Population Pharmacokinetics of Eryaspase in Patients with Acute Lymphoblastic Leukemia or Pancreatic Adenocarcinoma

Frank Hoke[1], Kara Schmelzer[2], Jianping Zhang[2],
Philip Lorenzi[3], Iman El Hariry[1]

[1]Erytech Pharma, Inc., [2]Parexel Intl, [3]MD Anderson Cancer Center

62nd ASH Annual Meeting and Exposition, December 5-8, 2020

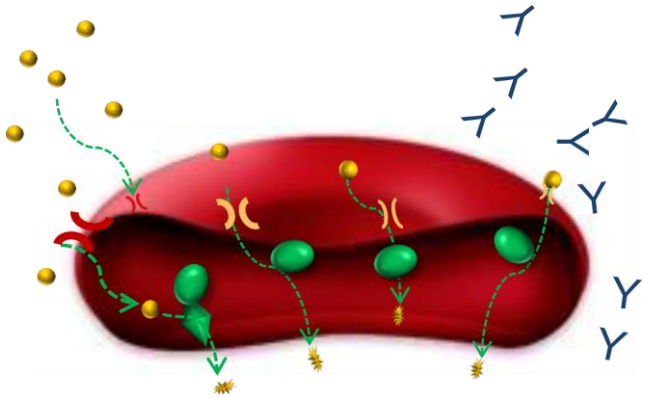
Abstract 2799

Disclosures

- **Hoke:** *Erytech:* Current Employment.
- **Lorenzi:** *Precision Pathways:* Consultancy.
- **El-Hariry:** *Erytech:* Current Employment.

Eryaspase Background

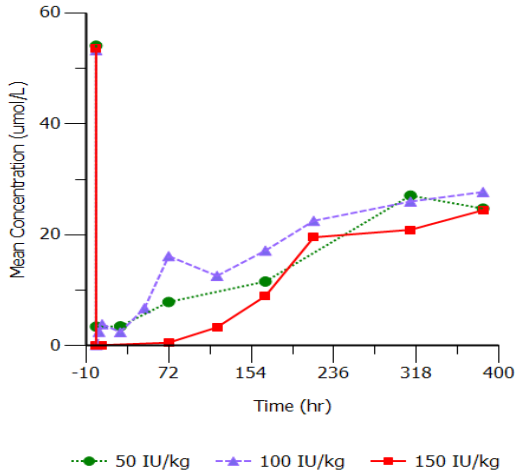
- Asparaginase
- Asparagine and glutamine
- Degradation products
- Antibody



Prolonged activity
Reduced toxicity

- Asparaginase has been an integral component in acute lymphoblastic leukemia (ALL) treatment for decades[1]
- Eryaspase is asparaginase (ASNase) encapsulated in red blood cells[2]
- Eryaspase is currently being investigated in ALL and Pancreatic Cancer[3,4]

Asparagine profile following single infusion[5]



1. Cecconello, D. K., et al. Hematol Transfus Cell Ther 2020;42(3):275-82
2. Thomas, X., et al. Int J Hematol Oncol 2016;5(1):11-25
3. Hunault-Berger, M., et al. Am J Hematol 2015;90(9):811-8
4. Hammel, P., et al. Eur J Cancer 2020;124(91-101
5. Walker, A, et al. AACR 2018

Population Pharmacokinetic Analysis Objectives

The primary objectives were:

- To develop a population pharmacokinetic (Pop PK) model following single and multiple IV infusions in a pooled population
- To estimate the Pop PK parameters and associated inter-subject variability and residual error
- To identify significant covariates that impact the PK variability of eryaspase
- To explore the impact of immunogenicity, (*i.e.,* presence of anti-drug antibodies [ADA]), on the clearance of eryaspase

Four Studies in the Pop PK Analysis

GRASPALL 2012-09[1] A phase 1 study of eryaspase in combination with the CALGB regimen in the treatment of adult patients with ALL/LBL	GRASPA 50, 100 and 150 U/kg was administered at Day 4 of induction, Days 15 and 43 of early intensification	Male or female patients, 18 years of age or older with a diagnosis of ALL/LBL N = 24
GRASPALL/GRAALL SA2-2008[2] An escalating-dose Phase 2a study of eryaspase in elderly patients with Ph- ALL, aged 55 years and above	Two infusions at escalating doses: 50, 100, 150 U/kg	Newly diagnosed ALL Ph- patients aged 55 years and above N = 30
GRASPALL 2009-06[3] Phase 2/3 study evaluating efficacy and safety of GRASPA versus reference ASNase in patients with first recurrence of Ph- ALL	Infusion of 150 U/kg every 2-3 weeks in combination with COOPRALL regimen	Patients 1 – 55 years old, with relapsed ALL Ph-, with or without known hypersensitivity to ASNase. N = 80
GRASPANC 2013-03[4] Phase 2 study exploring efficacy and safety of eryaspase with gemcitabine or FOLFOX4 in 2nd-line therapy for patients with metastatic pancreatic carcinoma	Infusion of 100 U/kg administered every 2 weeks	Adults 18 years or older with advanced or metastatic pancreatic adenocarcinoma N = 141

1. NCT01910428, L-asparaginase Encapsulated in Red Blood Cells (Eryaspase) for Treatment of Adult Patients With ALL or LBL
2. Hunault-Berger, M., et al. Am J Hematol 2015;90(9):811-8
3. Bertrand, Y., et al. Journal of Clinical Oncology 2015;33(15_suppl):7004
4. Hammel, P., et al. Eur J Cancer 2020;124(91-101

Covariates Evaluated in Pop PK Analysis

- Baseline body size (body weight, body surface area)
- Subject demographics (age, gender)
- Formulation (native vs recombinant ASNase)
- Patients with ALL vs patients with metastatic pancreatic cancer

Pop PK Analysis Methods

- Nonlinear Mixed Effects Modeling (NONMEM, Version VII, ICON Development Solutions)
- Diagnostic graphics, exploratory analyses, and post-processing of NONMEM output were performed using the R software (Version 3.5.2)

Summary of Patient Populations

- The Pop PK dataset consisted of 162 patients
- Patient age range from 2 to 84 years
- Body weight ranged from 12 to 139 kg
- 62% of patients were male and 38% female

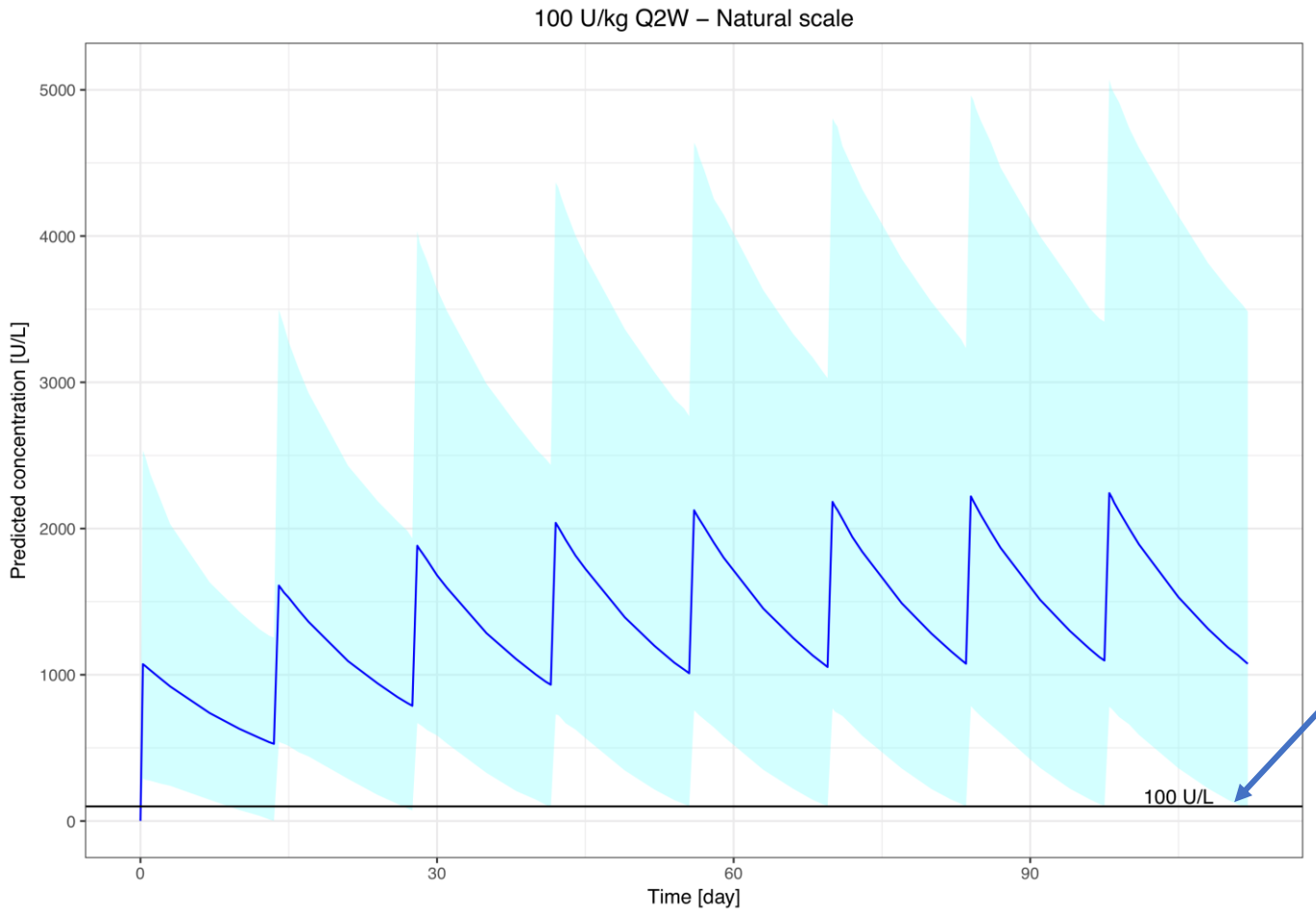
Pop PK Modeling Results

- Data best described using a one compartment model
- RBCs have a life-span of ~100-120 days
- Model uses first order elimination for simplicity
- Allows estimation of a half-life ($t_{1/2}$)

Final Population PK Parameters Estimates

Description	Estimate	%RSE
Clearance (CL): TVCL= θ1*((WEIGHT/70*θ3))		
Population Mean	0.29 L/day	4.7
WEIGHT~CL	0.71	14.3
Volume of Distribution (V): TVV = θ(2)*(WEIGHT/70)*θ(4))		
Population Mean	6.12 L	4.6
WEIGHT~V	0.815	7.3
Inter-individual variability (IIV) for CL	0.214	14.46
Inter-individual variability (IIV) for V	0.126	26.24
Proportional Error	0.076 (27.5%)	18.85
Additive Error	30500 (174)	27.9

Simulation of 100 U/kg every 2 weeks



Target for Clinical Activity

Conclusions

- Eryaspase PK adequately described by a one-compartment model with first order elimination.
- The clearance (CL) and volume of distribution (V) were estimated to be 0.29 L/hr and 6.12 L, respectively, and they both increased with the body weight.
- Immunogenicity in the form of nAb may increase clearance of the drug; however, the variability in the nAb signal, the small number of subjects with available data, and differences in sampling times do not reveal a consistent effect.
- There was no apparent difference in the PK between patients with pancreatic cancer and ALL, nor between patients receiving native vs recombinant ASNase
- The simulations demonstrate that 100 U/kg dosed every two weeks would achieve the clinical activity target levels of 100 U/L at trough in the majority of patients