A Phase 1 Study Of Eryaspase (L-Asparaginase Encapsulated In Red Blood Cells) In Combination With Induction And Consolidation Chemotherapy For Adult Patients With Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) (NCT01910428)

A. Walker MD [1], R. Klisovic MD [2], D. Rizzieri MD [3], A. Emadi MD [4], J.E. Kolitz MD [5], W Stock MD [6], D. Clancy [7], F. Hoke [7], H. Youssoufian [7], A. Hamm [8], I. El Hariry MD [7], R.A. Larson MD [6]

[1] The Ohio State University, [2] Emory University, [3] Duke University, [4] University of Maryland, [5] Monter Cancer Center of Northwell Health System, [6] University of Chicago, Chicago, IL, [7] Erytech Pharma, Cambridge, MA, [8] Cytel Inc, Cambridge, MA

Background

- L-asparaginase (ASNase) is an integral component of multi-agent chemotherapy regimens used during induction and consolidation phases for the treatment of acute lymphoblastic leukemia (ALL).
- The clinical benefit of integrating ASNase in ALL treatment in adult ALL patients is partially offset by the development of frequent and potentially severe adverse reactions, which occur in 10-35% of patients, especially hypersensitivity reactions, coagulopathy, hepatic and pancreatic toxicities.[1,2]
- Eryaspase is dispersion for infusion of E-coli-derived ASNase encapsulated in homologous red blood cells (RBCs) (**Figure 1**). RBCs are considered the most biocompatible carrier systems for various agents. The encapsulation of ASNase in RBCs was shown to reduce toxicity associated with the parent ASNase and silent inactivation, while prolonging its activity.[3,4]
- The mode of action is via elimination of the circulating asparagine (ASN) pool that is actively transported into erythrocytes where it is hydrolyzed by the encapsulated ASNase into aspartic acid and ammonium (**Figure 2**).
- Eryaspase is well tolerated with an acceptable safety profile:
  - Approximately 300 patients treated to date, including patients with ALL, AML, and pancreatic cancer.
  - Treatments have demonstrated a reduction in hypersensitivity reactions with ASNase, hepatic and pancreatic toxicities, and a sustained enzyme activity.
  - In a Phase 2/3 study, encouraging clinical activity was demonstrated, with improved complete remission rate compared to native ASNase enzyme, in patients with relapsed or refractory ALL
  - In a Phase 2b study in second line pancreatic cancer an overall and progression free survival benefit was demonstrated.

Figure 1. ERYCAPS Platform Encapsulation Process

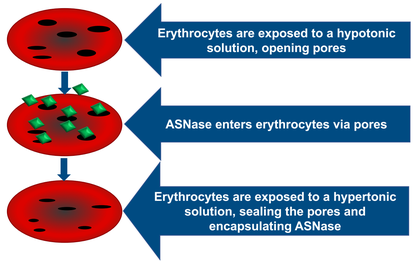
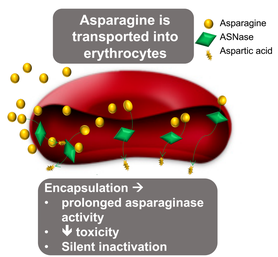


Figure 2. Encapsulated Asparaginase in RBCs



Study Design

Phase 1: Multicenter, Open Label, Dose-Finding Study

Adults with frontline Philadelphia chromosome-negative ALL (n = 14) → **INDUCTION (4 WKS) Modified CALGB 8811 + Eryaspase on Day 4** → **CONSOLIDATION Modified CALGB 8811 + Eryaspase on Day 15 and 43**

Study Design

- This was a US, multicenter, open label, Phase 1b trial, evaluating the maximum tolerated dose (MTD), the recommended Phase 2 dose (RP2D), the overall safety according to NCI-CTCAE (Version 4), and the pharmacokinetic (PK) / pharmacodynamic (PD) profile of eryaspase, as well as the complete response (CR) rate following induction and consolidation phases of the study
- The study enrolled male or female patients ≥18 years old (no upper limit on age) with a diagnosis of ALL or lymphoblastic lymphoma (LBL) who had received no more than one prior treatment for ALL/LBL, and had an ECOG performance status 0–2.

Dosing Schedule

- Patients received the modified CALGB 8811 regimen for a total of 24 months. Eryaspase was administered on Day 4 of Induction and Days 15 and 43 of both consolidation courses in place of pegylated ASNase.
- Patients were treated in one of 3 dose cohorts of eryaspase (50, 100, and 150 U/kg). Dose escalation followed a 3+3 design. A Steering Committee reviewed the safety information and recommended dose escalation following completion of each dose cohort. The MTD was defined as the highest dose level at which <1/3 of at least 6 pts experienced a dose-limiting toxicity (DLT) during induction.

Determination of PK and PD parameters

- Pharmacokinetic (PK) analysis was performed using Phoenix® WinNonlin® 6.3 (Certara, L.P., 1699 S. Hanley Road, St Louis, MO 63144 USA). A model for intravenous infusion using a linear up/log down calculation method was employed for the non-compartmental analysis.
- PK parameters included maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), clearance (CL), volume of distribution (V_d) and terminal half-life ($t_{1/2}$)
- AUC (0–∞) following the first infusion was used is the estimation of CL and V_d
- The pharmacodynamic variables were concentration of asparagine, aspartic acid, glutamine and glutamic acid.

Safety

Table 2: Safety Profile – Overall Summary

AE Category, n	50 U/kg		100 U/kg		150 U/kg		Total	
	Patients N=3	Events N	Patients N=6	Events N	Patients N=4	Events N	Patients N=13	Events N
TEAE	3	111	6	189	4	33	13 (100)	333 (100)
Related TEAE	3	40	6	138	2	5	11 (84.6)	183 (55)
Grade 3 or 4 TEAE	3	38	6	55	4	24	13 (100)	117 (35)
Related grade 3 or 4 TEAE	3	17	6	38	1	1	10 (76.9)	56 (17)
TESAE	2	2	3	3	4	7	9 (69.2)	12 (4)
Related TESAE	0	0	0	0	1	1	1 (7.69)	1 (0)
Fatal outcome#	0	0	0	0	1	1	1 (7.69)	1 (0)
TEAE leading to treatment discontinuation	1	1	0	0	0	0	1 (7.69)	1 (0)

TEAE: treatment-emergent adverse events; TESAE: treatment-emergent serious adverse events
#: the cause of death was septic shock, and was considered unrelated to study drug

Table 3: Related Grade 3/4 Adverse Events by Dose Group and Preferred Term

Preferred Term, n (%)	50 IU/kg N=3	100 IU/kg N=6	150 IU/kg N=4	Total N=13 (%)
Any G3 or 4 related events	3 (100)	6 (100)	1 (25.0)	10 (77)
Thrombocytopenia	2	5	0	7 (54)
Leukopenia	1	4	0	5 (39)
Lymphopenia	2	3	0	5 (39)
Neutropenia	2	3	0	5 (39)
Anemia	0	3	0	3 (23)
Febrile Neutropenia	0	1	1	2 (15)
Hyperbilirubinemia	1	0	0	1 (8)
Hypertriglyceridemia	0	1	0	1 (8)
Hyponatremia	0	1	0	1 (8)

Pharmacokinetics

Figure 3. Mean Concentration Time Profile for Blood Asparaginase Following 50, 100 and 150 U/kg Eryaspase

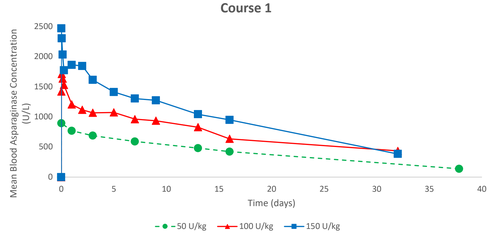


Figure 4. Blood and Plasma Asparaginase following 100 and 150 U/kg Eryaspase

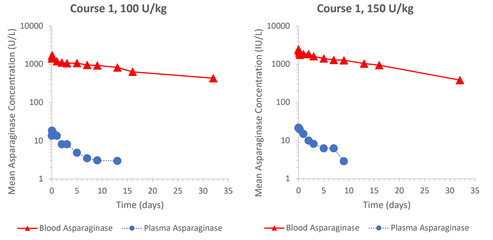
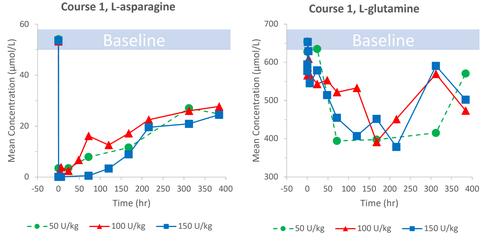


Figure 5. Asparagine and Glutamine Time Course following 50, 100, and 150 U/kg Eryaspase



Results

Table 1: Baseline Demographic Characteristics

	Eryaspase 50 U/Kg dose level N=3	Eryaspase 100 U/Kg dose level N=6	Eryaspase 150 U/Kg dose level N=4
Age (years)			
Mean (SD)	55.9 (3.0)	53.2 (17.8)	41.0 (19.8)
Median	55.2	56.4	39.1
Range	53.3–59.2	20.7–71.2	23.9–61.9
Age groups			
< 40 years	0	1	2
≥ 40 years	3	5	2
Gender			
Male	1	6	3
Female	2	0	1
Immunophenotype			
B	3	3	3
T	0	2	1
Bone marrow blasts (%)			
Mean (SD)	79.3 (14.4)	84.0 (9.4)	65.0 (33.7)
Median	85.0	84.5	67.0
Range	63.0–90.0	70.0–97.0	31.0-95.0

Pharmacokinetics

Table 4: Mean (SD) Pharmacokinetic Parameters following 50, 100, and 150 U/kg Eryaspase

Treatment (N=Sample Size)	C_{max} (U/L)	Half-Life (Days)	Clearance (mL/hr/kg)	Volume of Distribution (L/kg)
50 U/kg (N=3)	896.0 (219.9)	15.93 (10.23)	0.13 (0.09)	0.06 (0.02)
100 U/kg (N=6)	1775 (404.5)	20.21 (9.629)	0.15 (0.07)	0.09 (0.02)
150 U/kg (N=4)	2545 (672.2)	18.27 (13.84)	0.14 (0.05)	0.08 (0.03)

- C_{max} increases in proportion to dose
- Terminal $t_{1/2}$ of 16-20 days is consistent with previous studies
- Low clearance representative of slow elimination
- Volume of distribution consistent with blood volume

Results

Maximum Tolerated Dose and Recommended Phase 2 Dose

- Fourteen patients were enrolled but one patient was not treated, and therefore the safety population included 13 patients
- Median age was 55 years (range, 21–71)
- Cohorts enrolled n=3 at 50; n=6 at 100, and n=4 at 150 U/kg of eryaspase
- Treatment was generally well tolerated; the main adverse events were myelosuppression, consistent with ALL disease and myelosuppressive chemotherapy agents
- One DLT (Grade 3 hypertriglyceridemia) occurred at the 100 U/kg dose level. Thus, 3 additional patients were enrolled into the 100 U/kg cohort
- No other DLTs were identified, and no DLTs were reported at 150 U/kg dose level
- There was no further dose-escalation as PK and PD suggested no differences between the 100 and 150 U/kg dose levels.

Dose Level 1: 50 U/kg of eryaspase N=3 (No DLTs) → **Dose Level 2:** 100 U/kg of eryaspase N=3 (1 DLT) → **Dose Level 2:** 100 U/kg of eryaspase N=3 (No DLTs) → **Dose Level 3:** 150 U/kg of eryaspase N=4 (No DLTs)

Table 5: Response by Dose Group After Induction

Status, n	50 U/kg (N=3)	100 U/kg (N=6)	150 U/kg (N=4)
Complete Remission	3	3	2
Complete Remission with Incomplete Recovery	0	1	1
Partial Remission	0	1	1
Refractory Disease	0	1	0

Conclusions and Future Directions

- Eryaspase was well-tolerated when combined with the modified CALGB 8811 chemotherapy regimen for frontline treatment of adults with ALL.
- The safety profile was overall acceptable, with no hepatic or pancreatic toxicities observed. This is consistent with other safety profiles reported in the eryaspase program.[5]
- The terminal $t_{1/2}$ of 16-20 days provides prolonged duration of activity and supports every two weeks dosing.
- The MTD was not reached at the highest dose tested (150 U/Kg). Based on the pharmacokinetics and pharmacodynamics analyses, the recommended dose for further testing was defined as 100 U/Kg in combination with chemotherapy.
- This dose level is consistent with the outcome of the Phase 2a European study which evaluated the MTD of eryaspase in combination with chemotherapy in patients above 55 years of age who presented with ALL in the front line setting.[5]
- A pivotal study investigating the safety and efficacy of eryaspase in combination with chemotherapy for the treatment of adults with ALL is planned.

References:

1. Burke MJ. *Future Oncol.* (2014).
2. Andrade AF, Borges KS and Silveira VS. *Clinical Medicine Insights: Oncology* 2014:8 95–100.
3. Godfrin Y, Horand F, Franco R, et al. *Expert Opin. Biol. Ther.* (2012) 12(1):127-133.
4. Godfrin Y and Bax BE. *Drugs of the Future* 2012, 37(4): 263-272.
5. Hunault-Berger M, Leguay T, Huguet F et al. *Am. J. Hematol.* 2015 Sept; 90:811–818.

Acknowledgements: The authors wish to express their sincere thanks to the patients and their families, all investigators and their research staff, the CRO (CATO) and lab vendors, Richard Kay (consultant statistician), Adam Hamm (statistician, Cytel), Dan Clancy (Study Team Leader at Erytech), and the entire project team. Editorial assistance was provided by Cadence Research & Consulting, funded by Erytech Pharma.

Disclosures: I. El-Hariry is the Chief Medical Officer of Erytech Pharma; D. Clancy is the Study Team Leader at Erytech Pharma; H. Youssoufian is the Medical Monitor at Erytech Pharma; F. Hoke is the Clinical Pharmacology Leader at Erytech Pharma; A. Hamm is Head of Biostatistics at Cytel, Inc; R.A. Larson has received consulting fees and clinical trial research support from Erytech Pharma.

Study sponsored by: Erytech Pharma

Corresponding author: R.A. Larson