cecONCOLOGY

Maximizing Asparaginase Utility in Pediatric and AYA ALL/LBL

PRACTICAL TOOLS FOR ONCOLOGY NURSES

Presented by Creative Educational Concepts LLC • Supported through an independent educational grant from Jazz Pharmaceuticals

Belinda N. Mandrell
PhD, RN, PNP-AC, FAAN

Associate Member
Director, Division of Nursing Research
St. Jude Children's Research Hospital
Memphis, Tennessee

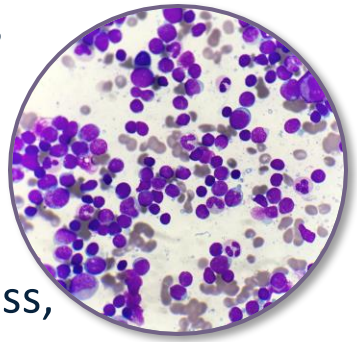
Learning Objectives

- Identify the essential role of asparaginase in pediatric and AYA ALL/LBL treatment protocols.
- Differentiate currently available asparaginase formulations by indication, formulation, route of administration, and safety profiles.
- Utilize recommended strategies to monitor and manage asparaginase-related toxicities and hypersensitivity.

Asparaginase in Pediatric and AYA ALL/LBL

Learning Objective #1: Identify the essential role of asparaginase in pediatric and AYA ALL/LBL treatment protocols.

Acute Lymphoblastic Leukemia (ALL)



- Aggressive hematologic neoplasm of B- or T-lymphoblasts
  - Acute lymphoblastic leukemia (ALL)
  - Lymphoblastic lymphoma (LBL)
- Clinical presentation
  - Cytopenia (bone marrow failure), adenopathy, mediastinal mass, hepatosplenomegaly, central nervous system
  - Constitutional symptoms (fatigue, fevers, sweats, weight loss, bone pain)
- Diagnosis: morphology (blasts) and immunophenotype (flow cytometry/immunohistochemistry [IHC]) to determine lymphoid (B or T) and maturity stage
  - B-lymphoblasts: CD10, CD19, CD20 (some), and CD22; Ig negative
  - T-lymphoblasts: cCD3 and other T-cell antigens

Slide courtesy of Dr. Marlise R. Luskin.

Puckett Y, et al. In: StatPearls. Updated January 2023. https://www.ncbi.nlm.nih.gov/books/NBK459149/.

Risk Stratification

Category	Age	Description	Potential Therapeutic Implications
B-cell Precursor Acute Lymphoblastic Leukemia			
Hyperdiploidy with more than 50 chromosomes	Children >> adults	Excellent prognosis; mutations in Ras signaling pathway and histone modifiers	Reduction in intensity
Near-haploid	Children-adults	24–31 chromosomes; poor prognosis; Ras-activating mutations; inactivation of *IKZF3*	BCL2 inhibitors
Low hypodiploid	Children < adults	32–39 chromosomes; poor prognosis; TP53 mutations (somatic and germline)	BCL2 inhibitors
iAMP21	Older children	Complex alterations of chromosome 21; requires high-risk therapy for good outcomes	Intensification of therapy
t(12;21) (p13;q22) encoding *ETV6-RUNX1*	Children >> adults	Excellent prognosis; cryptic rearrangement that is detectable by FISH	Reduction in intensity
ETV6-RUNX1–like	Children > adults	Absence of *ETV6-RUNX1* fusion; mutations in both *ETV6* and *IKZF1*	Reduction in intensity
t(1;19) (q23;p13) encoding *TCF3-PBX1*	Children-adults	Increased incidence of African Americans; favorable prognosis	
t(9;22) (q34;q11.2) encoding BCR-ABL1	Children << adults	Historically poor prognosis; improved with tyrosine kinase inhibitors; common deletions of IKZF1	ABL1 inhibitors, FAK inhibitors, rexinoids, BCL2 inhibitors
Ph-like	Children < adults	Kinase-activating lesions; poor outcome; potentially amenable to kinase inhibition	ABL1 inhibitors, JAK inhibitors, PI3K inhibitors, BCL2 inhibitors
CRLF2 rearranged *(IGH-CRLF2; P2RY8-CRLF2)*	Children < adults	Common in Down syndrome and Ph-like ALL; associated with *IKZF1* deletion and *JAK1/2* mutation	JAK inhibitors, BCL2 inhibitors
KMT2A (MLL) rearranged	Infants >> children-adults	Common in infant ALL; dismal prognosis; few co-operating mutations; commonly in RAS signaling pathway	DOT1L inhibitors, menin inhibitors, proteasome inhibitors, HDAC inhibitors, BCL2 inhibitors
DUX4 rearranged and *ERG* deregulated	Children-adults	Distinct gene expression profile; most have focal ERG deletions and favorable outcome despite *IKZF1* alterations	Reduction in intensity
MEF2D rearranged	Children-adults	Distinct gene expression profile; potentially sensitivity to HDAC inhibition	HDAC inhibitors
ZNF384 rearranged	Children	Pro-B ALL phenotype; expression of myeloid markers; increased expression of *FLT3*	FLT3 inhibitors
PAX5alt	Children > adults	PAX5 fusions, mutation, or amplifications; intermediate prognosis	
PAX5 P80R	Children < adults	Frequent signaling pathway alterations	Kinase inhibitors
IKZF1 N159Y	Children-adults	Rare; unknown prognosis	FAK inhibitors, rexinoids
NUTM1 rearranged	Children	Exclusively in children; rare; excellent prognosis	HDAC inhibitors; bromodomain inhibitors
t(17;19) (q22;p13) encoding TCF3-HLF	Children-adults	Rare; dismal prognosis	BCL2 inhibitors
BCL2/MYC rearranged	Children << adults	Poor prognosis	

Inaba H, Mulligan CG. *Haematologica*. 2020;105(11):2524–2539.

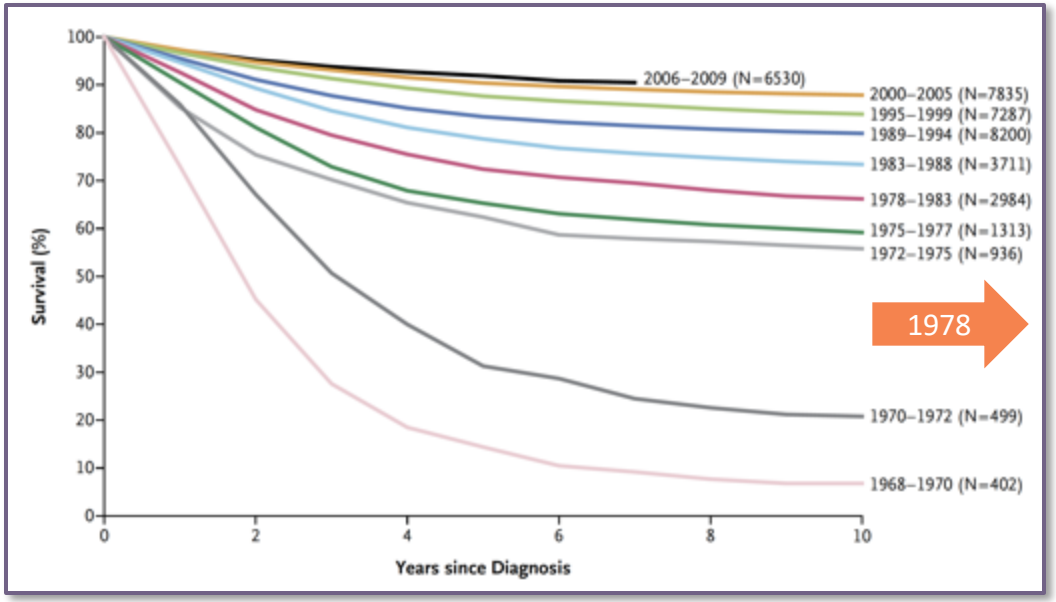
Risk Stratification

Category	Age	Description	Potential Therapeutic Implications
T-lineage Acute Lymphoblastic Leukemia			
TAL1 deregulation	Children-adults	Enrichment of mutation in PI3K signaling pathway	PI3K inhibitors, nelarabine, BCL2 inhibitors
TLX3 deregulation	Children-adults	Poor prognosis; frequent co-operating mutation in ubiquitination and ribosomal genes	Nelarabine, BCL2 inhibitors
HOXA deregulation	Children-adults	Frequent mutations in JAK-STAT pathway, *KMT2A* rearrangements	JAK inhibitors; nelarabine, BCL2 inhibitors
TLX1 deregulation	Children > adults	Favorable prognosis	Nelarabine, BCL2 inhibitors
LM02/LYL1 deregulation	Children-adults	Poor prognosis; enriched for ETP-ALL, frequent co-operating mutation in JAK-/STAT	JAK inhibitors; nelarabine, BCL2 inhibitors
NKX2-1 deregulation	Children-adults	Frequent co-operating mutation in ribosomal genes	Nelarabine, BCL2 inhibitors
NUP214-ABL1 with 9q34 amplification	Children-adults	Neutral prognosis, in contrast to kinase driven B-ALL; potentially amenable to tyrosine kinase inhibition	ABL1 inhibitors, nelarabine, BCL2 inhibitors
Early T-cell precursor ALL	Children-adults	Poor prognosis; genetically heterogeneous with mutations in hematopoietic regulators, cytokine and Ras signaling, and epigenetic modifiers	JAK inhibitors, BCL2 inhibitors

Inaba H, Mulligan CG. *Haematologica*. 2020;105(11):2524–2539.

Pediatric ALL Is a Medical Success Story

Overall Survival among Children with ALL in Clinical Trials, 1968–2009



All conventional upfront therapeutic regimens in pediatric ALL/LBL contain asparaginase

1978: First asparaginase approved by FDA (native *E. coli* derived L-asparaginase)

Survival trends due to:

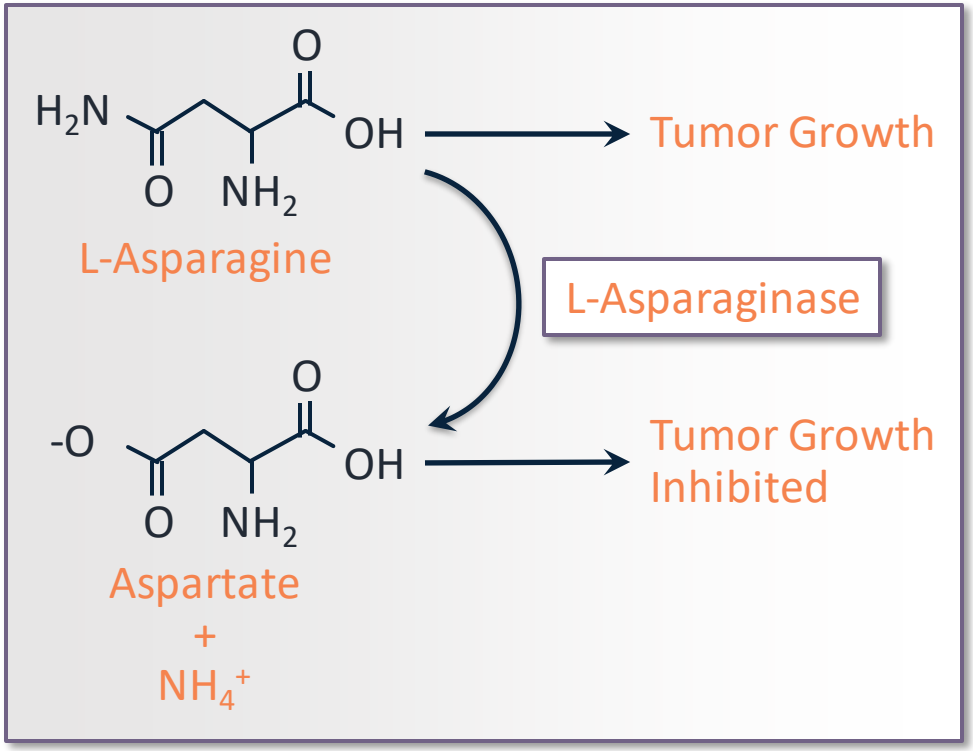
- CNS-directed therapy
- Combination chemotherapy
- MDR and TDM
- Rx intensification
- Rx reduction
- Inhibitors
- Immunotherapy
- Supportive care
- HCT

Hunger SP, et al. *N Engl J Med.* 2015;373(16):1541–1552.

Therapeutic Role

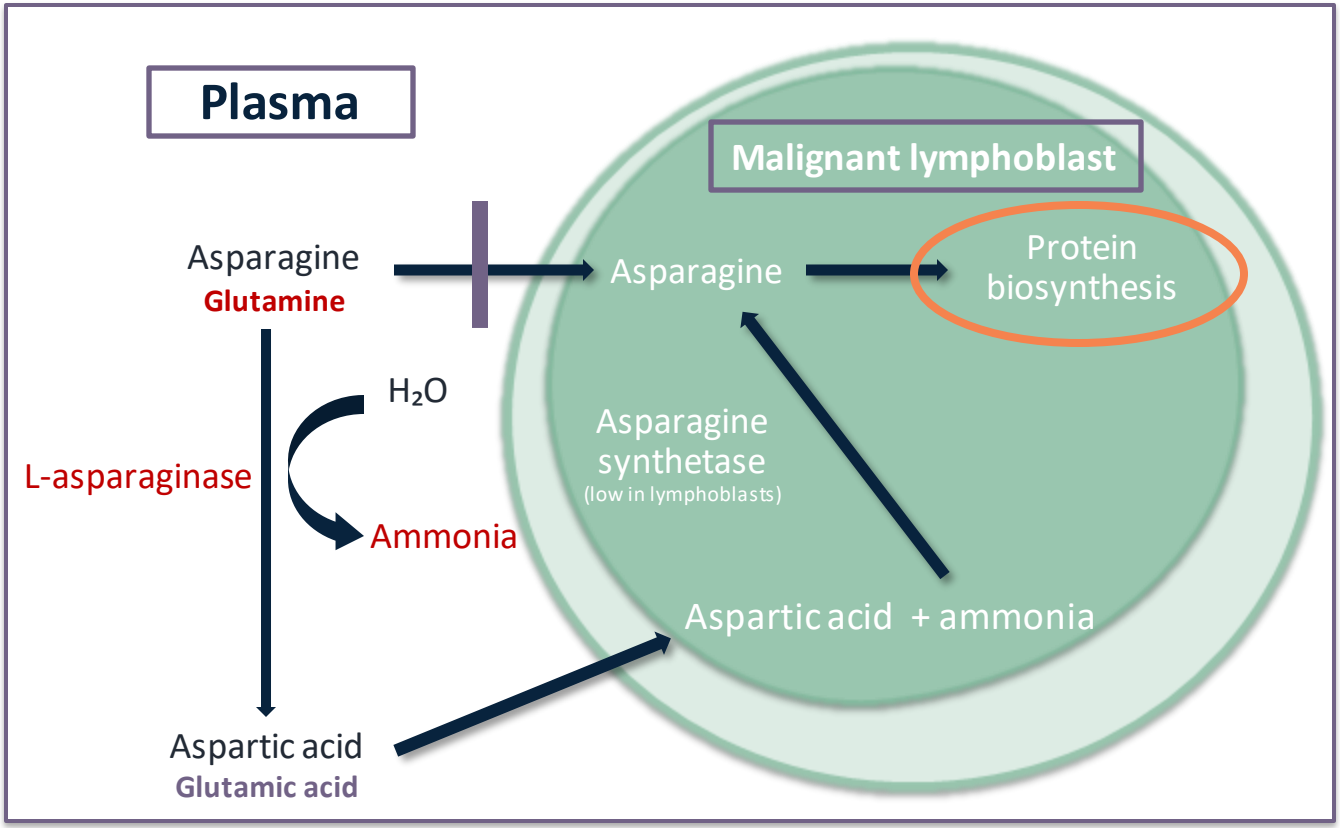
Asparagine depletion is a hallmark of ALL and LBL therapy and improves outcomes.

- The amnio acid asparagine is essential for the growth of leukemia
- Depleting plasma asparagine levels selectively kills lymphoblasts
- Asparaginase hydrolyzes L-asparagine to L-aspartate acid and ammonia, thus inhibits cell growth and activates apoptotic cell death



Egler RA, et al. *J Pharmacol Pharmacoth*er. 2016;7(2):62–71. Narta UK, et al. *Crit Rev Oncol Hematol*. 2007;61(3):208–221.

Asparaginase—A “Magic Bullet”

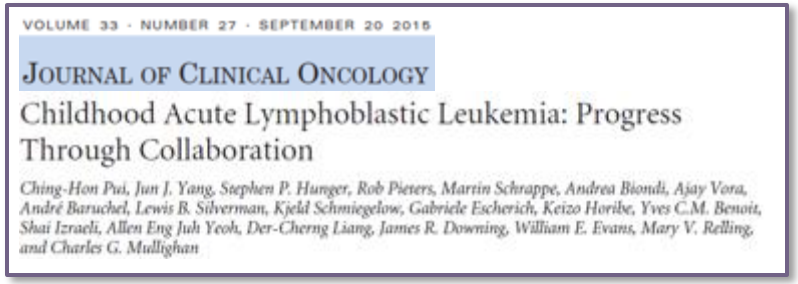


All proteins affected

...cure at a price

- Hypoalbuminemia
- Hyperlipidemia
- Drug metabolism
- Coagulation disturbances
- Hyperglycemia
- Organ toxicities

Pediatric ALL Treatment Asparaginase by Protocol

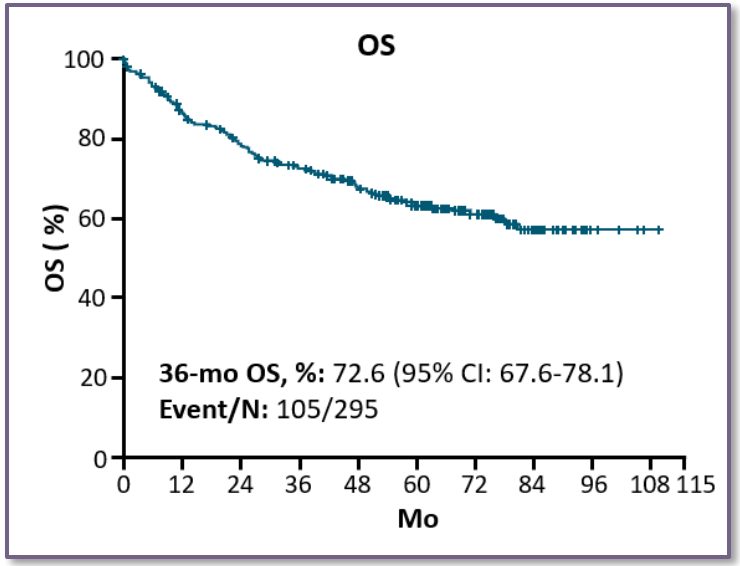


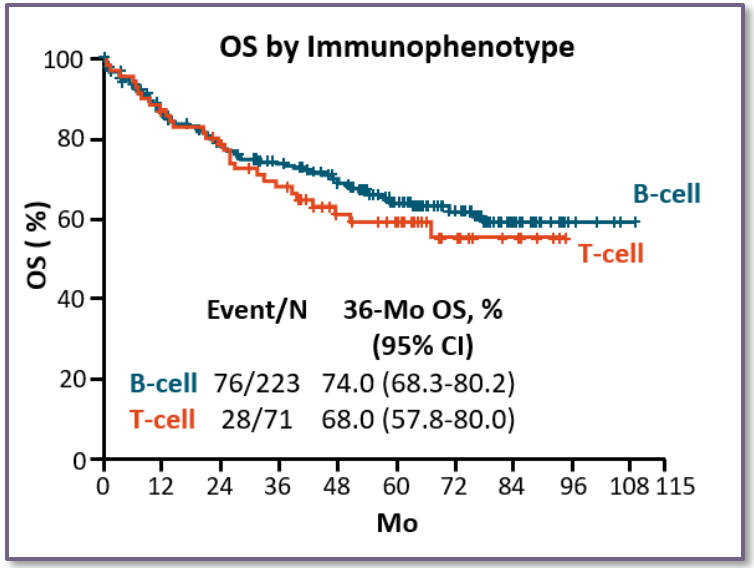
Ph-negative ALL	Induction	Consolidation
COG AALL0932 regimen (SR)	SR arm: dexamethasone, vincristine, **pegaspargase** IT therapy: cytarabine, then MTX	SR-low/-average arm: mercaptopurine, vincristine IT therapy: MTX
		SR-average/-high arm: cyclophosphamide, cytarabine, mercaptopurine, vincristine, **pegaspargase** IT therapy: MTX
COG AALL1131 regimen (HR)	HR arm: prednisone or dexamethasone, vincristine, **pegaspargase,** daunorubicin IT therapy: cytarabine, then MTX	HR arm: cyclophosphamide, cytarabine, mercaptopurine, vincristine, **pegaspargase** IT therapy: MTX
DFCI ALL protocol 11-001 regimen	Prednisone, vincristine, **pegaspargase,** doxorubicin, IT cytarabine, then IT triple therapy (ITT)	SR arm: high-dose MTX, vincristine, **peraspargase,** mercaptopurine, dexamethasone IT therapy: MTX or ITT
		HR/VHR arms: high-dose MTX, vincristine, **pegaspargase,** mercaptopurine, dexamethasone, doxorubicin, dexrazoxane IT therapy: MTX or ITT
Total therapy XVI regimen	Prednisone, vincristine, daunorubicin, **pegaspargase,** cyclophosphamide, cytarabine, mercaptopurine (6-MP), age-adjusted ITT	LR arm: high-dose MTX, mercaptopurine, ITT
		SR/HR arm: high-dose MTX, mercaptopurine, ITT

Pui CH, et al. *J Clin Oncol*. 2015;33(27):2938–2948. NCCN Guidelines. Pediatric ALL. v1.2024. https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf.

CALGB 10403: Improved Survival for Adolescents and Young Adults (17–39 years) on a Pediatric ALL Regimen

N=318





Key Points

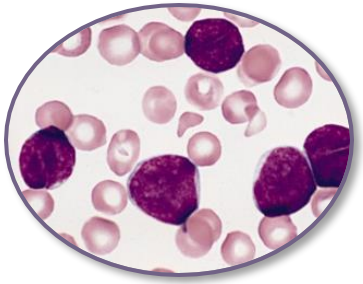
Using an intensive pediatric regimen for AYAs with ALL is feasible.

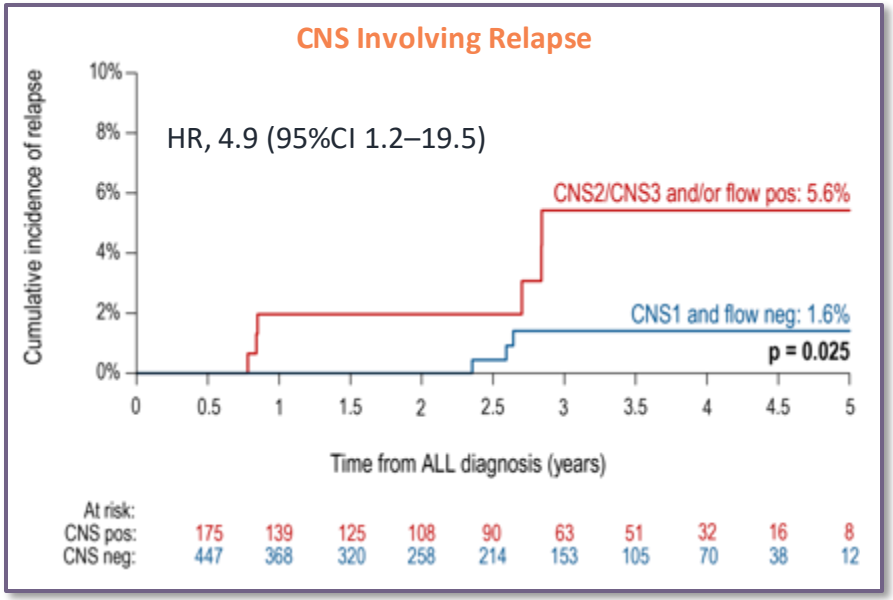
High rates of event-free survival (EFS) and overall survival (OS) were seen compared with controls.

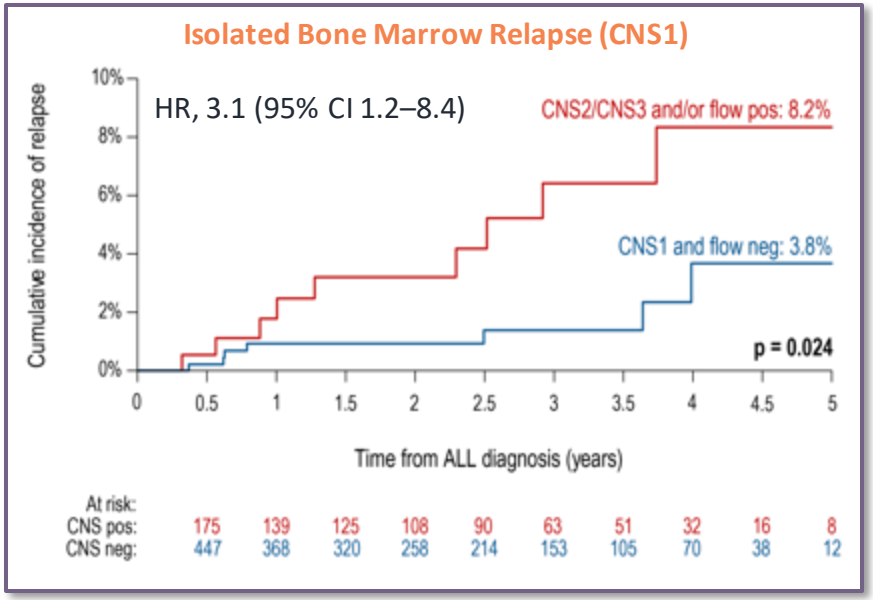
Stock W, et al. *Blood.* 2019;133(14):1548–1559.

CNS Involvement and Relapse Risk (NOPHO ALL2008)

	Cytospin (register data)		Flow Cytometry Study	
CNS Leukemia	Positive	Negative	Positive (median: 25/mL)	Negative
BCP-ALL	171 (10.7%)	1,427 (89.3%)	122 (20.8%)	464 (79.2%)
T-ALL	65 (27.1%)	175 (72.9%)	49 (56.3%)	38 (43.7%)







BCP-ALL, B-cell precursor acute lymphoblastic leukemia.

Thastrup M, et al. *Leukemia*. 2020;34(2):336–346. Thastrup M, et al. *Blood*. 2018;132(1):657. Image from https://bestpractice.bmj.com/topics/en-gb/273.

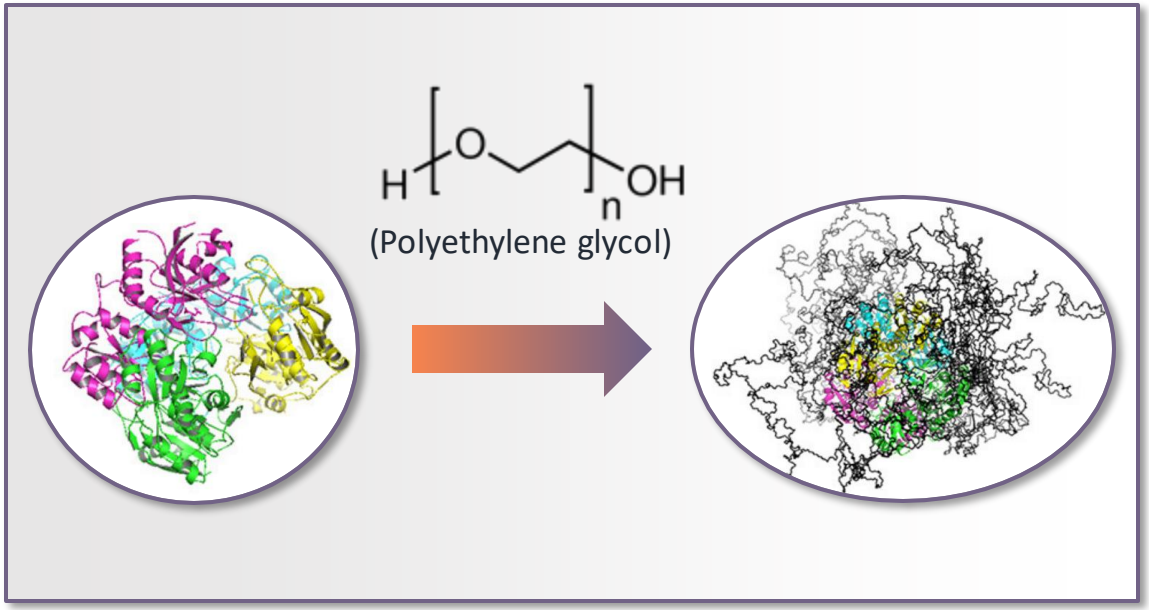
CNS Leukemia

- Central nervous system (CNS) leukemia is underestimated
- Asparaginase is important in treating CNS leukemia
- CNS positive by flow risk is higher for CNS relapse and isolated bone marrow relapse
- Traumatic tap, if negative by flow, the relapse risk is low

Asparaginase in Treatment of ALL/LBL

Learning Objective #2: *Differentiate currently available asparaginase formulations by indication, formulation, route of administration, and safety profiles.*

PEGylation



- Increases size, molecular weight
- Improves pharmacokinetics and pharmacodynamics
  - Water solubility
  - Protection from enzymatic degradation
  - Reduced renal clearance
  - Limiting immunogenic and antigenic reactions
- Increased half-life → less frequent administration

Brumano LP, et al. *Front Bioeng Biotechnol.* 2019;10(6):212.

Pegylated Asparaginase

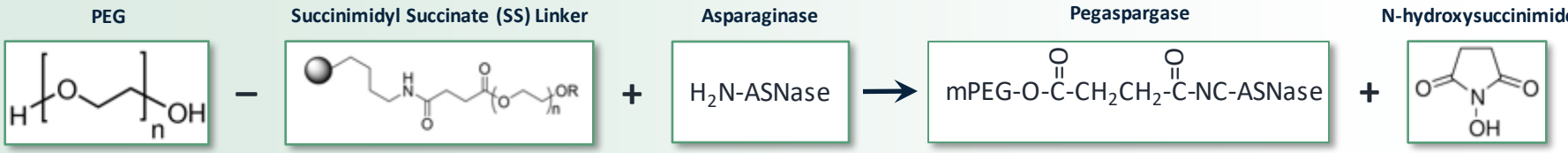
Formulation	Derived from *E. coli*	FDA-approved Indication	Half-life	Administration
Pegylated asparaginase (pegaspargase)	Yes	As a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with • First-line ALL • ALL and hypersensitivity to native forms of L-asparaginase	IM: 5.8 days IV: 5.3 days	Dose: 2,000–2,500 IU/m^2 Route: IM or IV Frequency: every 2 weeks
Calaspargase pegol-mknl	Yes	As a component of a multi-agent chemotherapeutic regimen for the treatment of ALL in pediatric and young adult patients age 1 month to 21 years	IV: 16.2 days	Dose: 2,500 IU/m^2 Route: IV Frequency: every 3 weeks

IM, intramuscular; IV, intravenous.

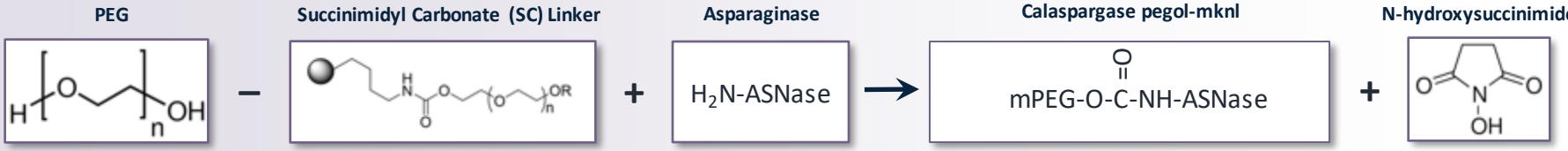
Vrooman LM, et al. *J Clin Oncol*. 2021;39(31):3496–3505. Juluri KR, et al. *Blood Lymphat Cancer*. 2022;12:55–79.
FDA-approved drug: pegaspargase. Revised December 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/103411s5205lbl.pdf.
FDA-approved drug: calaspargase pegol-mknl. Revised December 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761102s008lbl.pdf.

PEGylataion

Pegaspargase



Calaspargase pegol-mknl



Angiolillo AL, et al. *J Clin Oncol.* 2014;32(34):3874–3882. Angiolillo AL, et al. *J Clin Oncol.* 2012;30(15_suppl):9543.

Erwinia Asparaginase Products

Product Name	Indication*	Dosing	Half-life	Important Considerations
Asparaginase *Erwinia chrysanthemi*[**1]	Adult and pediatric patients with ALL and hypersensitivity to *E. coli*–derived asparaginase	• To replace PEG-ASNase: 25,000 IU/m^2 IV or IM 3 × week given Monday/ Wednesday/Friday for 6 doses • To replace native *E. coli* ASNase: 25,000 IU/m^2 IV or IM for each scheduled *E. coli* ASNase dose	• 7.5 hours (IV) • 16 hours (IM)	• Derived from Erwinia chrysanthemi • Identical products • Import of crisantaspase from the United Kingdom into the United States complex because only 1 batch approved by FDA for direct importation
Asparaginase *Erwinia chrysanthemi* (recombinant)-rywn[2,3]	Adult and pediatric patients (aged ≥1 month) with either ALL or LBL and hypersensitivity to *E. coli*–derived asparaginase	• To replace long-acting ASNase: 25 mg/m^2 IM given every 48 hours or 25 mg/m^2 IM Monday/Wednesday morning, then 50 mg/m^2 Friday afternoon	• 18.2 hours	• Derived from *Pseudomonas fluorescens* genetically engineered to contain the *Erwinia chrysanthemi* asparaginase gene • Approved under FDA real-time oncology review program on June 30, 2021 • New dosing regimen approved November 18, 2022

ASH 2022 Abstract 4044: results from study AALL1931 of recombinant *Erwinia* asparaginase[3]

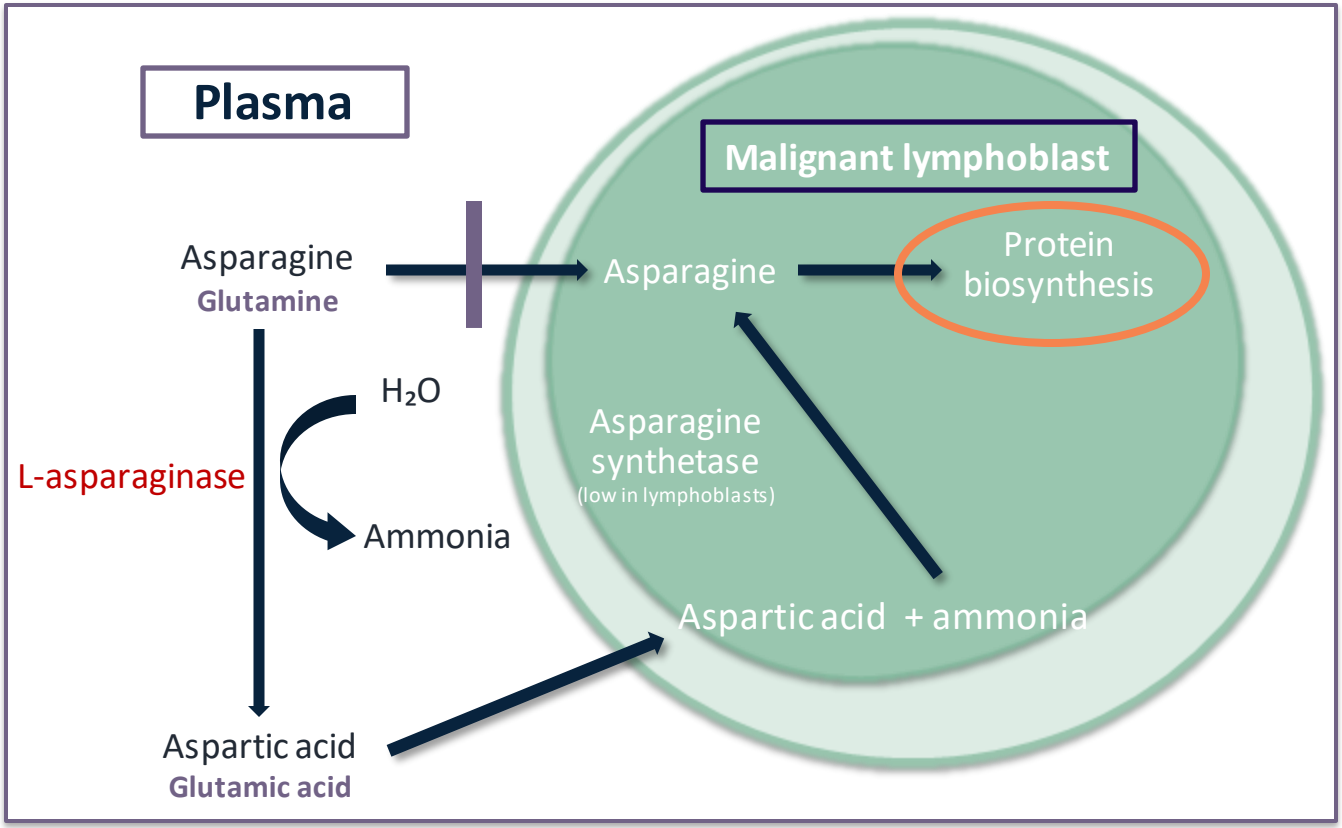
*As component of multiagent chemotherapeutic regimen. ****Non-recombinant asparaginase *Erwinia chrysanthemi* no longer available in United States.**

[1]Salzer WL, et al. *Blood.* 2013;122(4):507–514. [2]FDA-approved drug: asparaginase erwinia chrysanthemi (recombinant) rywn. Revised November 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761179s001lbl.pdf. [3]Maese L, et al. *Blood. 2023;*141(7):704–712.

Asparaginase Toxicity

Learning Objective #3: *Utilize recommended strategies to monitor and manage asparaginase-related toxicities and hypersensitivity.*

Asparaginase—A Magic Bullet!
Not Always a Bullet, Not Always Magic

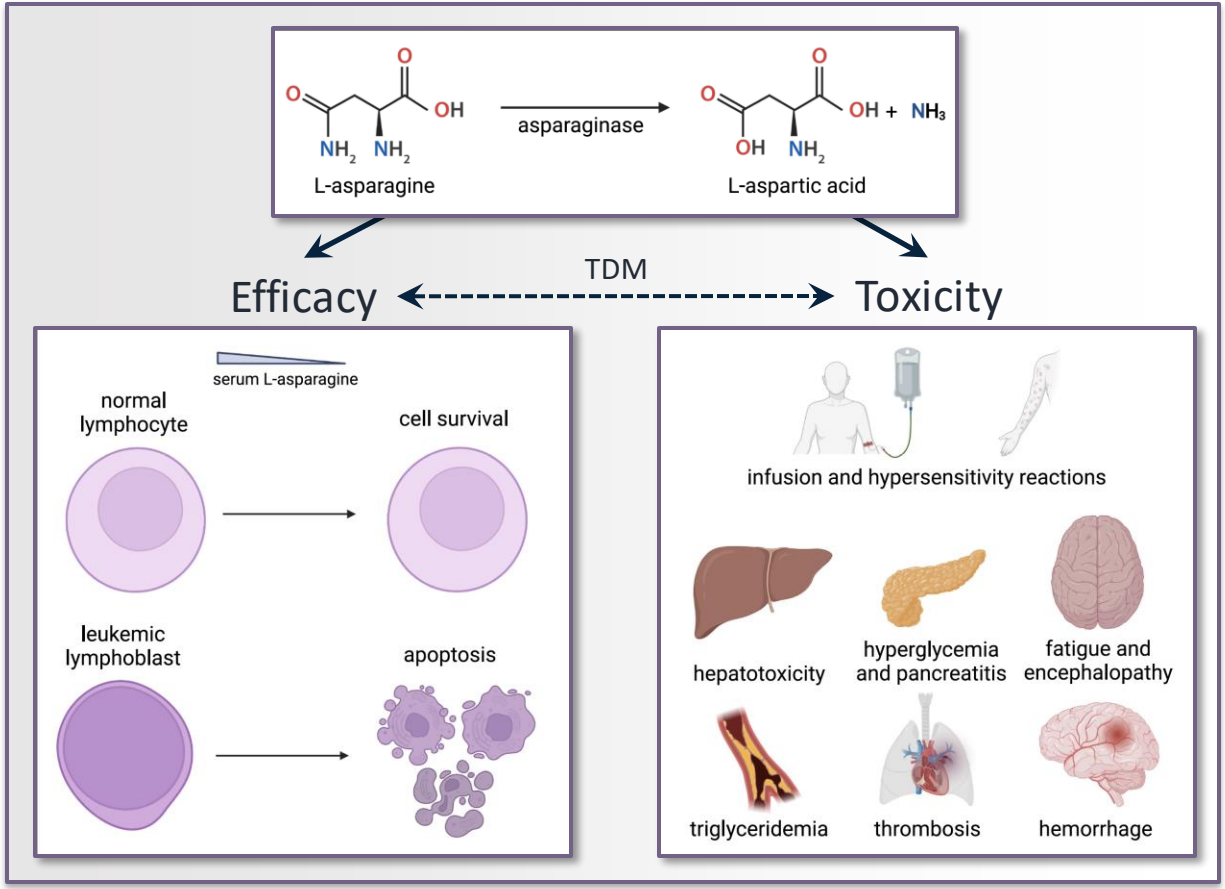


All proteins affected

...cure at a price

- Hypoalbuminemia
- Hyperlipidemia
- Hyperglycemia
- Coagulation disturbances
- Changed drug metabolism
- Organ toxicities

Pharmacologic Effects of Asparaginase



Juluri KR, et al. *Blood Lymphat Cancer*. 2022;12:55–79.

Common Asparaginase-related Toxicities

Toxicity	Presentation	Incidence of Grade 3/4 AEs, %
Hypersensitivity	• Allergic reaction • Silent inactivation	2–10
Hepatotoxicity	• Hyperbilirubinemia • Transaminitis	25–40 >50
Thrombosis	• DVT/PE • Cavernous sinus thrombosis	7–27
Pancreatitis	• Laboratory finding • Clinical	2–18
Hypertriglyceridemia	• Laboratory finding	7–51
CNS toxicity	• Fatigue • Encephalopathy	2–14

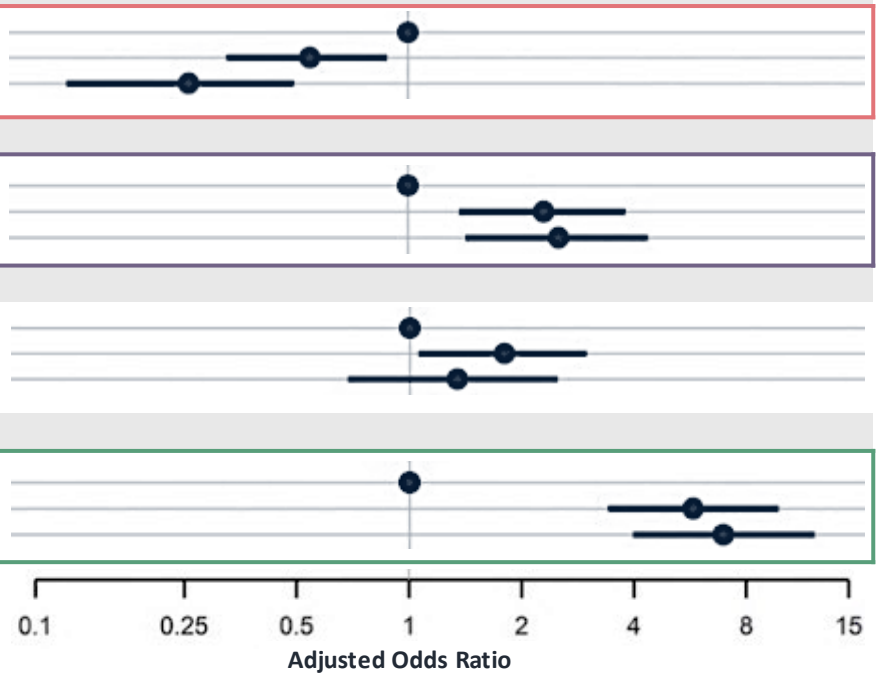
AE, adverse event; DVT, deep vein thrombosis; PE, pulmonary embolism.

Burke PW, et al. *ESMO Open*. 2020;5(5):e000858. Aldoss I, et al. *Eur J Haematol.* 2016;135(11):804–813. Toft N, et al. *Leukemia*. 2018;32(3):606–615.

Predictors of Asparaginase Toxicity

Age

Age Range	Y/N (%)	OR (95% CI)	P	P Trend
Anaphylactic Reaction to Asparaginase				
1–9	146/863 (14.5)	1.0 (1.0–1.0)		<0.001
10–17	25/237 (9.5)	0.6 (0.4–0.9)	0.016	
18–45	11/201 (5.2)	0.3 (0.1–0.5)	<0.001	
Pancreatitis				
1–9	60/949 (5.9)	1.0 (1.0–1.0)		<0.001
10–17	29/233 (11.1)	2.2 (1.3–3.5)	0.001	
18–45	24/188 (11.3)	2.4 (1.4–4.0)	0.001	
Hyperlipidemia				
1–9	72/937 (7.1)	1.0 (1.0–1.0)		0.12
10–17	26/236 (9.9)	1.7 (1.0–2.8)	0.027	
18–45	15/197 (7.1)	1.3 (0.7–2.3)	0.37	
Thrombosis				
1–9	36/973 (3.6)	1.0 (1.0–1.0)		<0.001
10–17	40/222 (15.3)	5.0 (3.1–8.2)	<0.001	
18–45	37/175 (17.5)	6.0 (3.6–10.1)	<0.001	



Prospective database analysis of 1,509 consecutive patients (1–45 years of age) with Ph-negative ALL treated at Nordic and Baltic centers July 2008–December 2014.

Toft N, et al. *Leukemia*. 2018;32(3):606–615.

Predictors of Asparaginase Toxicity
BMI

CALGB 10403 Protocol

Obesity and Asparaginase-associated Toxicities

Select Grade 3/4 AEs, n (%)	BMI <30 kg/m² n=197 (%)	BMI 30–40 kg/m² n=71 (%)	BMI ≥40 kg/m² n=21 (%)	*P*-value
Nonhematologic toxicity	152 (77.2)	57 (80.3)	18 (85.7)	0.685
Hepatic toxicity	61 (31.0)	37 (52.1)	13 (61.9)	0.001
Infection	43 (21.8)	19 (26.8)	9 (42.9)	0.092
ALT increase	47 (23.9)	25 (35.2)	11 (52.4)	0.009
AST increase	14 (7.1)	17 (23.9)	6 (28.6)	<0.0001
Hyperbilirubinemia	23 (11.7)	22 (31.0)	10 (47.6)	<0.0001
Pancreatitis	4 (2.0)	2 (2.8)	2 (9.5)	0.123
Hyperglycemia	52 (26.4)	28 (39.4)	10 (47.6)	0.030

Advani AS, et al. *Blood Adv.* 2021;5(2):504–512.

Silent Inactivation

- Antibody development may lead to inactivation of L-asparaginase
- Monitored via measurement of serum asparaginase activity via therapeutic drug monitoring
- Cannot measure asparagine levels because asparaginase in blood would continue to breakdown the asparagine ex vivo
- Serum asparaginase level of ≥0.1 IU/mL correlates with clinical efficacy

van der Sluis IM, et al. *Haematologica*. 2016;101(3):279–285.

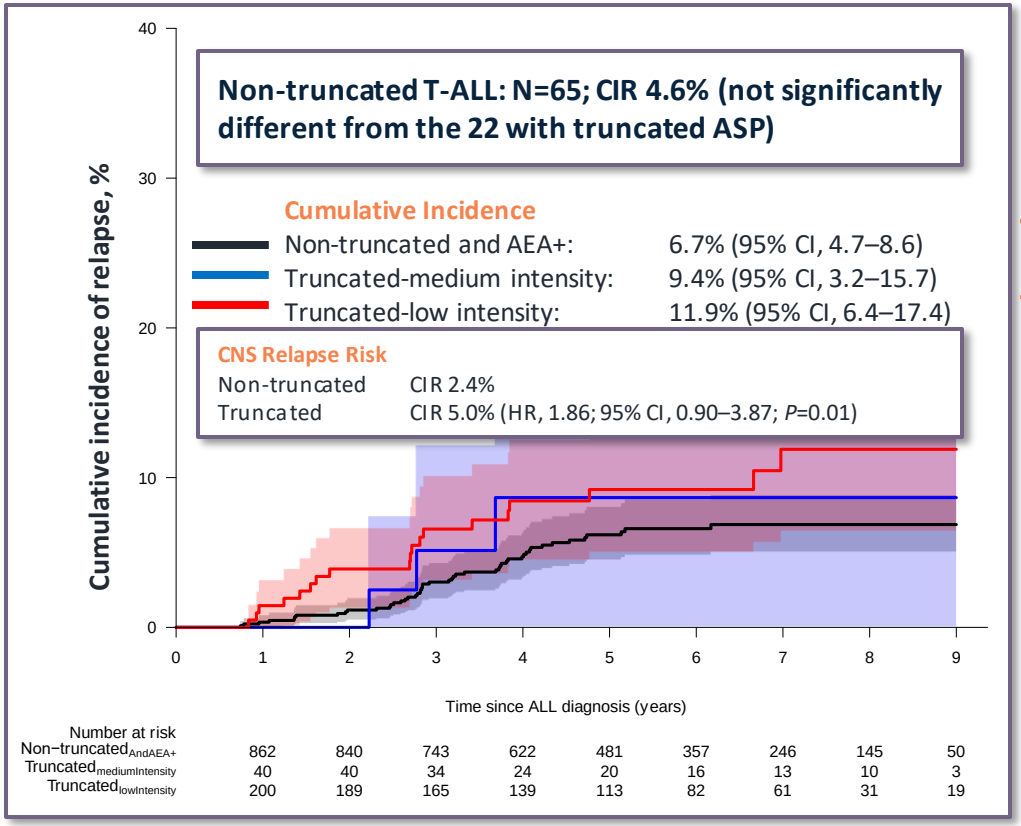
Reasons for Discontinuation of ASNase in Children Aged 1–17 Years on NOPHO ALL2008

Reason for Discontinuation	Main Cohort, n (%) (n=1,401)	Subcohort,* n (%) (n=1,115)	No ASNase Enzyme Activity,† n
Clinical hypersensitivity	208 (14.8)	157 (14.1)	139
Pancreatitis	88 (6.3)	53 (4.8)	1
Thrombosis	24 (1.7)	14 (1.3)	—
Hyperlipidemia	10 (0.7)	8 (0.7)	—
Liver toxicity	7 (0.5)	7 (0.6)	—
Other (sepsis, seizure, study refusal, abdominal pain)	21 (1.5)	16 (1.4)	—
Silent inactivation	—		46
Total number of truncated patients	358 (25.5)	255 (22.9)	140

*Patients with ASNase enzyme activity measurements. †Only applies to patients in the subcohort.

Gottschalk Højfeldt S, et al. *Blood*. 2021;137(17):2373–2382.

Impact of Truncation of ASNase Therapy NOPHO ALL2008 (1.0–17.9 years)



Cox regression (included age < or ≥ 10 years; day 29 minimal residual disease [MRD]; WBC and CNS3 at diagnosis). Relapse HR, 1.69 (95% CI, 1.05–2.74; *P*=0.03. If not including ASNase activity: HR, 1.33; *P*=0.20)

HRm, 1.49; *P*=0.3

HR, 1.80; *P*=0.03
Low vs high ASNase intensity

Asparaginase Therapy Intensity

- Low intensity: <10 weeks of ASNase treatment OR no ASNase enzyme activity (AEA; 5%–15% off target)
- Intermediate: ≥10 weeks of ASNase treatment
- High intensity: no ASNase truncation **and** positive AEA

AEA, asparaginase enzyme activity.

Gottschalk Højfeldt S, et al. *Blood*. 2021;137(17):2373–2382.

Predictors of Asparaginase Toxicity
Pharmacogenomics

Toxicity	Gene/Variant	Mechanism
Hypersensitivity[1–3]	*HLA DRB1* *07:01 *HLA-DRB1* *04:05 *HLA-DRB1* *04:08 *HLA-DQA1* *NFATC2*	Alterations in binding pocket of HLA-DR
Hepatotoxicity[4,5]	*SOD2* rs4880 CC *PNPLA3* rs738409	Fatty liver disease?
Pancreatitis[6–9]	*1 asparaginase synthetase *CPA2* *ULK2* rs281366 *PRSS1/PRSS2*	Pancreatic enzymes?

[1]Fernandez CA, et al. *Blood*. 2014;124(8):1266–1276. [2]Fernandez CA, et al. *Blood*. 2015;126(1):69–75. [3]Højfeldt SG, et al. *Br J Haematol*. 2019;184(3):405–417. [4]Alachkar H, et al. *Pharmacogenomics J*. 2017;17(3):274–279. [5]Liu Y, et al. *Clin Pharmacol Ther*. 2017;102(1):131–140. [6]Ben Tanfous M, et al. *Clin Cancer Res*. 2015;21(2):329–334. [7]Liu C, et al. *J Clin Oncol*. 2016;34(18):2133–2140. [8]Wolthers BO, et al. *Leukemia*. 2017;31(2):325–332. [9]Wolthers BO, et al. *Haematologica*. 2019;104(3):556–563.

Risk Factors for Hypersensitivity to Asparaginase

- Formulation of asparaginase
- Route of administration
- Schedule of administration: second dose and future doses
- *HLA-DRB1* polymorphism
- Younger age
- Allergy to PEG due to exposure to other PEG-related containing products
- Asparaginase activity level is only associated with liver toxicity

Aldoss I, Douer D. *Blood*. 2020;135(13):987–995. Pourhassan H, et al. *Curr Oncol Rep*. 2022;25(1):51–61.
NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf.

Management of Hypersensitivity

Patient Case

The patient is a 12-year-old male with pre–B-cell ALL, *iAMP21* (copy number variation [CNV]).

Upon examination, his white blood cell (WBC) count is <50,000 cells/µL. He is found to be CNS-2, positive CSF flow cytometry; and he is high risk.

He develops hypersensitivity after the third PEG-ASNase dose (1,500 IU/m^2 IV). His grade 3 symptoms include rash, stomach pain, bronchospasm, and reduced blood pressure.

CNS2, leukemic cells in a cerebrospinal fluid sample that contains fewer than 5 WBCs/µL.

Options in the Case of ASNase Hypersensitivity Reactions

- Permanently discontinue ASNase therapy
- Switch to native *E. coli* ASNase, anticipating hypersensitivity toward PEG moiety
- Continue with PEG-ASNase with premedication (e.g., H1 and H2 blockers, steroids)
- Prescribe premedication at next PEG-ASNase dose and perform therapeutic drug monitoring (assuming it is available)
- Switch to IM ASNase, anticipating less hypersensitivity than with IV
- Switch to non–cross-reactive ASNase formulation (*Erwinia* ASNase)

Option

Permanently Discontinue ASNase Therapy

ASNase Truncation Increases Relapse Rates in ALL

Observational Studies

Update on Pieters 2011	Efficacy		*P*<0.05
	Less-intensive ASNase, %	More-intensive ASNase, %	
Extra 20 weeks ASNase in T-ALL POG 87042 (EFS)	55	68	Yes
Extra 20 weeks ASNase in T-NHL POG 87042 (4-year CCR)	64	78	Yes
≤ or >25 weeks ASNase DFCI 91-013 (5-year EFS)	73	90	Yes
Extra 20 weeks ASNase in IRG AIEOP ALL-914 (DFS)	72	76	No
Erwinase vs *E. coli* ASNase EORTC-CLG 588815 (EFS)	60	73	Yes
Extra 20 weeks ASNase I-BFM-SG/IDH-ALL-916 (DFS)	79	88	Yes
Erwinase vs *E. coli* ASNase DFCI 95-017 (5-year EFS)	78	89	Yes
Truncated vs continued ASNase (*Erwinia*) (COG AALL0331/AALL0232)8 (DFS)	Event HR, 1.5	Event HR, 1.1	Yes
Truncated (including no activity) vs continued ASNase (NOPHO ALL2008)	Relapse risk 11.1	Relapse risk 6.7	Yes

Pieters R, et al. *Cancer*. 2011;117(2):238–249. Amylon MD, et al. *Leukemia*. 1999;13(3):335–342. Silverman LB, et al. *Blood*. 2001;97(5):1211–1218. Rizzari C, et al. *J Clin Oncol*. 2001;19(5):1297–1303. Duval M, et al. *Blood*. 2002;99(8):2734–2739. Pession A, et al. *J Clin Oncol*. 2005;23(28):7161–7167. Moghrabi A, et al. *Blood*. 2007;109(3):896–904. Gupta S, et al. *J Clin Oncol*. 2020;38(17):1897–1905. Gottschalk Hojfeldt S, et al. *Blood*. 2021;137(17):2373–2382.

PEG-asparaginase Discontinuation in Young Adults with ALL

Post-hoc analysis of the CALGB 10403 study:

- Study discontinuation was defined as <4 of 5–6 planned doses
- 176 patients, 57 with early therapy discontinuation
- Survival was lower, but not statistically significant (*P*=0.06)
- Patients with standard risk, early discontinuation significantly impacted OS (*P*=0.04)
- No impact in patient with high-risk disease

Aldoss I, et al. *Blood Adv*. 2023;7(2):196–204.

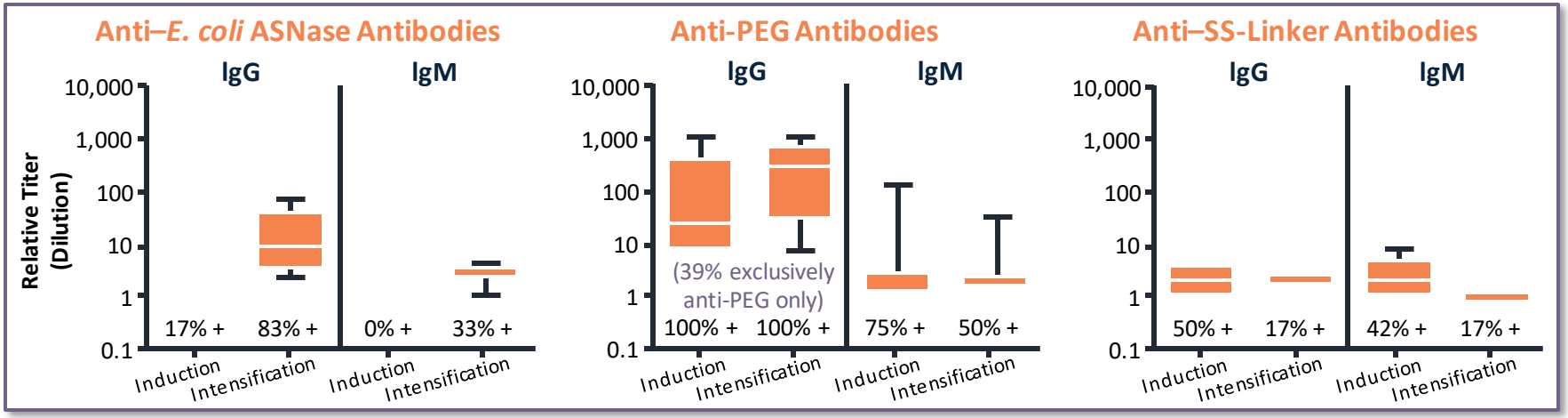
Option

Switch to Native E. coli ASNase

(Anticipating Hypersensitivity toward PEG Moiety)

Hypersensitivity Reactions to PEG Moiety of PEG-ASNase

- Many patients (and healthy individuals) have PEG antibodies, but hypersensitivity is rare on first dose
- Antibodies against PEG moiety, ASNase, and SS-linker detected in 18 patients with neutralizing hypersensitivity (12 during induction, 6 during intensification)



PEG antibodies moderately reduce ASNase levels, but reactions are generally weak and primarily arise with first ASNase administration.

SS, succinimidyl succinate.

Kloos R, et al. *Br J Haematol*. 2020;189(3):442–451.

ASNase Allergy and Inactivation

- Hypersensitivity reactions are closely associated with ASNase inactivation due to neutralizing ASNase antibodies[1,2]
  - Uncertainty: grade 1 reactions; other drugs; intolerance
  - 90% of patients with clinical hypersensitivity have no ASNase activity[2]
- **Antihistamines/steroids *do not* mitigate this ASNase inactivation** in patients who have had clinical hypersensitivity[3]
- Shifting to alternative/non–cross-reactive ASNase formulation is mandatory![3]
  - Unless therapeutic drug monitoring demonstrates appropriate ASNase activity

[1]Tong WH, et al. *Blood*. 2014;123(13):2026–2033.
[2]Gottschalk Højfeldt S, et al. *Blood*. 2021;137(17):2373–2382.
[3]van der Sluis IM, et al. *Haematologica*. 2016;101(3):279–285.

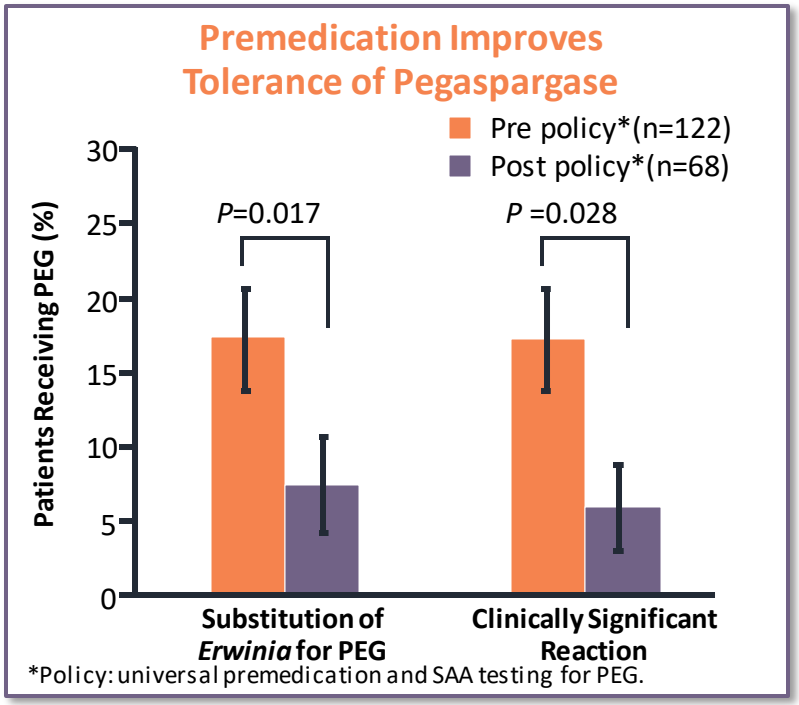
Option

Prescribe Premedication at Next PEG-ASNase Dose and Perform Therapeutic Drug Monitoring

(Assuming Available)

Premedication and Therapeutic Drug Monitoring for Prevention of Hypersensitivity Reactions

- **Premedication** 20–30 minutes prior to ASNase reduces hypersensitivity reactions[1,2]
  - Antihistamine, H2-receptor antagonist (gastro-intestinal [GI] symptoms), or glucocorticosteroids
- **Requires therapeutic drug monitoring**
  - PEG-ASNase: 7 (14) days later (prior to every dose)
  - *Erwinia*: 2 days later
- **Interpret** SAA trough levels
  - ≤0.1 units/mL despite adequate dose, change to *Erwinia* ASNase
  - ≥0.1 units/mL and reaction not severe, rechallenge with PEG
- **Cost effective**



SAA, serum asparaginase activity.

Cooper ST, et al. *Pediatr Blood Cancer*. 2019;66(8):e27797. McCormick M, et al. *Pediatr Blood Cancer*. 2021;68(8):e29051.

Option

Switch to IM ASNase
Anticipating Less Hypersensitivity Than with IV

PEG-Asparaginase
IV vs IM

- 7 study groups (aged 1–24 years) received first-line treatment with PEG-ASNase (N 5,880)
  - IV: 1,500 or 2,500 IU/m^2 in 1–2 hours
  - IM: 1,000 IU/m^2
- Hypersensitivity reactions (allergies and allergic-like)
  - 2% (95% CI, 1%–3%) during induction
  - 8% (95% CI, 5%–11%) during postinduction
- Median incidence of hypersensitivity reactions (*P*=0.43)
  - IV: 8.9% (range, 8.6%–10.5%)
  - IM: 6.5% (range, 5.5%–14.8%)

Brigitha LJ, et al. *Eur J Cancer*. 2022;162:65–75.

Option

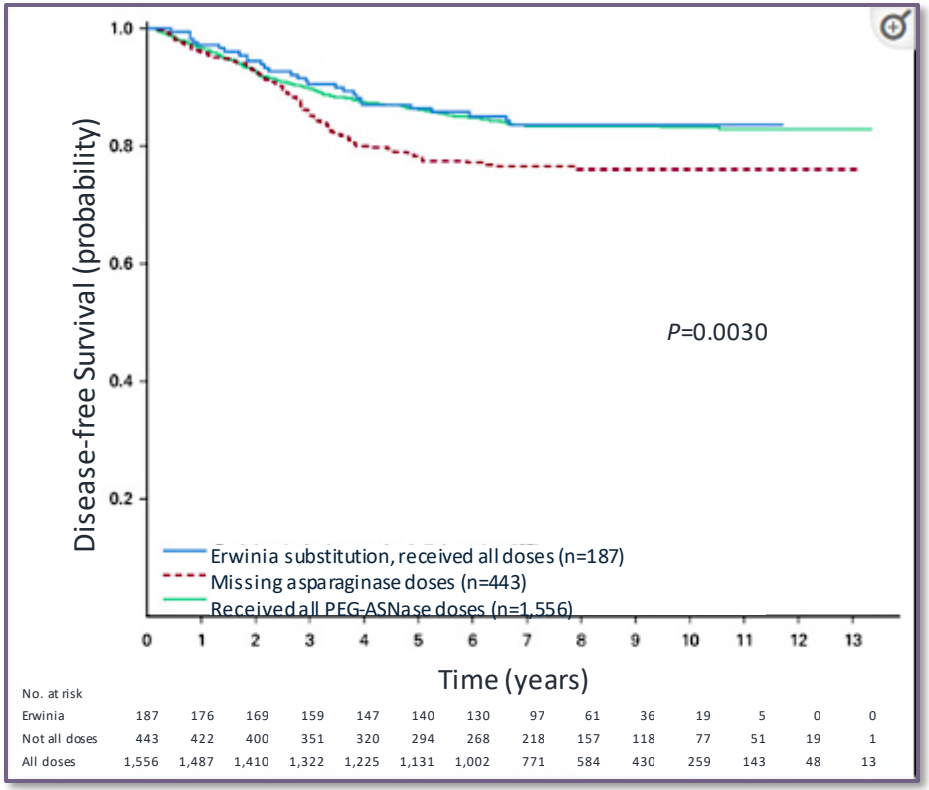
Switch to Non–cross-reactive ASNase Formulation

(Erwinia ASNase)

Asparaginase Discontinuation and *Erwinia* Replacement on Outcome in Childhood ALL

Report from the Children's Oncology Group

DFS of NCI *High-risk* Patients on COG AALL0232



*Age ≥10 years a/o WBC ≥50 × 10^9/L

DFS HR, disease-free survival hazard ratio; NCI, National Cancer Institute; NCI-HR, NCI high risk; NCI-SR, NCI standard risk.

Gupta S, et al. *J Clin Oncol*. 2020;38(17):1897–1905.

Therapeutic Drug Monitoring (TDM)

- Serum ASNase activity levels are best indicators of ASNase efficacy
- Trough levels ≥0.1 IU/mL (“safe” concentration)
- Symptomatic or silent (5%–10%) inactivation (TDM)
  - PEG-ASNase D7 <0.1 IU/mL and/or D14 <LLQ
  - *Erwinia* ASNase trough level <LLQ
- PEG-ASNase antibodies and p-asparagine measurements of no clinical use
- Grade 1 reactions → TDM (grade 2–4: always shift)
- Intolerance reactions (1%–5%; not antibody-mediated; often not immediate)
  - Vomiting, stomachache, rash; no inactivation
- TDM is mandatory in case of premedication!

LLQ, lower limit of quantification.

van der Sluis IM, et al. *Haematologica*. 2016;101(3):279–285. Schmiegelow K, et al. *Lancet Oncol*. 2016;17(6):e231–e239.

Reaction to Erwinia

- <1% of all leukemia patients will have a reaction
- Therapeutic drug monitoring prior to next dose

Burke MJ, Zalewska-Szewczyk B. *Future Oncol.* 2022;18(10):1285–1299.

Patient Case

The patient is a 12-year-old male with pre–B-cell ALL, *iAMP21* (copy number variation [CNV]).

Upon examination, his white blood cell (WBC) count is <50,000 cells/µL. He is found to be CNS-2, positive CSF flow cytometry; and he is high risk.

He develops hypersensitivity after the third PEG-ASNase dose (1,500 IU/m^2 IV). His grade 3 symptoms include rash, stomach pain, bronchospasm, and reduced blood pressure.

CNS2, leukemic cells in a cerebrospinal fluid sample that contains fewer than 5 WBCs/µL.

What is the optimal strategy to manage ASNase therapy for a patient who develops a hypersensitivity reaction to PEG-ASNase?

A. Permanently discontinue ASNase therapy
B. Switch to native *E. coli* ASNase, anticipating hypersensitivity toward PEG moiety
C. Continue with PEG-ASNase with premedication (e.g., H1 and H2 blockers, steroids
D. Prescribe premedication at next PEG-ASNase dose and perform therapeutic drug monitoring (assuming available)
E. Switch to IM ASNase, anticipating less hypersensitivity that with IV
F. Switch to non–cross-reactive ASNase formulation (Erwinia ASNase)

Adverse Event Prevention and Mitigation
Hypersensitivity

- Treatment based on grade of infusion-related reaction
  - **Grade 1 or 2** without bronchospasm, hypotension, edema, or need for parenteral intervention (rash, flushing, urticaria, and drug fever ≥38° C) the asparaginase that caused the reaction may be continued, with consideration for anti-allergy premedication (such as hydrocortisone, famotidine or ranitidine, diphenhydramine, cetirizine, and acetaminophen)
  - **Grade 2** or higher systemic allergic reactions, urticaria, or anaphylaxis can be (but are not necessarily) associated with neutralizing antibodies and lack of efficacy
  - **Grade ≥3** merit permanent discontinuation of the type of asparaginase that caused the reaction
    - Erwinia formulations (erwinia, erwinia-rywn) may be used as a second-line agent in patients who have developed a systemic allergic reaction or anaphylaxis due to pegaspargase

Aldoss I, Douer D. *Blood.* 2020;135(11):804–813. Pourhassan H, et al. *Curr Oncol Rep*. 2022;25(1):51–61.
NCCN Guidelines. Acute Lymphoblastic Leukemia. v2.2023. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf.
U.S. Department of Health and Human Services. CTCAE. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

PEG-ASNase Hypersensitivity Reactions
Summary

- Hypersensitivity-like reaction (requires therapeutic drug monitoring)
  - Slower infusion rate, premedication, re-exposure to PEG-ASNase
- Hypersensitivity toward PEG moiety (especially if reaction to first/second dose)
  - Very few centers can measure specific PEG or SS-linker antibodies
  - True PEG-ASNase hypersensitivity
  - Always ASNase inactivation! Switch to alternative ASNase
    - Asparaginase *erwinia* chrysanthemi (recombinant)-rywn (FDA approved 2021)
      - 25 mg/m^2 (~25,000 IU/m^2) every 48 hours
      - New dosing (FDA approved 2022): 25 mg/m^2 Monday/Wednesday morning, then 50 mg/m^2 Friday afternoon

Burke MJ, Zalewska-Szewczyk B. *Future Oncol.* 2022;18(10):1285–1299. van der Sluis IM, et al. *Haematologica*. 2016;101(3):279–285.

SMART Goals
Specific, Measurable, Attainable, Relevant, Timely

Put information into action! Consider the following goals; then set a time frame that fits with your work environment and a reasonable improvement target that aligns with your patient population.

- Decrease the number of pediatric and AYA patients with ALL/LBL who **discontinue asparaginase** earlier than recommended per treatment protocols.
- Increase the number of pediatric and AYA patients with ALL/LBL who are **appropriately managed** following a hypersensitivity reaction to PEG-ASNase, based on the grade of infusion-related reaction.

Questions?

cecONCOLOGY

Maximizing Asparaginase Utility in Pediatric and AYA ALL/LBL

PRACTICAL TOOLS FOR ONCOLOGY NURSES

Presented by Creative Educational Concepts LLC • Supported through an independent educational grant from Jazz Pharmaceuticals