Expert Review in Acute Lymphoblastic Leukemia (ALL): Asparaginase Therapy and the Role for Therapeutic Drug Monitoring

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Asparaginase and ALL Treatment

- Asparaginases are accepted as a key component in ALL treatment protocols[1]
- Used for remission induction, and consolidation (intensification) in all pediatric regimens for ALL[1]
- Maximum benefit with asparaginase seen when patients receive intensive asparaginase treatment through optimal dosing and treatment schedules resulting in sustained depletion of asparagine[2,3]
- A 2011 consensus article (including clinicians from Europe and the United States) stated that an asparaginase treatment schedule that ensures an NSAA level of at least 100 IU/L (0.1 IU/mL) is essential to maintain adequate asparagine depletion[1]

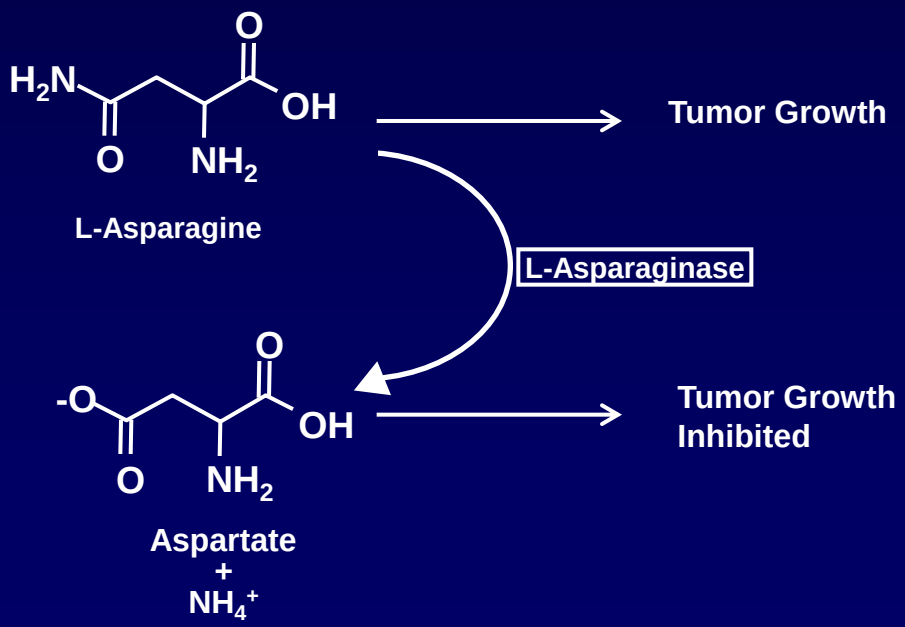
NSAA, nadir serum asparaginase activity

1. Pieters R, et al. *Cancer.* 2011;117(2):238-249. 2. Silverman LB, et al. *Blood.* 2001;97(5):1211-1218. 3. Ogawa C, et al. *Blood.* 2005;106(11):Abstract 878.

Mechanism of Action of Asparaginase

Leukemic lymphoblasts have very low levels of **L-asparagine synthetase,** and thus rely on asparagine present in serum for survival

L-**a**sparaginase catalyses the hydrolysis of **L-asparagine to L-aspartic** acid and ammonia



Narta UK, et al. *Crit Rev Oncol Hematol.* 2007;61(3):208-221.

Types of Approved Asparaginases

	Bacterial Origin	Route	Comments
L-asparaginase*	*Escherichia coli*	IM	Antilymphoma activity identified in guinea pig serum (1953)
PEGaspargase	*E coli*	IM, IV	PEGylation → less immunogenicity, longer half-life
Erwinia chrysanthemi	*Erwinia*	IM	Reduced cross-immunogenicity with *E coli* ASPs

*No longer available in the United States (as of December 2012)

- All types of asparaginase share the same mode of action in terms of depletion of asparagine[1]
- Differences in the pharmacokinetic properties of the asparaginases mean that the 3 agents are not interchangeable at the same dose and frequency[1,2]

1. Pieters R, et al. *Cancer.* 2011;117(2):238-249. 2. Asselin BL, et al. *J Clin Oncol.* 1993;11(9):1780-1786.

Asparaginase Hypersensitivity

- As with all large proteins, asparaginases can induce a host response, stimulating development of antiasparaginase antibodies[1]
- Antibodies can affect asparaginase activity and are commonly associated with an overt clinical reaction[2]
- However, in some patients the presence of antiasparaginase antibodies does not lead to clinical signs and symptoms, yet may still affect asparaginase activity[2]
- Approximately 30% of patients experience hypersensitivity reactions after repeated dose of *E coli*–derived asparaginases

Clinical hypersensitivity (symptomatic)

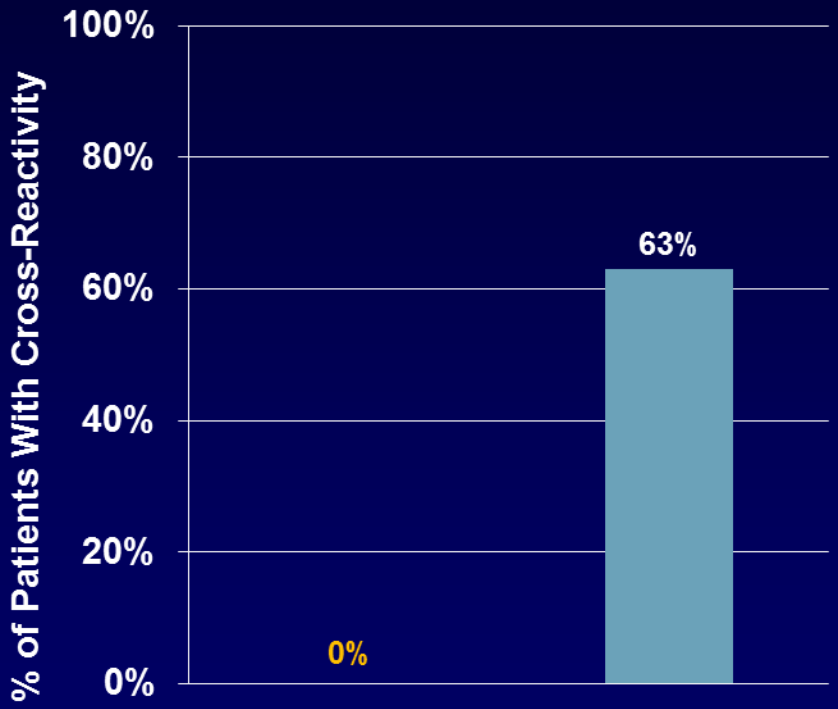
- Clinical allergic reactions
- One of the most significant toxicities of asparaginase therapy that limits its further use[2]

Subclinical hypersensitivity (asymptomatic) (silent activation)

- Development of antiasparaginase antibodies may cause inactivation of asparaginase in the absence of clinical signs and symptoms of allergy[3]
- Currently, can only be identified by laboratory tests

1. Rizzari C et al. *Curr Opin Oncol.* 2013;25(Suppl 1):S1-S9. 2. Raetz EA, et al. *J Pediatr Hematol Oncol* 2010;32(7):554-563. 3. Pieters R, et al. *Cancer.* 2011;117(2):238-249.

Cross-Reactivity Between Asparaginases



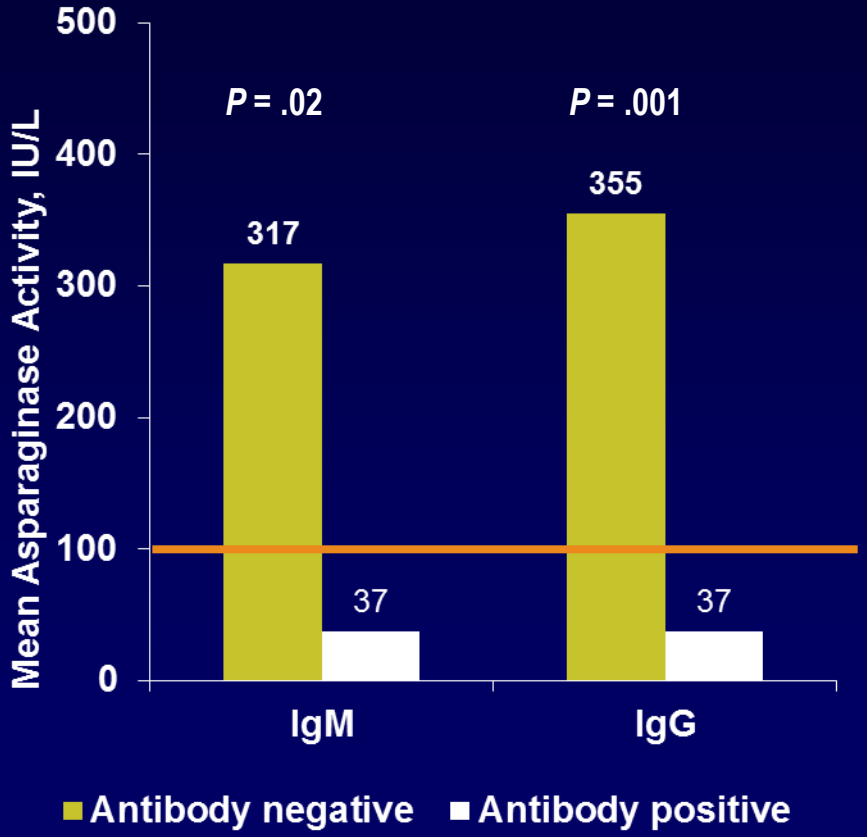
- Patients with ALL and hypersensitivity reactions and/or antibodies to native *E coli* asparaginase during re-induction (n = 16)
- 63% (10/16) showed cross-reactivity to PEGasparaginase
- No cross-reactivity to *E chrysanthemi* asparaginase

Erwinia chrysanthemi asparaginase
PEGasparaginase

PEG, pegylated

Zalewska-Szewczyk B, et al. *Clin Exp Med.* 2009;9(2):113-116.

Subclinical Hypersensitivity to Asparaginase and Asparaginase Activity[1]



Recommended level of asparaginase reflecting effective depletion of asparagine (≥100 IU/L) denoted by the orange line.

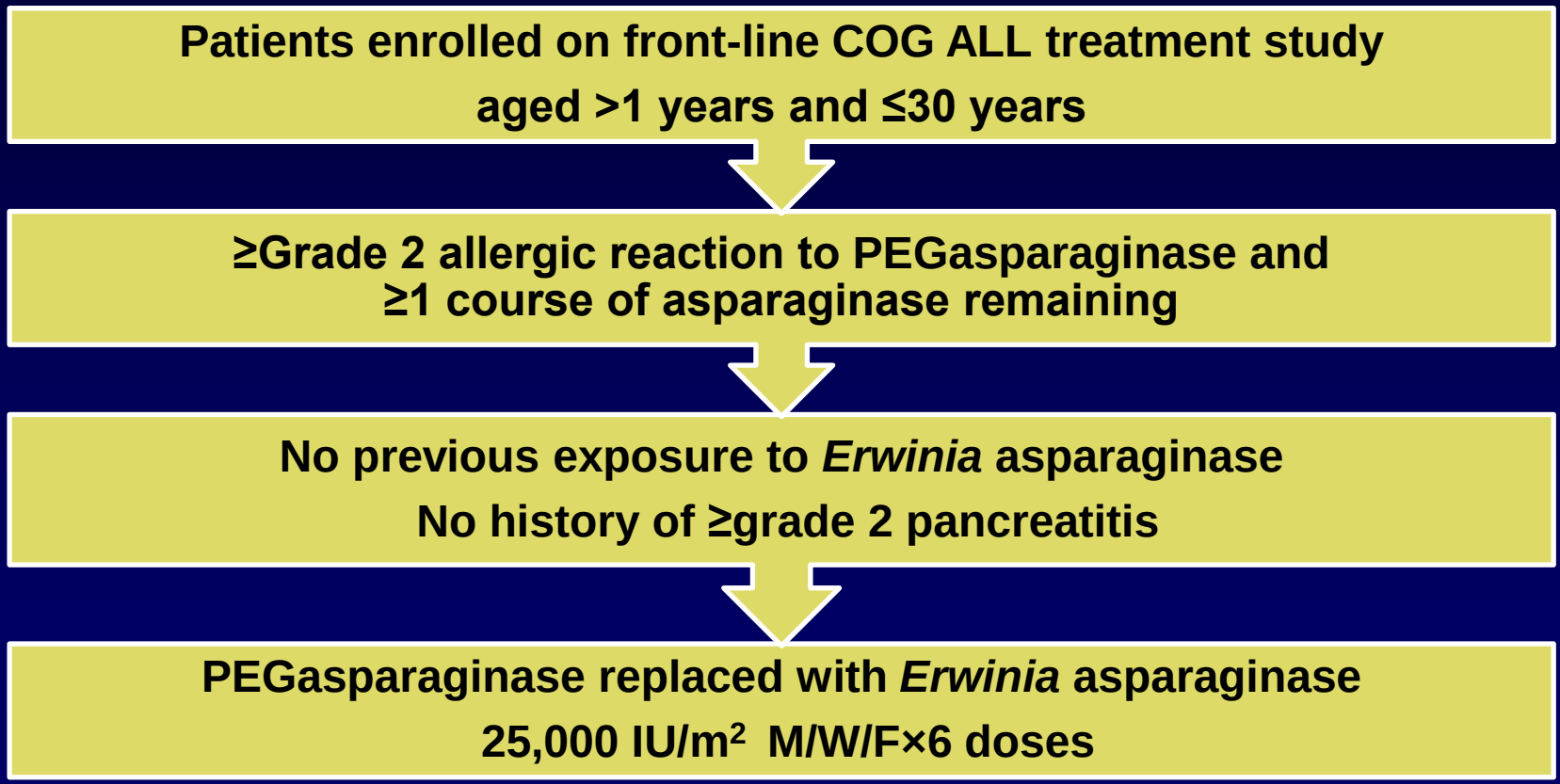
- Children with newly diagnosed ALL (n = 47)
- Subclinical hypersensitivity (presence of antiasparaginase antibodies and no symptoms of hypersensitivity) following re-induction treatment with native *E coli* asparaginase led to a reduction in asparaginase activity of almost 90%
- Mean asparaginase activity was below 100 IU/L in antibody-positive children

Zalewska-Szewczyk B, et al. *Leuk Lymphoma.* 2007;48(5):931-936.

Erwinia Asparaginase Achieves Therapeutic Activity After PEGaspargase Allergy: A Report from the Children's Oncology Group

Salzer WL, et al. *Blood*. 2013;122(4):507-514.

AALL07P2 Study: Study Design



COG, Children's Oncology Group; M/W/F, Monday/Wednesday/Friday

Salzer WL, et al. *Blood.* 2013;122(4):507-514.

AALL07P2 Study: Objectives

Primary Objectives

- To determine if 48-hour NSAA is ≥100 IU/L in at least 70% of patients
- To determine the frequency of asparaginase-related toxicities

Secondary Objectives

- To determine the 72-hour NSAA
- To determine if plasma asparagine is adequately depleted predose 6

Salzer WL, et al. *Blood.* 2013;122(4):507-514.

AALL07P2 Study: Baseline Characteristics and Demographics

- 59 patients enrolled into the study from February 2008 to April 2010
- All patients who enrolled in the study and received at least 1 dose of study drug were included in safety analyses (58 patients)
- The study population was predominantly male (58.6%) and white (77.6%)
- The study population had a mean age of 9.7 years with a range of 2-18 years

Characteristic	(N = 58)
Gender, n (%)	
Males	34 (58.6)
Females	24 (41.4)
Age, mean (range), years	9.7 (2-18)
Race, n (%)	
White	45 (77.6)
Black or African American	6 (10.3)
Other	7 (12.1)
Primary Disease, n (%)	
Precursor B-cell ALL	51 (88)
T-cell ALL	7 (12)

Salzer WL, et al. *Blood.* 2013;122(4):507-514.

AALL07P2 Study: Efficacy Results

Summary Statistics for 48-hour and 72-hour NSAA Data for Each Course of Therapy

		NSAA ≥0.10 IU/mL			
		Patients		Samples	
Trough Time, hours	Cycle	No.	%	No.	%
48	1	50	100	151	97.4
48	2	23	92.0	26	92.9
48	3	28	96.6	36	97.3
48	4	16	100	23	95.8
48	≥5	10	83.3	16	84.2
48	All	52	100	252	95.8
72	1	49	98.0	73	84.9
72	2	15	78.9	15	78.9
72	3	16	88.9	16	88.9
72	4	6	85.7	6	85.7
72	≥5	10	90.9	15	83.3
72	All	52	100	125	84.5

Salzer WL, et al. *Blood.* 2013;122(4):507-514.

AALL07P2: Targeted Toxicities

Toxicity	N	%
Allergy	6	10.9
Grade 2	4	
Grade 3	2	
Hyperglycemia	6	10.9
Grade 1	3	
Grade 2	2	
Grade 3	1	
Pancreatitis	1	1.8
Grade 1	1	
Hemorrhage/thrombosis	0	0
Grade 3-4	0	

Salzer WL, et al. *Blood.* 2013;122(4):507-514.

Conclusions

- ***Erwinia*** **asparaginase at a dose of 25,000 IU/m^2 for 6 doses IM M/W/F can be safely substituted for each dose of pegaspargase in the event of an allergy**
- ***Erwinia*** **asparaginase is well-tolerated**

Postinduction Dexamethasone and Individualized Dosing of *E coli* L-Asparaginase Each Improve Outcome of Children and Adolescents With Newly Diagnosed Acute Lymphoblastic Leukemia: Results From a Randomized Study – Dana-Farber Cancer Institute Consortium Protocol 00-01

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Protocol 00-01: Objectives

- To determine the relative toxicity, tolerability, and efficacy of:
  1. Dexamethasone and prednisone administered during postinduction treatment
  2. Weekly IM *E coli* L-asparaginase administered as the standard fixed dose (FD) and a pharmokinetically guided individualized dose (ID)

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Protocol 00-01: Therapy

Induction Phase (4 weeks)

↓

CNS Therapy (3 weeks)

↓

Intensification Phase (30 weeks)

Vincristine 2 mg/m^2 D1; 6-MP 50 mg/m^2 QD x 14 days;
MTX 30 mg/m^2 (1 mg/kg if 0.6 m^2) IV or IM 1x/week;

Corticosteroid, Randomized:

Dexamethasone 6 mg/m^2 per day, divided into 2 doses
D1-5 of each 3 week cycle
OR
Prednisone 40 mg/m^2 per day divided into 2 doses

***E coli* asparaginase Randomized:**

Fixed-dosing: 25,000 IU/m^2 IM, once per week x 30 weeks
OR
Individualized dosing: 12,500 IU/m^2 IM (starting dose), once per week x 30 weeks

↓

Continuation Phase (74 weeks)

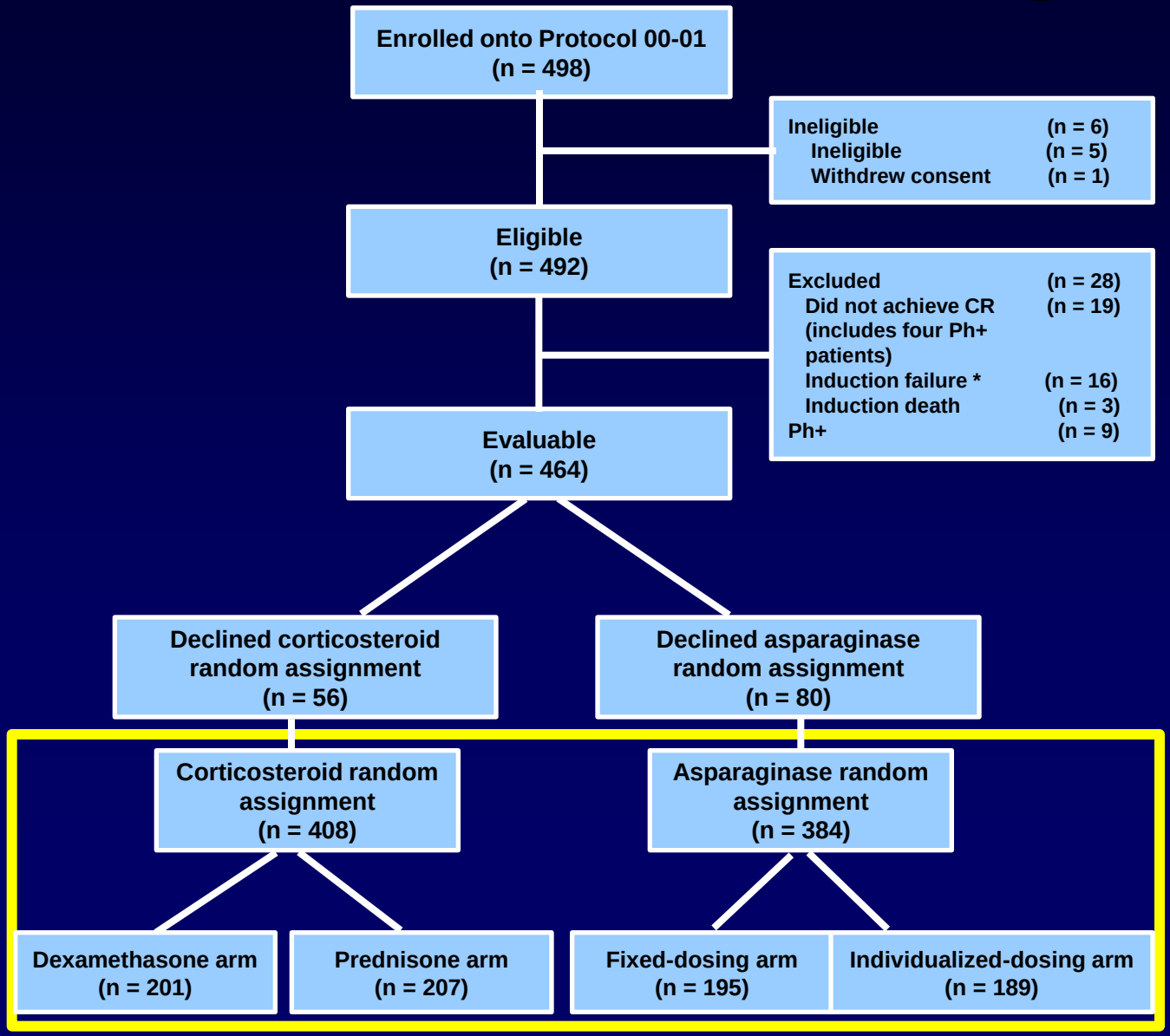
Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Asparaginase Individualized Dosing by NSAA Levels

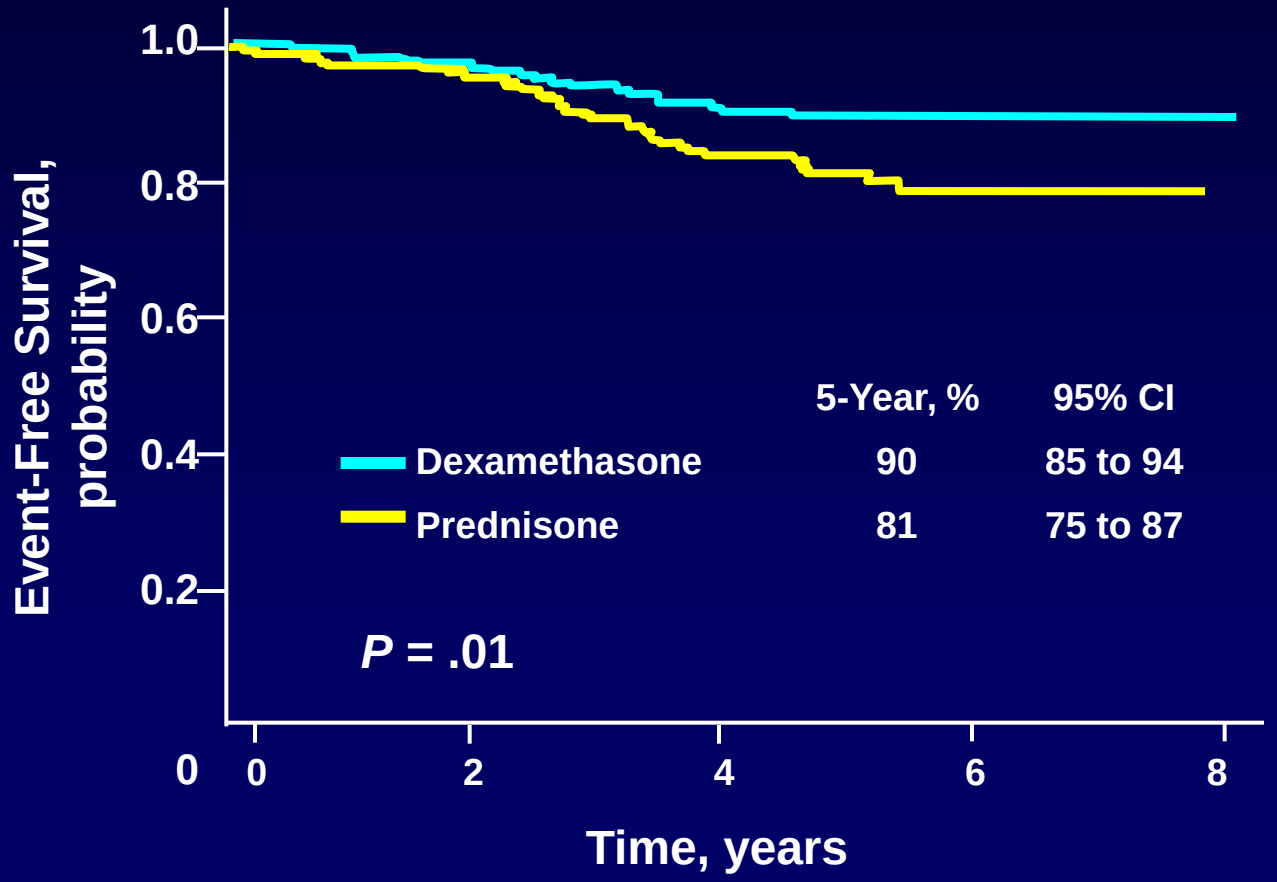
NSAA (IU/mL)	Change in Subsequent Dosing
<0.025	Increase by 80%; send urgent *E coli* asparaginase antibody
0.025 to <0.05	Increase by 60%
0.05 to <0.08	Increase by 40%
0.08 to <1.0	Increase by 20%
0.1 to <0.14	No change
0.14 to <0.20	Decrease by 20%
>0.20	Decrease by 40%

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Protocol 00-01 Flow Diagram



Event-Free Survival: Corticosteroid Randomization



CI, confidence interval

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

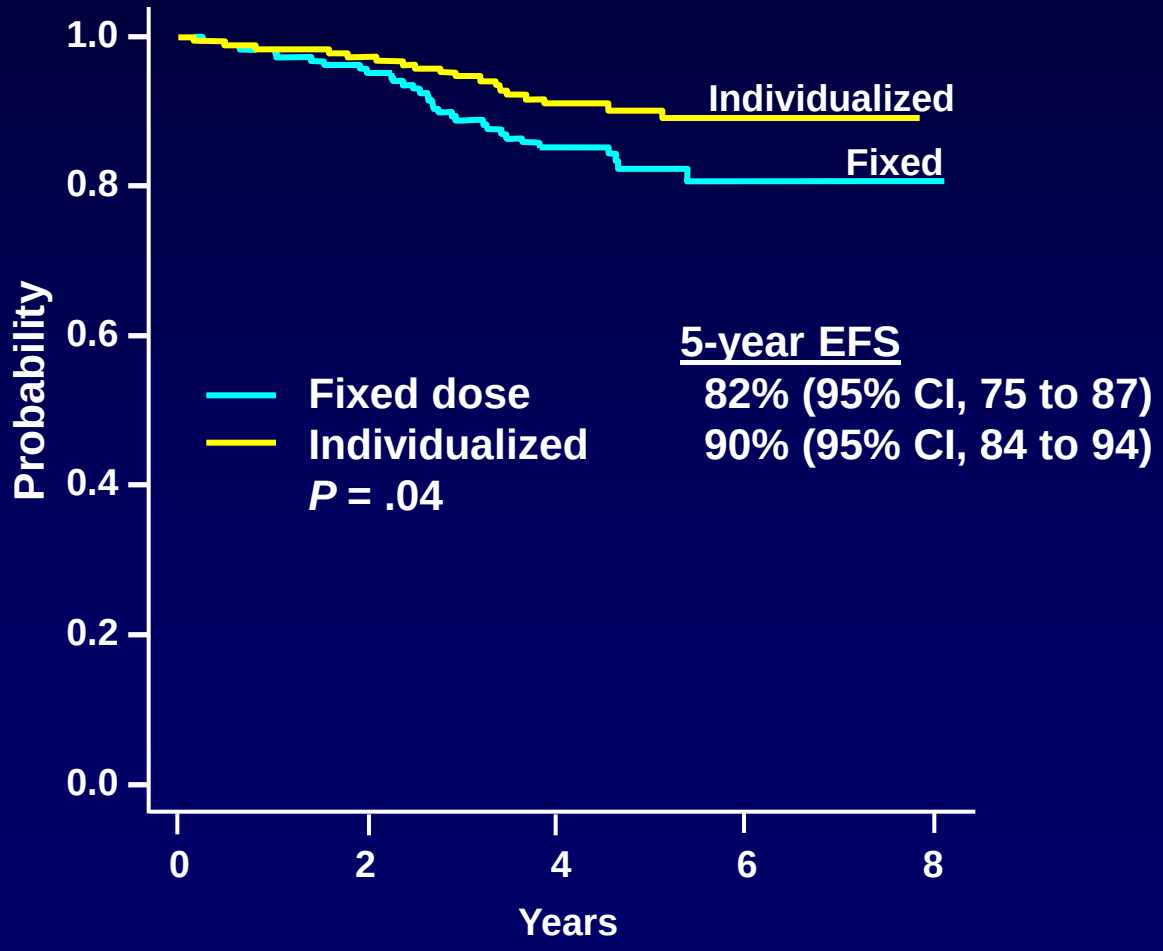
Protocol 00-01: Toxicity – Corticosteroid Randomization

	Dexamethasone	Prednisone	*P*
Osteonecrosis*	23%	5%	.02
Bone fracture*	29%	10%	.06
Risk of infection	19%	11%	.03

*In patients 10-18 years of age

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Protocol 00-01: EFS Asparaginase Randomization



Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Protocol 00-01: Toxicity Asparaginase Randomization

Characteristic	Fixed Dose n	Fixed Dose %	Individualized Dose n	Individualized Dose %	*P*
Patients randomly assigned	195		189		
EC-asparaginase dose, IU/m^2	25,000		17,500		
Any toxicity	63	32	59	31	.83
EC-asparaginase clinical allergy	39	20	40	21	.80
Pancreatitis	10	5	12	6	.66
Thrombosis	16	8	13	7	.70
Completed ≥25 week asparaginase	172	88	164	86	.76

- No difference in frequency of asparaginase-associated toxicity including clinical allergy, pancreatitis, or thrombosis

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Protocol 00-01: Reasons for Change in Asparaginase Preparation

	Fixed Dose		Individualized Dose		
	n	%	n	%	*P*
Asparaginase preparation changed	43	22	64	34	.01
EC-asparaginase clinical allergy	39	20	39	21	
Silent inactivation	N/A	--	19	10	
Other	4	2	6	3	

- No difference in percentage of patients who switched to another asparaginase preparation due to clinical allergy
- 10% of patients on the individualized dose arm switched due to silent inactivation

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

EFS by Subsets

	Fixed Dose	Individualized Dose	
	%	%	*P*
5-year EFS of other subsets, &			
Maximum NSAA ≥0.10 IU/mL			
EFS	85	90	
95% CI	78 to 90	83 to 95	
Maximum NSAA <0.10 IU/mL			.16
EFS	73	91	
95% CI	52 to 86	79 to 97	
Maximum NSAA <0.10 IU/mL, did not change asparaginase preparation			0.58
EFS	76	78	
95% CI	38 to 92	35 to 94	
Changed asparaginase for silent inactivation			.99
EFS	N/A	95	
95% CI		68 to 99	

Vrooman LM, et al. *J Clin Oncol.* 2013;31(9):1202-1210.

Conclusions

- **Postinduction dexamethasone and individualized dose of L-asparaginase each improved EFS in pediatric patients with newly diagnosed ALL**
- **Fixed-dose arm patients with low NSAA but no clinical allergy had 76% EFS compared to 95% in the individualized-dose arm**
- **Suggests prospective monitoring for development of silent inactivation leading to change in asparaginase formulation may improve outcomes**

A Prospective Study on Drug Monitoring of PEGasparaginase and *Erwinia* Asparaginase and Asparaginase Antibodies in Pediatric Acute Lymphoblastic Leukemia

Tong WH, et al. ***Blood.*** **2014;123(13):2026-2033.**

Overview

- This study prospectively analyzed the efficacy of prolonged courses of pegylated *E coli* asparaginase and *Erwinia* asparaginase
- Patients received 8 doses native *E coli* asparaginase (5000 IU/m^2) every 3 days during induction (DCOG ALL-10 protocol)
- PEGasparaginase (2500 IU/m^2) given every 2 weeks during intensification
  - Trough levels and asparaginase antibodies (AAAs) were measured at the beginning of intensification; weeks 2, 4, 6, 8, 10, 14, 16, 24, and 28; also 1 week after administration in weeks 3, 9, 15, and 25
  - Serum asparagine, aspartic acid, glutamine, and glutamic acid levels were measured at weeks 0, 2, 4, 14, and 24
- Patients who developed an allergy were switched to asparaginase *E chrysanthemi* (20,000 IU/m^2) administered IV 3 times weekly

Tong WH, et al. *Blood.* 2014;123(13):2026-2033.

PEGasparaginase Study Results

- 22% (20/89) of PEGasparaginase patients developed allergy
  - 90% of the reactions occurred on the 2nd dose
- 8% (7/89) showed silent inactivation
- Patients without allergy or silent inactivation showed mean trough asparaginase activity of 899 IU/L
- PEGasparaginase level was 0 in allergic patients
- All allergic patients were switched to *Erwinia* asparaginase

Tong WH, et al. *Blood.* 2014;123(13):2026-2033.

Erwinia Asparaginase Results

- 3% of patients (2 of 59) developed a clinical allergy to *Erwinia* asparaginase
  - Both had asparaginase activity level of 0
  - These patients did not receive further asparaginase therapy
- No patients had silent inactivation
- 96% of patients (55 of 57) had at least 1 *Erwinia* asparaginase level of ≥100 U/L and 100% of patients had activity level of ≥50 U/L
- In 65% of all patients, all *Erwinia* asparaginase activity levels were ≥100 U/L; 85% of patients had level ≥50 U/L
- Median trough asparaginase activity of 183 IU/L at 48 hours
- 33% (19 patients) were switched to twice weekly dosing due to high activity levels

Tong WH, et al. *Blood.* 2014;123(13):2026-2033.

Conclusions

- **Use of native *E coli* asparaginase in induction therapy leads to significant clinical allergy and silent inactiviation of PEGasparaginase in intensification**
- **Switching to *Erwinia* asparaginase in the case of allergy to or silent inactivation of PEGasparaginase is effective**
- **Close monitoring is necessary to ensure adequate drug levels**

prIME POINTS™

- *Erwinia* asparaginase can be safely substituted for PEGasparaginase in the event of an allergy
- Use of native *E coli* asparaginase in induction therapy leads to clinical allergy and silent activation of PEGasparaginase during intensification phase
- Individualized dosing of asparaginase based on drug levels is associated with improved outcomes in patients with ALL