Eryaspase has been previously shown to be a well-investigational drug product eryaspase. Though inconclusive, this study left the possibility that a safer form of ASNase could be generated and a selected dose for Phase 2 would have needed to be below the expected biologically effective range. In addition, in Phase 1 study, pegylated ASNase (Oncaspar) showed promising anti-tumor activity against human pancreatic tumor cell lines. In vitro studies have demonstrated promising anti-tumor effects for l-asparaginase (ASLase) against human pancreatic tumor cell lines.

Pancreatic adenocarcinoma (PAC) is characterized by extensive reprogramming of cellular death pathways. Perturbation of these pathways results in a poor, hypoxic microenvironment. Perturbation of these pathways deaths by 2035 if new screening and treatment options are not implemented. Brain metastasis is allowed, if stable.

In a recent randomized phase 2 study in patients with advanced PAC whose disease progressed following gemcitabine chemotherapy alone (NCT02195180), the addition of eryaspase to chemotherapy demonstrated clinically meaningful improvement in median OS (8.6 vs. 4.4 months, respectively), with a 65% reduction in the risk of death. The overall response rate (ORR) was 15% (95% CI: 7.3 – 26.1), with 5% (95% CI: 0.9 – 9.7) of those patients achieving a complete response (CR).

Key Eligibility Criteria
- **Eligible** (16 years of age or older)
- Histologically confirmed pancreatic adenocarcinoma (PAC)

Treatment Administration
- **Eryaspase** (100 U/kg) will be given every two weeks (on Day 1 and 15 of each 4-week cycle) intravenously (IV) via a standard infusion line over approximately 30 minutes, followed by chemotherapy.
- **Chemotherapy** will be one of the following two treatment regimens, according to the previous therapy received:
  - **Gemcitabine** (900 mg/m²) i.v. (240 min) over 46 hours, followed by 2400 mg/m² bolus followed by 2400 mg/m² infused over 240 minutes, followed by 2400 mg/m² infused over 240 minutes, followed by 2400 mg/m² infused over 240 minutes.
  - **Irinotecan** (125 mg/m²) i.v. bolus followed by 2400 mg/m² infused over 46 hours.

**Primary Objectives**
- Improvement in OS compared to chemotherapy alone.

**Secondary Objectives**
- To compare progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and the disease control rate (DCR) between treatment arms.
- To evaluate the safety and tolerability of eryaspase in combination with chemotherapy versus chemotherapy alone.
- To assess the effect of eryaspase on quality of life (QoL).
- To determine the pharmacodynamics and pharmacokinetics of eryaspase.
- To assess the immunogenicity of eryaspase in terms of induction of anti-asparagine antibody and anti-eryaspase antibody.
- To evaluate the relationship of clinical outcomes with relevant biomarkers and genetic changes present at tumor tissues and blood samples.

**Statistical Plan**
- Patients are enrolled in a two-arm (1:2) randomization scheme in combination with chemotherapy or placebo.
- Treatment scheduled for up to 6 months, and the study will be based on the enrollment of approximately 300 patients.
- There will be a proportional limit-stratified analysis built into the study, when appropriate. This will help with the planning of additional effective patients.
- The key efficacy outcome in the primary analysis will be OS measured from the date of randomization to death.
- An interim analysis will be performed at the time of 2500 patients.

**Additional Information**
- The study is sponsored by Erytech Pharma, Inc.
- Additional information for patients and their families, including a set of ethical considerations and additional support was provided by Sabine Bokemeyer.

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**Study Rationale**
- The observed morbidity rate of pancreatic cancer in the United States has continued to increase over the past three decades and is one of the leading causes of cancer-related deaths by 2035 if screening and treatment options are not implemented.
- Pancreatic adenocarcinoma (PAC) is characterized by extensive reprogramming of cellular metabolism, such as constitutive expression of KRAS signaling and adaptation of angiogenesis and resistance to the microenvironment. Perturbations of these pathways are associated with resistance to chemotherapy and/or immunotherapy.

**Study Design**

**Study Objectives**

**Primary Objectives**
- **Eryaspase** (100 U/kg) will be given every two weeks (on Day 1 and 15 of each 4-week cycle) intravenously (IV) via a standard infusion line over approximately 30 minutes, followed by chemotherapy.
- **Chemotherapy** will be one of the following two treatment regimens, according to the previous therapy received:
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**Secondary Objectives**
- To compare progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and the disease control rate (DCR) between treatment arms.
- To evaluate the safety and tolerability of eryaspase in combination with chemotherapy versus chemotherapy alone.
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**Key Criteria**
- **Eryaspase** can be a well-investigational drug product eryaspase. Though inconclusive, this study left the possibility that a safer form of ASNase could be generated and a selected dose for Phase 2 would have needed to be below the expected biologically effective range. In addition, in Phase 1 study, pegylated ASNase (Oncaspar) showed promising anti-tumor activity against human pancreatic tumor cell lines.