM) model will be developed to analyze the CFB over study visits. Patients in the ITT population having at least a baseline value and one value after randomization were included in this analysis (PRO population).

The model will consider CFB as the dependent variable and include the following variables: Treatment, visit, stratification factors, baseline value and their interactions with visit. Patient will be a random effect. Least square means and their 95% confidence intervals will be computed. Visits with less than 30 patients in either treatment are excluded from the model.

6.4.4.1. Time to QoL first worsening/improvement analysis

For each subscale score of EORTC QLQ-C30, time to first worsening will be defined as the date of randomization to the date of first worsening occurred, where worsening definition for each subscale score is summarized in Table 6-9. Patients who did not have any worsening will be censored at date of last measurement or at baseline if no measurement is available post-baseline. Partially completed questionnaires will still be utilized, with missing components ignored.

Similarly, time to first improvement will be defined as the date of randomization to the date of first improvement occurred, where improvement definition for each subscale score is summarized in the table below. Patients who did not have any improvement will be censored at date of last measurement or at baseline if no measurement is available post-baseline.

The analysis will be performed using the PRO population. Kaplan-Meier curves will be provided for both time to first worsening and time to first improvement. p-Values for these analyses will not be provided.

Table 6-9 Worsening/Improvement definition for EORTC QLQ-C30

Score Name	Worsening definition	Improvement definition
Global Health Status/QoL	Change from baseline<=-10	Change from baseline>=10
Physical functioning	Change from baseline<=-10	Change from baseline>=10

Role functioning	Change from baseline<=-10	Change from baseline>=10
Emotional functioning	Change from baseline<=-10	Change from baseline>=10
Cognitive functioning	Change from baseline<=-10	Change from baseline>=10
Social functioning	Change from baseline<=-10	Change from baseline>=10
Fatigue	Change from baseline>=10	Change from baseline<=-10
Pain	Change from baseline>=10	Change from baseline<=-10
Nausea and Vomiting	Change from baseline>=10	Change from baseline<=-10
Dyspnea	Change from baseline>=10	Change from baseline<=-10
Insomnia	Change from baseline>=10	Change from baseline<=-10
Appetite Loss	Change from baseline>=10	Change from baseline<=-10
Constipation	Change from baseline>=10	Change from baseline<=-10
Diarrhea	Change from baseline>=10	Change from baseline<=-10
Financial difficulties	Change from baseline>=10	Change from baseline<=-10

6.5. Subgroup Analyses

A full list of subgroups is shown in section 4.9. Hazard ratios and 95% confidence intervals will be calculated for OS within subgroups using the Cox proportional hazards model with stratification factors as covariates as in the primary analysis of OS but excluding the factor used to define that subgroup where appropriate and displayed in a Forest plot in order to evaluate the consistency of treatment effect. The overall treatment effect and 95% confidence interval should also be included in the Forest plot.

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 adjusted odds ratios and corresponding 95% confidence intervals with the same rules regarding stratification factors as for OS.

7. DRUG EXPOSURE

Study drug exposure will be calculated based on the drug exposure eCRF pages and the End of Treatment eCRF page.

Analyses of exposure to study drugs will be based on the Safety Population. Summaries will provide summary statistics (mean, median, standard deviation, and range) overall and by treatment group.

A listing with visit (cycle) dates, drug administration start and end dates and times, end of study status will also be provided. Patients with missing or delayed doses will be listed by treatment group.

The following information will be summarized separately for each study drug:

- Study duration (months)
- Duration of exposure (weeks): overall and for each study drug

- Total cumulative dose for each study drug.
- Absolute and Relative dose intensity in weeks.
- Total number of cycles received, and the number (%) of patients treated in each cycle.
- Number of patients with at least one missed or delayed dose for each study at any time during the study.
  - The reasons for missed/delayed doses for each study drug will also be summarized as follows:
    - Safety reasons of adverse events, abnormal lab values
    - Non safety reasons
- Percentage of patients with discontinued treatment overall and by reason

Study duration will be derived in months and defined as the number of days between the randomization and the last known study visit, i.e., (date of last visit - date of randomization +1) /30.4375.

Treatment duration in weeks = last administration date – first administration date +1) / 7

For patients who die prior to Day 15 of the last cycle, the duration of exposure will be calculated as the date of death minus the date of first treatment plus 1 day.

For each study drug, the date of last dose is as recorded in the End of Treatment eCRF page

The cumulative dose received for each study drug will be calculated as:

$$\text{Cumulative dose received (units)} = \sum_{i=1}^{n} \text{Dose}_i$$

Where dose i = i^{th} dose received, and n = total number of doses received

Planned dose intensity:

The planned dose intensity for each study drug will be expressed as the total intended dose of the study drug per cycle.

Absolute dose intensity:

The absolute dose intensity for each study drug will be expressed as the actual dose of the study drug received by the patient, divided by the duration of treatment in weeks for each treatment

$$\text{Absolute Dose Intensity} = \frac{\text{Total (cumulative) dose of study drug (U/kg, or mg/m2)}}{\text{Duration of exposure (weeks)}}$$

Relative dose intensity:

This will be expressed as the ratio of absolute dose intensity and intended dose intensity, Table 7-1

$$\text{Relative Dose Intensity} = \frac{\text{Absolute dose intensity}}{\text{Planned dose intensity}} * 100\%$$

Table 7-1 Summary of the rules for defining drug exposure

Study Drug	Duration of Exposure (weeks)	Absolute Dose Intensity	Planned Dose Intensity per cycle
Eryaspase	(Last dose date – First dose date +14)/ 7	Cumulative actual dose received divided by (last dose date – first dose date +1)/7	100 U/kg x 2
Gemcitabine	(Last dose date – First dose date +7)/ 7	Cumulative actual dose received divided by (last dose date – first dose date + 1)/7	1000 mg/m2 x 3
Abraxane	(Last dose date – First dose date +7)/ 7	Cumulative actual dose received divided by (last dose date – first dose date + 1)/7	125 mg/m2 x 3
Onivyde	(Last dose date – First dose date +14)/ 7	Cumulative actual dose received divided by (last dose date – first dose date + 1)/7	70 (50 in case of UGT1A1*28)[1] mg/m2 x2
Irinotecan	(Last dose date – First dose date +14)/ 7	Cumulative actual dose received divided by (last dose date – first dose date + 1)/7	180 mg/m2 x 2
5 FU	(Last dose date – First dose date +14)/ 7	Cumulative actual dose received divided by (last dose date – first dose date + 1)/7	2400 mg/m2 x 2 (NALIRI) (2400 + 400) mg/m2 x 2 (FOLFIRI)
Leucovorin	(Last dose date – First dose date +14)/ 7	Cumulative actual dose received divided by (last dose date – first dose date + 1)/7	400 mg/m2 (or flat dose [2] in some centers) x2

1. A starting planned dose of 50mg/m2 in the presence of UGT1A1*28 would be considered a full planned dose at Cycle 1.
2. Some site will use a flat dose, eg 200mg. These situations should not be considered as dose reductions

7.1. Dose Reductions

A **dose reduction** is defined as actual dose less than 80% of planned protocol dose. When dose has been reduced in consecutive prior visit, the next dose is only considered as reduced if it is lower than the prior dose level. If a patient, due to a dosing error, received a higher dose than planned dose, and moves down to the planned starting dose, this dose will not be considered a dose reduction.

Frequency tables on number of patients with at least one dose reduction of any study drug will be provided. Patients receiving less than 60% of planned dose will also be summarized. Time to first dose reduction is earliest date of a dose reduction – first dose date + 1.

Dose reductions will be summarized as follows:

- Number of dose reductions per patients
- Level (<80% and <60%) of dose reduction
- Time to first dose reduction
- Which cycles a patient experienced a dose reduction

8. SAFETY AND TOLERABILITY ANALYSES

All safety summaries and analyses will be based upon the Safety population, which includes all patients who received at least 1 dose of study drug.

The analysis of safety and tolerability data includes an overall summary of tolerability, AEs (incidence, intensity, seriousness, and relationship of AEs to the study drug), drug exposure (duration of treatment, dosing information), concomitant medications, clinical laboratory results, ECG findings, vital signs, physical examination, body weight, ECOG PS, and treatment and study termination status.

Certain related adverse events and laboratory parameters that are similar in nature may be grouped manually to fully characterize the effect. For example, “neutrophil count decreased” and “neutropenia” will be combined as “neutropenia”. Trade and generic names for the prior cancer medications will also be grouped and presented under 1 name (e.g., gemcitabine, gemzar).

In general, inferential statistical tests are not performed for AE incidence rates.

8.1. Adverse Events

All AEs and SAEs will be collected and reported in the patient’s eCRF throughout study duration (i.e. for time patient signs the informed consent and at least 30 days (90 days in Amendment 1) after last administration of eryaspase or chemotherapy. All deaths and deaths occurring during the study (i.e. deaths after start of treatment and within 28 days after last dose of study treatment) as recorded in the “End of Study” eCRF section will be tabulated by

treatment group and chemotherapy regimen. In addition, dates will be provided in individual patient data listings together with related AE information (PT, verbatim term from eCRF, start date of AE, end date of AE, related to eryaspase (Yes/No), related to chemotherapy (Yes/No) and action taken). All AEs reported in the eCRF will be listed with the SOC, PT and Investigator's verbatim term.

AEs will be coded using the MedDRA version 21.0. The NCI CTCAE will be used to grade the severity of AEs. For AEs not included in the NCI CTCAE, categorization by mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening (Grade 4), or death (Grade 5) will be used.

Treatment-Emergent Adverse Events (TEAE) are defined as AEs that started or worsened during the treatment period; The treatment period begins on the date of first administration of study treatment until at least 30 days after date of last administration of study treatment.

The following tabular summaries of the incidence of treatment-related TEAEs by System Organ Class (SOC) and Preferred Term (PT) (in alphabetic order) with the number and percentages of patients experiencing at least one AE will be provided:

- Overall AE summary table:
  - TEAE
  - Grade 3 or higher TEAE
  - TE SAE
  - TEAE leading to dose reduction
  - TEAE resulting in study drug discontinuation
  - TE SAE resulting in study drug discontinuation
  - TEAE with an outcome of death
- Overall Study-drug related AE summary table:
  - Study-drug related TEAE
  - Study-drug related Grade 3 or higher TEAE
  - Study-drug related SAE
  - Study-drug related leading to dose reduction
  - Study drug-related TEAE resulting in study drug discontinuation
  - Study drug-related TE SAE resulting in study drug discontinuation
  - Study drug-related TEAE with an outcome of death
- All TEAEs:
  - By SOC and PT
  - By decreasing frequency of PT

  - By decreasing frequency of PT in at least 5% of Patients
  - By SOC and PT and Maximum Severity (CTCAE Grade)
  - By PT and Maximum Severity (CTCAE Grade)
- Study-drug related TEAEs:
  - By SOC and PT
  - By decreasing frequency of PT
  - By PT and Maximum Severity (CTCAE Grade)
- Grade 3 or 4 TEAEs:
  - By SOC and PT
  - By decreasing frequency of PT
  - Related to study drug by decreasing frequency of PT
- TEAE leading to study drug discontinuation:
  - By SOC and PT
  - By decreasing frequency of PT
- TEAE leading to dose reduction:
  - By decreasing frequency of PT
- TEAE resulting in death:
  - By SOC and PT
  - By decreasing frequency of PT
- Serious TEAEs:
  - By SOC and PT
  - By decreasing frequency of PT
  - By PT and Maximum Severity (CTCAE Grade)
  - Study-drug related by SOC and PT
  - Study-drug related by decreasing frequency of PT
  - Leading to permanent discontinuation of study drug by PT
- The time to first Grade 3 or 4 TEAE, by treatment group, presented using Kaplan-Meier methods. Data from patients without a reported Grade 3 or 4 TEAE by the data cutoff

will be censored at the end of the treatment-emergent period, or the data cutoff date, whichever occurs first.

  - Time to first Grade 3 or 4 TEAE (months) = (the date of first Grade 3 or 4 TEAE or censoring – date of first treatment + 1)/30.4375

- Subgroup tabulations of Grade 3 or 4 TEAEs by treatment group will be created for:
  - Age: < 65 VS ≥ 65
  - Baseline body mass index (BMI): BMI≤ 18, 18<BMI ≤23, and BMI> 23

The following general rules apply to adverse events:

- If an AE is reported for a given patient more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.
- In table summaries, patients will be counted only once at the PT level if multiple incidences of the same event occur within a SOC. Patients will be counted only once at the SOC level if multiple events occur within that SOC. For example, a patient who experiences an event of anemia and an event of neutropenia will be counted twice at the PT level (anemia, neutropenia) and once at the SOC level (vascular disorders).
- For the presentation of adverse events by PT, specific terms will be grouped (in bold) as in APPENDIX 5.
- In case a patient had AEs with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

8.1.1. Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be summarized by treatment group, APPENDIX 6. These will include:

- Hepatic events
- Diarrhea
- Transfusion Reactions
- Pancreatic Events
- Impaired coagulation related events that include: Hemorrhagic/thrombo-embolic/impaired coagulation parameters

Using AE CRF information, each AESI table will present: number of patients with event, overall number of events, patients occurrences, event characteristics, maximum severity, outcome, action taken, number of dose interruptions, time to onset and duration of events.

- **Time to Event Onset** is date of first TE-AESI – first dose date +1.
- **Event Duration** is end date of TE-AESI - start date of TE-AESI +1.

8.2. Clinical Laboratory Data

Local laboratories are being used for this clinical study for hematology and blood chemistry. For each individual laboratory used, laboratory reference ranges and units are collected. Reference ranges will be entered into the local laboratory normal range.

The following tests will be performed centrally: PK and pharmacodynamic (asparaginase activity, asparagine and glutamine), and anti-asparaginase antibodies.

The laboratory collection CRFs (hematology and serum chemistry) include fields for additional, non-protocol-required clinically significant laboratory tests, including laboratory test name, result, units, normal range low, and normal range high.

NCI CTCAE version 5 will be used for grading applicable laboratory tests.

Standard biological assessments will be performed at the local laboratory of the Investigator's site at selection, before any eryaspase administration and at the end of each course of chemotherapy as follows:

- Hematology: complete blood count (CBC).
- Coagulation: partial thromboplastin time (PTT), fibrinogen, Antithrombin III (ATIII), international normalized ratio (INR).
- Serum Electrolytes: bicarbonate, sodium, potassium, calcium, chloride.
- Serum Biochemistry: ammonia, amylase, creatinine, albumin, glucose, triglycerides, lactate dehydrogenase (LDH), cholesterol, total bilirubin, ALT, AST, gamma glutamyl transpeptidase (γGT), alkaline phosphatase, lipase, urea, uric acid.

For laboratory parameters (i.e., hematology, coagulation, serum electrolytes, and standard biochemistry), shift analyses will be performed on laboratory abnormalities of the highest NCI CTCAE grade or the worst severity if there is no NCI CTCAE grade. Shift from baseline grade to the worst CTCAE grade overall will be presented for all laboratory parameters that have an associated CTCAE grade. Both scheduled and on treatment unscheduled (see TEAE) values will be considered for worst CTCAE grade. These summaries will be presented by treatment group and overall.

Normalized values will be graphed in a trellis plot, baseline value against maximum or minimum post-baseline value. Values are normalized by dividing by the high normal-range for all chemistry, except albumin; otherwise, values are normalized by dividing by the low normal-range. The Trellis plot will use multiples of the upper or lower limit for axis scales.

A Hy's Law analysis will be performed on elevations of liver related assessments, summarized by treatment. Patients with the following results at the same post-baseline visit (a)ALT or AST > 3 x ULN and (b) ALP or BIL > 2 x ULN are counted. In addition, individual elevation of ALT > 3 x ULN, AST > 3 x ULN, ALP > 2 x ULN or BIL > 2 x ULN are also summarized.

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant abnormal laboratory values. This listing will present all lab values for any parameter with at least one clinically significant abnormal value so that a time course for that lab parameter can be presented.

8.3. Performance Status

For ECOG Performance Status, shift tables from baseline score to worst post-baseline scores (PS 1, 2, 3, or 4) will be presented by treatment group and overall.

By-patient listings of all ECOG measurements will also be presented in data listings.

8.4. Vital Signs, Physical Examinations and Performance Status

Vital signs parameters will include body temperature (°C), height (cm), weight (kg), heart rate (beats/min), systolic and diastolic blood pressures (mmHg) and will be evaluated by treatment group and overall.

The actual value and change from baseline to each on study evaluation will be summarized for vital signs.

By-patient listings of all vital sign measurements will also be presented in data listings

Physical examination shifts from baseline to the worst post-baseline assessment will be presented. Both scheduled and on treatment unscheduled (see TEAE) values will be considered for worst assessment. All physical examination findings will be presented in a data listing.

8.5. Concomitant Medications

Previous and Concomitant medication are summarized by treatment with the ITT population.

Concomitant medications will be defined as all medications taken by the patient any time on-study (on or after the first infusion date of any of eryaspase or chemotherapy) or within 28 days after the last administration date. Previous medication will be defined as all medications taken by the patient before the first infusion of any of eryaspase or chemotherapy. A table will be constructed for the number of patients having at least one subsequent anti-cancer therapies, defined as medications collect by the Post-Treatment Anti-Cancer Therapies CRF page.

In case the date value does not allow allocation of a medication to previous or concomitant category, this medication will be considered as concomitant.

Concomitant and previous medications, not including subsequent anti-cancer therapies, will be summarized using data recorded in the “Previous and concomitant treatments” eCRF pages. Subsequent anti-cancer therapies will also be summarized separately.

Concomitant medications will be coded using the WHO Drug dictionary. Results will be tabulated by Anatomic Therapeutic Class (ATC) and Preferred Term.

For the presentation of concomitant medications, ATC level 2 will be used. In addition, medication names provided in the data base will be replaced by “Preferred Term”; these will be provided by the Sponsor in a spread sheet and will based on Generic name or the common name (as provided by WHO INN).

Medications will be listed by patient number, start date of medication and drug name as recorded in the eCRF, separately for prior and concomitant medications. The use concomitant medications will be included in by-patient data listings.

9. Subsequent Anti-Cancer Therapies

Types of Subsequent Anti-Cancer Therapies will be determined by the sponsor’s designation of Post-Treatment Anti-Cancer Therapies CRF data. Results will be presented for the ITT population and the following categories, will be summarized by treatment group:

- Subjects with Any Post-Treatment Anti-Cancer Therapies, Palliative radiation therapy or Systemic anti-cancer therapy
- Combination chemotherapy and name of therapy.
- Single agent chemotherapy and name of therapy.
- Number of lines of subsequent chemotherapy

10. COVID-19 IMPACT

The COVID-19 worldwide pandemic has impacted the conduct of this study. Challenges led 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. Erytech recognizes that patients may encounter difficulties having all protocol required laboratory assessments completed due to possible local laboratory closures or shortages of lab personnel. Erytech implemented several emergency measures, including waiving some laboratory assessments to ease the burden on sites, without compromising the patients' overall safety, Table 10-1.

Table 10-1 Trybeca-1 COVID-19 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
Coagulation:	Partial thromboplastin time (PTT)	waived
	Fibrinogen	X
	Antithrombin III (AT III)	X
	Albumin	X
	Alkaline phosphatase	waived

Category	Parameter	Must Be Performed
Serum Chemistry and Tumor Markers:	Alanine aminotransferase (ALT)	X
	Ammonia	waived
	Amylase	X
	Aspartate aminotransferase (AST)	X
	Bicarbonate	waived
	Calcium	X
	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 done on two separate samples	X
	Irregular antibody screening test (IAST)	X
	Pregnancy test for women of childbearing potential	X

10.1. By-Patient COVID-19 Listings

A by-patient listing of COVID-19 impact codes by visit displays visits with abbreviated labels in separate columns for the ITT analysis set. Spanning headers above the visits display the analysis period. Each column denotes an analysis visit and displays the COVID-19 visit impact code. If a patient has multiple COVID-19 visit impact codes in an analysis visit window, then results are displayed sorted by visit date and comma-concatenated across all COVID-19 visit dates in the analysis visit window.

A by-patient listing of COVID-19 visit impact is provided for the ITT analysis set. The listing displays analysis period, analysis visit, COVID-19 visit date, study day derived from COVID-19 visit date, treatment day derived from COVID-19 visit date, visit type (scheduled or unscheduled), visit impact type, visit impact characteristics, visit impact relationship with specify text, and premature study termination (yes; no; not applicable).

11. CHANGES TO PLANNED ANALYSES

Not applicable

12. REFERENCES

1. Hammel P, Fabienne P, Mineur L, et al: Erythrocyte-encapsulated asparaginase (eryaspase) combined with chemotherapy in second-line treatment of advanced pancreatic cancer: An open-label, randomized Phase IIb trial. European Journal of Cancer 124:91-101, 2020

2. 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. The Lancet 387:545-557, 2016

3. Paluri RK, Kasi A, Young C, et al: Second-line treatment for metastatic pancreatic cancer. Clin Adv Hematol Oncol 18:106-115, 2020

4. Guidance for Industry - Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, in Administration USDoHaHSFaD, (CDER) CfDEaR, (CBER) CfBEaR (eds), 2015

5. Amit O, Mannino F, Stone AM, et al: Blinded independent central review of progression in cancer clinical trials: Results from a meta-analysis. European Journal of Cancer 47:1772-1778, 2011

6. Stone A, Gebski V, Davidson R, et al: Exaggeration of PFS by blinded, independent, central review (BICR).

7. Eisenhauer EA, Therasse P Fau - Bogaerts J, Bogaerts J Fau - Schwartz LH, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).

13. CLINICAL STUDY REPORT APPENDICES

14. APPENDIX 1: RANDOMIZATION SPECIFICATION

RANDOMIZATION SCHEDULE DESIGN SPECIFICATIONS

This randomization schedule is prepared to assign study treatments to patients in a randomized fashion, according to the study design.

Design: Parallel

Number of Randomization Numbers on Schedule 4800
Block Size 2

Sample Subject Randomization Number as it will appear on randomization list: 10001 - 14800

Blinding: Open-label

Site Stratification: No
Other Stratification Factors: Yes **Accomplished by:** Randomization Schedule

Other Stratification Factors Included in Randomization Schedule	Stratification Levels*
ECOG PS Score	2
Time interval since diagnosis of advanced disease	2
Chemotherapy regimen	2

* Add details below to show combined levels for STRAT and STRAT_TXT

Treatments:

Arm	Description	Ratio
1	Arm A - Investigational Arm	1
2	Arm B - Control Arm	1

RANDOMIZATION VARIABLES

Variable Name	Purpose
REC_NUM	Record or Sequence Number
BLOCK	Block Number
BLK_SIZ	Block Size
RAND_NUM	Randomization Number
STRAT	Stratum Number

STRAT_TX	Stratum Description
ARM	Arm Code
ARM_TX	Arm Description

File Format(s):

☑ PPD - IVRS standard (pipe-delimited) ☐ comma delimited ☐ Other, specify: _____

☑ SAS dataset ☐ PPD - MW standard for CSR (RTF) ☑ pdf

Combined Stratification Levels as They Should Appear on Randomization Schedule

STRAT	STRAT_TXT
1	ECOG=0, <6 months, gemcitabine/abraxane
2	ECOG=0, <6 months, irinotecan based treatment
3	ECOG=0, >=6 months, gemcitabine/abraxane
4	ECOG=0, >=6 months, irinotecan based treatment
5	ECOG=1, <6 months, gemcitabine/abraxane
6	ECOG=1, <6 months, irinotecan based treatment
7	ECOG=1, >=6 months, gemcitabine/abraxane
8	ECOG=1, >=6 months, irinotecan based treatment

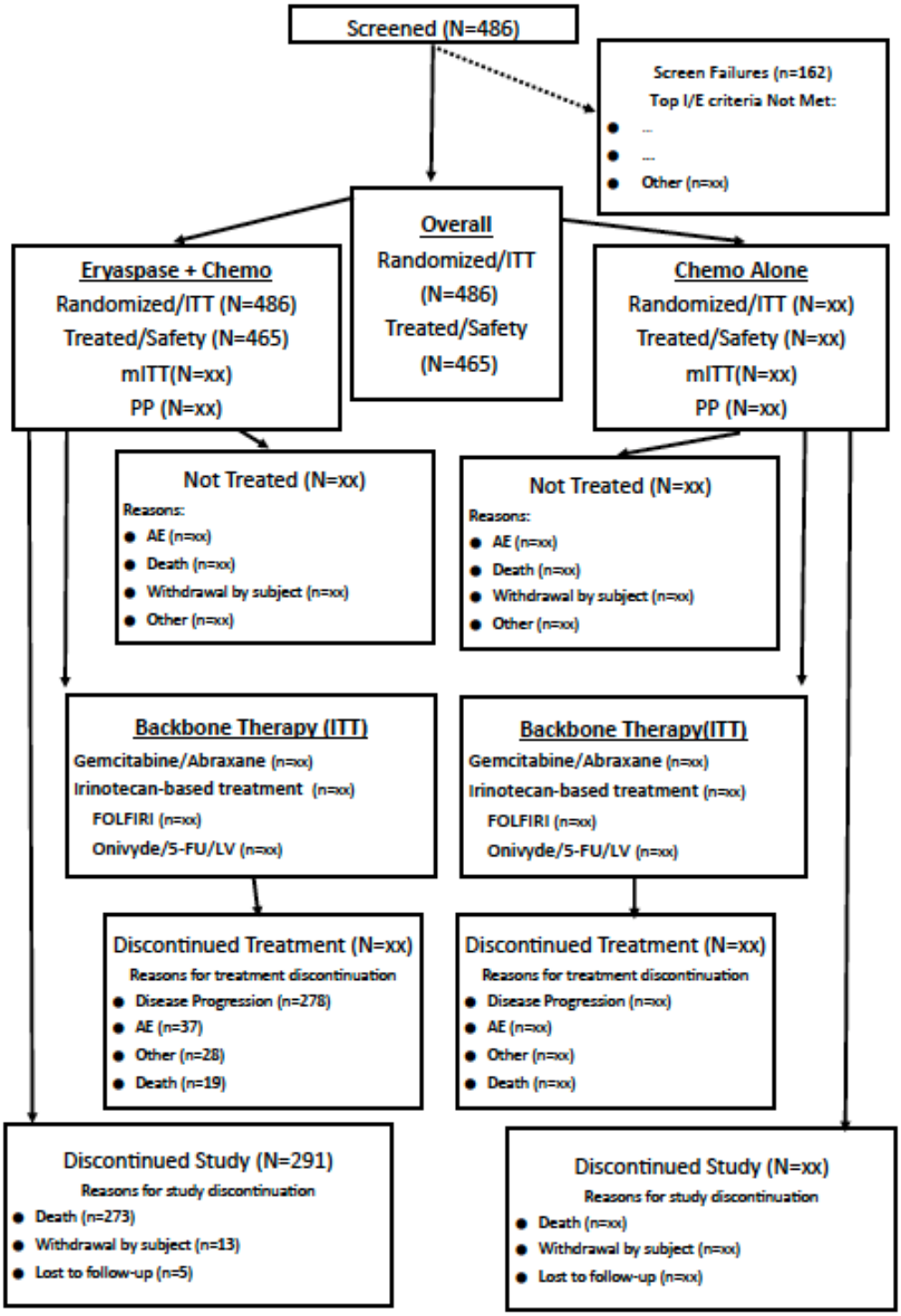
15. APPENDIX 2: PROTOCOL DEVIATIONS

Major protocol deviations to exclude from Per Protocol Population	
Must be 18 years of age or older	Inclusion Criterion #1
Must have Stage III or IV disease	Inclusion Criterion #3
Must have received one line of systemic chemotherapy 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	Inclusion Criterion #4
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	Inclusion Criterion #5
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)	Inclusion Criterion #6
Must have adequate performance status (ECOG 0 or 1)	Inclusion Criterion #8
Resectable or borderline resectable pancreatic adenocarcinoma at the time of signing the informed consent	Exclusion Criterion #1
Histology other than pancreatic ductal adenocarcinoma (for example, but not inclusive: neuroendocrine, adenosquamous	Exclusion Criterion #2
More than 1 line of prior treatment in advanced or metastatic setting	Exclusion Criterion #3
Failure to obtain written informed consent from patient	Inclusion Criterion #14
Important protocol deviations (to be included in CSR)	
Must be 18 years of age or older	Inclusion Criterion #1

Must have Stage III or IV disease	Inclusion Criterion #3
Must have received one line of systemic chemotherapy 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	Inclusion Criterion #4
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	Inclusion Criterion #5
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)	Inclusion Criterion #6
Must have adequate performance status (ECOG 0 or 1)	Inclusion Criterion #8
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.	Inclusion Criterion #13
Resectable or borderline resectable pancreatic adenocarcinoma at the time of signing the informed consent	Exclusion Criterion #1
Histology other than pancreatic ductal adenocarcinoma (for example, but not inclusive: neuroendocrine, adenosquamous	Exclusion Criterion #2
More than 1 line of prior treatment in advanced or metastatic setting	Exclusion Criterion #3
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	Exclusion Criterion #5

metastases are radiologically and clinically stable, and the patient is off steroids for at least 1 month prior to randomization.	
Bone as the only site of metastatic disease from pancreatic cancer (bone-only disease)	Exclusion Criterion #7
Incorrect stratification (distinguish between ECOG status, Chemo regimen, time interval since initial diagnosis of advanced disease errors)	
Failure to obtain written informed consent from patient	Inclusion Criterion #14
History of other malignancies	Exclusion Criterion #14

16. APPENDIX 3: CONSORT DIAGRAM



17. APPENDIX 4: FINAL ANALYSIS LIST OF TABLES, LISTINGS AND FIGURES

The full list of outputs is located in mock TLF shell document. Of the full list, the following will be provided for topline results:

Table 14.1.1.1: Overall Patients Disposition - All Patients

Table 14.1.1.4: Overall Deaths - ITT Population

Table 14.1.3.1.1: Patient Demographics - ITT Population

Table 14.1.3.1.2: Patient Demographics - PP Population

Table 14.1.3.3.1: Baseline Characteristics of Pancreatic Cancer - ITT Population

Table 14.1.3.3.2: Baseline Characteristics of Pancreatic Cancer by Backbone Chemotherapy - ITT Population

Table 14.1.3.3.3: Baseline Characteristics of Pancreatic Cancer - PP Population

Table 14.1.4.1: Prior Cancer Related Therapy and Disease Response - ITT Population

Table 14.1.6.3: Subsequent Anti-Cancer Therapies - ITT Population

Table 14.1.7.2.1: Summary of Overall Exposure to Eryaspase - Safety Population

Table 14.2.1.1: Summary of Overall Survival by Treatment Group - ITT Population

Table 14.2.1.2: Summary of Overall Survival by Treatment Group - PP Population

Table 14.2.1.4: Restricted Mean Survival Time of Overall Survival by Treatment Group - ITT Population

Table 14.2.1.5: Multivariate Cox Regression of Overall Survival - ITT Population

Table 14.2.2.1: Summary of Progression Free Survival (Investigator Assessment) by Treatment Group - ITT Population

Table 14.2.2.3: Summary of Progression Free Survival (Investigator Assessment) by Treatment Group - PP Population

Table 14.2.3.1: Summary of Disease Response per RECIST Criteria (Investigator Assessment) by Treatment Group - ITT Population

Table 14.2.3.1.1: Summary of Disease Response per RECIST Criteria (Investigator Assessment) by Treatment Group and subgroup: Chemotherapy regimen - ITT Population

Table 14.3.1.1.1: Overall Summary of Treatment Emergent Adverse Events - Safety Population

Table 14.3.1.2.1: Incidence of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Safety Population

Table 14.3.1.2.9: Incidence of Treatment Emergent Adverse Events Occurring in at least 5% of Patients in either Treatment Group by Preferred Term - Safety Population

Figure 14.1.1.3: CONSORT Diagram for Patient- All Patients

Figure 14.2.1.1: Overall Survival by Treatment Group - Kaplan Meier Curves - ITT Population

Figure 14.2.1.2: Overall Survival by Treatment Group - Kaplan Meier Curves - PP Population

Figure 14.2.1.3.1: OS by Treatment Group - Kaplan Meier Curves - Safety Population

"Sensitivity analyses: Actual Treatment and Stratification factors determined according to baseline characteristics" - Safety Population

Figure 14.2.1.3.2: OS by Treatment Group - Kaplan Meier Curves - ITT Population

Sensitivity analyses: Stratification factors determined according to baseline characteristics" - ITT Population

Figure 14.2.1.3.3: OS by Treatment Group - Kaplan Meier Curves - ITT Population

"Sensitivity Analysis: Censored at the date of subsequent anticancer therapy" - ITT Population

Figure 14.2.1.3.4: OS by Treatment Group - Kaplan Meier Curves - ITT Population

"Sensitivity Analysis: Lost to follow-up considered death - ITT Population

Figure 14.2.2.1: PFS by Treatment Group - Kaplan Meier Curves - ITT Population

Figure 14.2.2.3: PFS by Treatment Group - Kaplan Meier Curves - PP Population

Figure 14.2.3.1: DoR by Treatment Group - Kaplan Meier Curves - ITT Population

Figure 14.2.1.6: Forest Plot of OS Hazard Ratios in Subgroups - ITT Population

Figure 14.2.1.7: Forest Plot of OS Hazard Ratios in Subgroups - PP Population

Figure 14.2.2.8: Forest Plot of PFS Hazard Ratios in Subgroups - ITT Population

Figure 14.2.3.3: Waterfall Plots: Percent Change from Baseline in Sum of Longest Diameter Best Response (RECIST 1.1) - ITT Population

18. APPENDIX 5: Grouping rules for Adverse Events

The following is taken from Erytech's "AE grouping rules-ISS's SAP 1.0.0-5 Jul21":

All analysis will be performed considering the grouped term identified with an "*" next to the grouped term, including those per SOC. In case of grouped term including PTs under different SOCs, the primary SOC of the grouped term will be considered. The exception to this rule is where the SOC is mentioned in brackets next to the grouped term.
In addition, several tables with non-grouped PTs could be generated when specified.
Ex.: Anaemia*: Anaemia, Haemoglobin decreased
PT = Anaemia corresponds to SOC = Blood and lymphatic system disorders
PT = Haemoglobin decreased corresponds to SOC = Investigations
For "per PT" analysis: "Anaemia*" will be used to classify all cases under this grouped term denomination
For "per SOC" tables: Anaemia* --- PT identical with grouped term denomination, so all cases grouped under Anaemia* will be counted in SOC Blood and lymphatic system disorders.

For the presentation of adverse events by PT, specific terms will be grouped (in bold) with an "*" next to the grouped term as follow:

Grouped preferred Term	Relevant Preferred Term
Abdominal pain*	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain.
Alloimmunisation*	Alloimmunisation, Anti Kell antibody test positive, Antibody test positive, Anti-erythrocyte antibody positive, Anti-erythrocyte antibody, Anti A antibody positive, Anti B antibody positive, Cold agglutinins positive, Coombs direct test positive, Coombs indirect test positive, Coombs test positive, Rhesus antibodies positive, ABO incompatibility, Blood type incompatibility, Rhesus incompatibility.
Anaemia*	Anaemia, Haemoglobin decreased, Iron deficiency anaemia.
Aspergillus infection*	Aspergillus infection, Bronchopulmonary aspergillosis.
Asthenia*	Asthenia, Fatigue.
Bacteraemia*	Acinetobacter bacteraemia, Bacillus bacteraemia, Bacteraemia, Bacteroides bacteraemia, Citrobacter bacteraemia, Clostridium bacteraemia, Corynebacterium bacteraemia, Cronobacter bacteraemia, Device related bacteraemia, Enterobacter bacteraemia, Enterococcal bacteraemia, Escherichia bacteraemia, Granulicatella bacteraemia, Haemophilus bacteraemia, Klebsiella bacteraemia, Meningococcal bacteraemia, Pneumococcal bacteraemia, Pseudomonal bacteraemia, Salmonella bacteraemia, Serratia bacteraemia, Shewanella algae bacteraemia, Sphingomonas paucimobilis bacteraemia, Staphylococcal bacteraemia, Stenotrophomonas bacteraemia, Streptococcal bacteraemia, Yersinia bacteraemia.
Blood albumin decreased*	Hypoalbuminaemia, Blood albumin decreased.
Blood chloride increased*	Blood chloride increased, Hyperchloraemia.

Blood cholesterol decreased*	Hypocholesterolaemia, Blood cholesterol decreased.
Blood cholesterol increased*	Blood cholesterol increased, Hypercholesterolaemia.
Blood creatinine increased*	Blood creatinine increased, Hypercreatininaemia.
Blood fibrinogen decreased*	Hypofibrinogenaemia, Blood fibrinogen decreased.
Blood fibrinogen increased*	Hyperfibrinogenaemia, Blood fibrinogen increased.
Blood lactic acid increased*	Blood lactic acid increased, Hyperlactacidaemia.
Cellulitis*	Administration site cellulitis, Anorectal cellulitis, Application site cellulitis, Breast cellulitis, Catheter site cellulitis, Cellulitis, Cellulitis enterococcal, Cellulitis gangrenous, Cellulitis of male external genital organ, Cellulitis orbital, Cellulitis pasteurella, Cellulitis staphylococcal, Cellulitis streptococcal, Eosinophilic cellulitis, External ear cellulitis, Implant site cellulitis, Incision site cellulitis, Infusion site cellulitis, Injection site cellulitis, Lacrimal sac cellulitis, Medical device site cellulitis, Perineal cellulitis, Periorbital cellulitis, Post procedural cellulitis, Pseudocellulitis, Puncture site cellulitis, Stoma site cellulitis, Vaccination site cellulitis, Vaginal cellulitis, Vessel puncture site cellulitis, Vulval cellulitis.
Device malfunction*	Device dislocation, Device leakage, Device malfunction, Device occlusion, Stent malfunction.
Diarrhoea*	Diarrhoea, Diarrhoea infectious, Faeces soft, Bacterial diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious neonatal, Diarrhoea neonatal, Overflow diarrhoea, Post procedural diarrhoea, Viral diarrhoea.
Dysphagia*	Dysphagia, Odynophagia.
Oedema*	Oedema, Oedema peripheral, Lymphoedema, Localised oedema.
Folliculitis*	Folliculitis, Furuncle.
Gastrointestinal haemorrhage*	Gastrointestinal haemorrhage, Upper gastrointestinal haemorrhage, Gastric haemorrhage, Intestinal haemorrhage, Small intestinal haemorrhage, Rectal haemorrhage, Duodenal ulcer haemorrhage.
General physical health deterioration*	General physical health deterioration, Performance status decreased, Eastern Cooperative Oncology Group performance status worsened.
Graft versus host disease*	Acute graft versus host disease, Acute graft versus host disease in intestine, Acute graft versus host disease in liver, Acute graft versus host disease in skin, Acute graft versus host disease oral, Chronic graft versus host disease, Chronic graft versus host disease in eye, Chronic graft versus host disease in intestine, Chronic graft versus host disease in liver, Chronic graft versus host disease in skin, Chronic graft versus host disease oral, Graft versus host disease, Graft versus host disease in eye, Graft versus host disease in gastrointestinal tract, Graft versus host disease in liver, Graft versus host disease in lung, Graft versus host disease in skin.

Hyperbilirubinaemia*	Hyperbilirubinaemia, Blood bilirubin increased.
Hypercalcaemia*	Blood calcium increased, Hypercalcaemia.
Hyperglycaemia*	Hyperglycaemia, Blood glucose increased.
Hyperkalaemia*	Blood potassium increased, Hyperkalaemia.
Hypernatraemia*	Blood sodium increased, Hypernatraemia.
Hyperphosphataemia*	Hyperphosphataemia, Blood phosphorus increased.
Hypertriglyceridaemia*	Hypertriglyceridaemia, Blood triglycerides increased.
Hyperuricaemia*	Hyperuricaemia, Blood uric acid increased.
Hypocalcaemia*	Blood calcium decreased, Hypocalcaemia.
Hypoglycaemia*	Hypoglycaemia, Blood glucose decreased.
Hypokalaemia*	Blood potassium decreased, Hypokalaemia.
Hyponatraemia*	Blood sodium decreased, Hyponatraemia.
Hypophosphataemia*	Blood phosphorus decreased, Hypophosphataemia.
Injection site reaction*	Injection site reaction, Injection site haematoma, Injection site inflammation, Injection site oedema, Infusion site pain.
Gastrointestinal obstruction *	Intestinal obstruction, Gastrointestinal obstruction, Small intestinal obstruction, Duodenal obstruction, Subileus, Intestinal pseudo-obstruction, Ileus, Obstruction gastric.
Leukocytosis*	Leukocytosis, White blood cell count increased.
Leukopenia*	Leukopenia, White blood cell count decreased.
Lymphopenia*	Lymphopenia, Lymphocyte count decreased.
Monocytopenia*	Monocyte count decreased, Monocytopenia.
Mouth haemorrhage*	Mouth haemorrhage, Gingival bleeding.
Neuropathy peripheral*	Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy, Hypoaesthesia, Dysaesthesia, Hyperaesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Polyneuropathy, Sciatic nerve neuropathy.
Neutrophilia*	Neutrophilia, Neutrophil count increased.
Neutropenia*	Neutropenia, Neutrophil count decreased.
Oral disorder*	Stomatitis, Aphthous ulcer, Mouth ulceration, Tongue ulceration, Gingivitis, Mucosal ulceration, Mucosal inflammation, Oral disorder, Gingival disorder, Swollen tongue, Tongue oedema.
Pancreatic enzymes abnormal*	Amylase abnormal, Amylase creatinine clearance ratio abnormal, Amylase increased, Blood trypsin increased, Hyperamylasaemia, Hyperlipasaemia, Lipase abnormal, Lipase increased, Lipase urine increased, Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, Pancreatic enzymes increased.
Pancreatitis*	Pancreatitis, Pancreatitis acute.
Protein total decreased*	Protein total decreased, Hypoproteinaemia
Protein total increased*	Protein total increased, Hyperproteinaemia
Pyrexia*	Pyrexia, Hyperthermia

Renal failure*	Renal failure, Acute kidney injury, Postrenal failure, Prerenal failure.
Respiratory tract congestion*	Respiratory tract congestion, Lower respiratory tract congestion, Upper respiratory tract congestion.
Sepsis*	**all PT which contain "sepsis" in the wording:** Abdominal sepsis, Acinetobacter sepsis, Actinomycotic sepsis, Anthrax sepsis, Bacterial sepsis, Biliary sepsis, Brucella sepsis, Burkholderia cepacia complex sepsis, Campylobacter sepsis, Candida sepsis, Capnocytophaga sepsis, Citrobacter sepsis, Clostridial sepsis, Corynebacterium sepsis, Device related sepsis, Enterobacter sepsis, Enterococcal sepsis, Erysipelothrix sepsis, Escherichia sepsis, Fungal sepsis, Group B streptococcus neonatal sepsis, Haemophilus sepsis, Helicobacter sepsis, Herpes sepsis, Herpes simplex sepsis, Intestinal sepsis, Klebsiella sepsis, Leptospira sepsis, Listeria sepsis, Meningococcal sepsis, Micrococcal sepsis, Neutropenic sepsis, Nocardia sepsis, Pelvic sepsis, Plague sepsis, Pneumococcal sepsis, Post procedural sepsis, Postpartum sepsis, Pseudallescheria sepsis, Pseudomonal sepsis, Pseudosepsis, Pulmonary sepsis, Salmonella sepsis, SARS-CoV-2 sepsis, Sepsis, Sepsis neonatal, Sepsis pasteurella, Sepsis syndrome, Serratia sepsis, Shigella sepsis, Staphylococcal sepsis, Stenotrophomonas sepsis, Streptococcal sepsis, Umbilical sepsis, Urosepsis, Varicella zoster sepsis, Viral sepsis, Wound sepsis, Yersinia sepsis.
Serum ferritin increased*	Serum ferritin increased, Hyperferritinaemia.
Sleep disorder*	Sleep disorder, Insomnia.
Transaminases increased*	Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased.
Thrombocytosis*	Thrombocytosis, Platelet count increased.
Thrombocytopenia*	Thrombocytopenia, Platelet count decreased.
Upper respiratory tract infection*	Upper respiratory fungal infection, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Upper respiratory tract infection helminthic, Viral upper respiratory tract infection, Acute sinusitis, Nasopharyngitis, Sinusitis, Chronic sinusitis, Pharyngitis, Tracheitis, Rhinitis, Viral rhinitis.
Upper limb fracture*	Upper limb fracture, Humerus fracture, Forearm fracture.
Urinary tract infection*	Urinary tract infection, Campylobacter urinary tract infection, Cytomegalovirus urinary tract infection, Escherichia urinary tract infection, Genitourinary tract gonococcal infection, Genitourinary tract infection, Prophylaxis urinary tract infection, Providencia urinary tract infection, Streptococcal urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection fungal, Urinary tract infection neonatal, Urinary tract infection pseudomonal, Urinary tract infection staphylococcal, Urinary tract infection viral.

19. APPENDIX 6: ADVERSE EVENTS OF SPECIAL INTEREST

This appendix explains AESI retrieval strategy, the content of the AESIs for the final outputs.

The analysis will be performed on non-grouped AE database. However, the final AESI outputs for the AESI will apply the grouping rules as presented in Appendix 4.

The methodology for the AESI data retrieval and analysis will be:

- The programmer retrieves the relevant cases by applying the Standardized MedDRA Queries as defined below.
- The listings will be reviewed by Erytech to ensure that the identified AEs terms are appropriate and eliminate the cases that are not of interest for the AESI categories.

The following AESI categories will be presented:

19.1. Transfusion events

This category will include 2 subcategories:

a) Transfusion reactions

b) Hemolytic reactions

19.1.1. Transfusion reactions

The AE term retrieval for this sub-category will include all PTs as follows:

- Allergic transfusion reaction
- Delayed serologic transfusion reaction
- Febrile non-hemolytic transfusion reaction
- Hypotensive transfusion reaction
- Transfusion reaction
- Transfusion-related complication
- Transfusion-related acute lung injury (TRALI)
- Transfusion-related alloimmune neutropenia
- Transfusion-related circulatory (volume) overload
- Anaphylactic transfusion reaction

19.1.2. Hemolytic disorders

The AE term retrieval for this subcategory include the following PTs:

- Acute hemolytic transfusion reaction
- Autoimmune anemia
- Autoimmune hemolytic anemia
- Hemolytic anemia

- Delayed hemolytic transfusion reaction
- Extravascular hemolysis
- Hemolysis
- Hemolytic transfusion reaction
- Hemolytic uremic syndrome
- Intravascular hemolysis
- Iso-immune hemolytic disease
- Microangiopathic hemolytic anemia

19.2. Pancreatic events

This category will be presented with 2 subgroups as defined below:

19.2.1. Clinical Pancreatitis

The AE term retrieval for this subcategory will use:

- Acute Pancreatitis
- Pancreatitis

19.2.2. Biochemical Pancreatitis

The AE term retrieval for this sub-category will include:

- Amylase abnormal
- Amylase increased
- Blood trypsin increased
- Hyperamylasemia
- Hyperlipasemia
- Lipase abnormal
- Lipase increased
- Pancreatic enzyme abnormality
- Pancreatic enzymes abnormal
- Pancreatic enzymes increased

19.3. Hepatic Events

This category will include the following search terms:

- Jaundice
- Jaundice hepatocellular
- Hepatocellular injury
- Hyperbilirubinemia

- Blood bilirubin increased

19.4. Impaired coagulation

This category will be presented with 3 subcategories as below:

19.4.1. Impaired coagulation parameters

AE term retrieval for this category will include:

- Antithrombin III decreased
- Blood fibrinogen abnormal
- Blood fibrinogen decreased
- Blood thrombin abnormal
- Blood thromboplastin abnormal
- Blood thromboplastin decreased
- Coagulation factor decreased
- Any of the coagulation factors abnormal/decreased: Factor IX level, Factor V level, Factor VII level,Factor X level
- INR abnormal
- INR decreased
- Prothrombin level abnormal
- Prothrombin level decreased
- Prothrombin time abnormal
- Prothrombin time prolonged

19.4.2. Embolic and thrombotic events

- This includes events (SMQ) [20000081]

19.4.3. Hemorrhagic events

- Hemorrhage terms
- Gastrointestinal hemorrhage