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# 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

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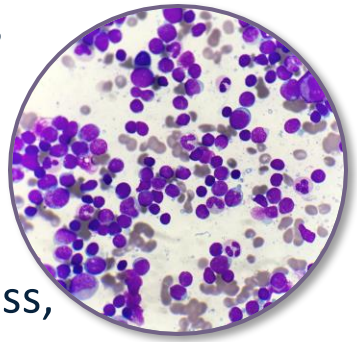
# Learning Objectives

- 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.

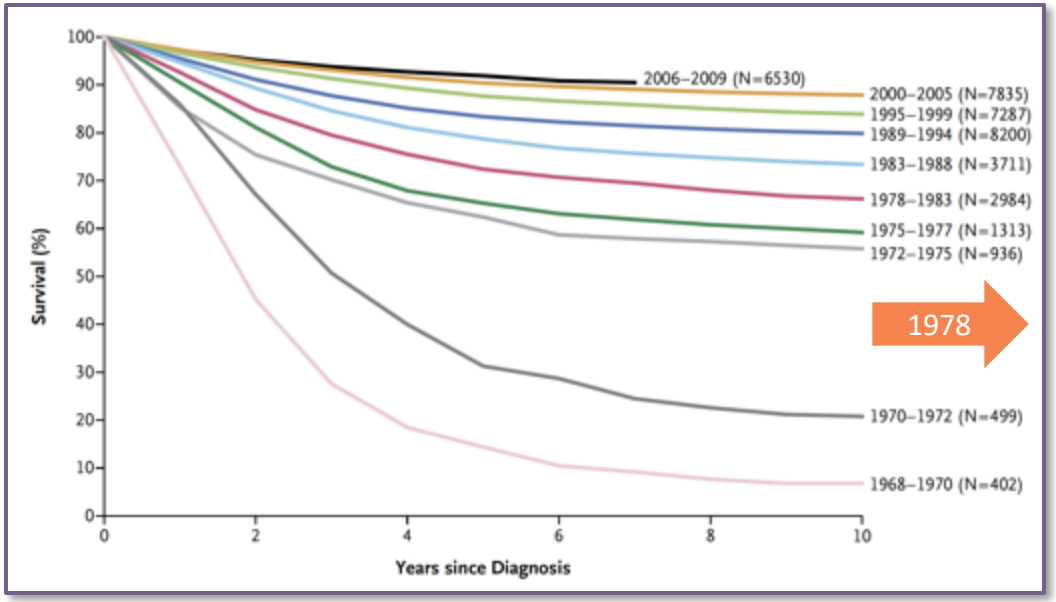
# Risk Stratification

| 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:**

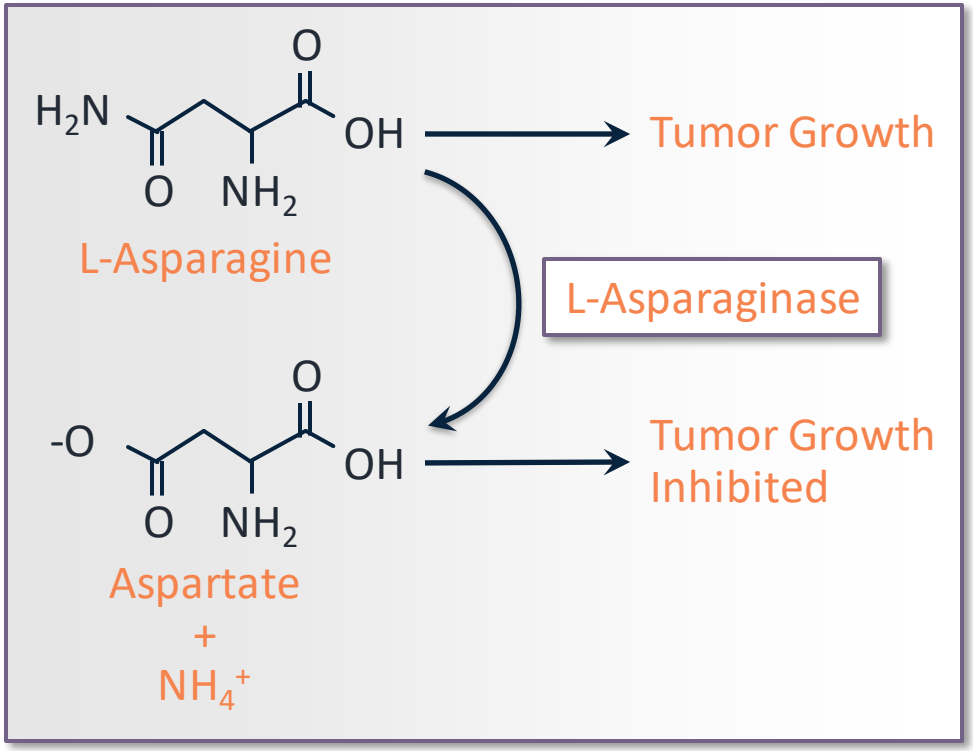
- CNS-directed therapy
- Combination chemotherapy
- MDR and TDM
- Rx intensification
- Rx reduction
- Inhibitors
- Immunotherapy
- Supportive care
- HCT

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

# Therapeutic Role

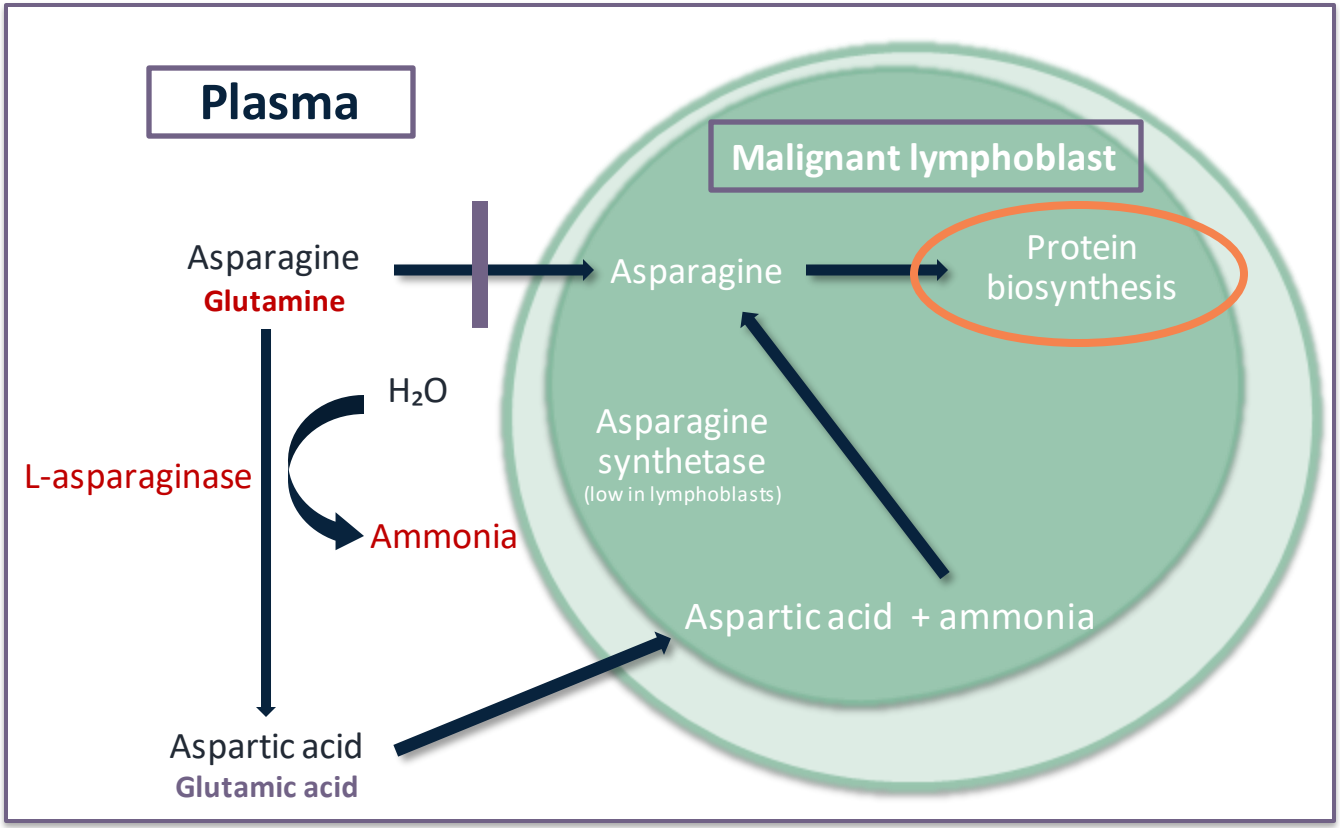
Asparagine depletion is a hallmark of ALL and LBL therapy and improves outcomes.

- 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”

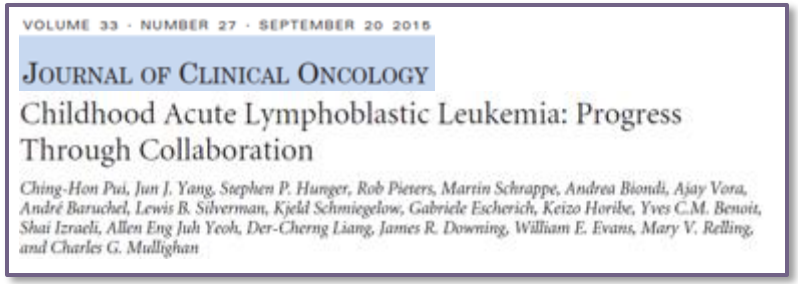



**All proteins affected**

**...cure at a price**

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

# Pediatric ALL Treatment Asparaginase by Protocol

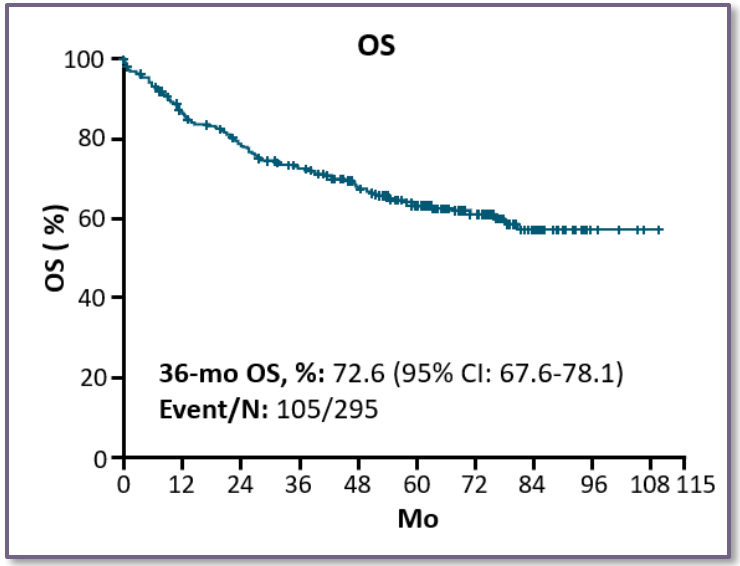


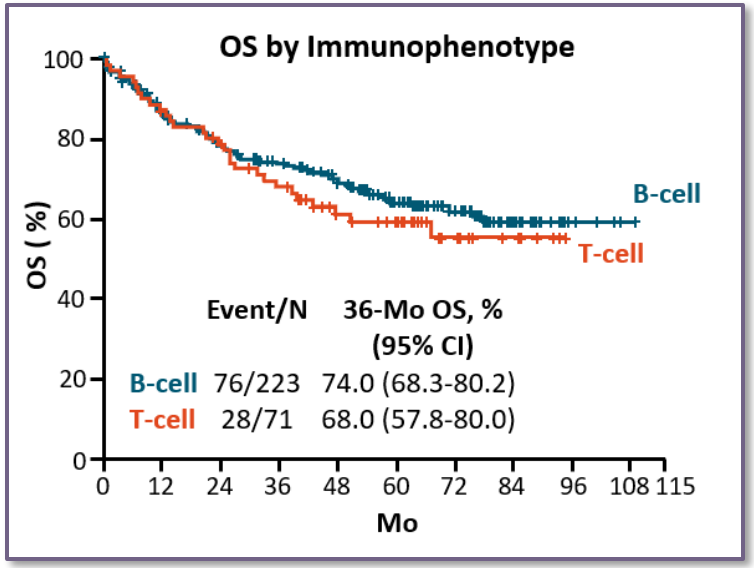

| Ph-negative ALL | Induction | Consolidation |
|---|---|---|
| **COG AALL0932 regimen (SR)** | SR arm: dexamethasone, vincristine, **pegaspargase**<br>IT therapy: cytarabine, then MTX | SR-low/-average arm: mercaptopurine, vincristine<br>IT therapy: MTX |
| | | SR-average/-high arm: cyclophosphamide, cytarabine, mercaptopurine, vincristine, **pegaspargase**<br>IT therapy: MTX |
| **COG AALL1131 regimen (HR)** | HR arm: prednisone or dexamethasone, vincristine, **pegaspargase,** daunorubicin<br>IT therapy: cytarabine, then MTX | HR arm: cyclophosphamide, cytarabine, mercaptopurine, vincristine, **pegaspargase**<br>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<br>IT therapy: MTX or ITT |
| | | HR/VHR arms: high-dose MTX, vincristine, **pegaspargase,** mercaptopurine, dexamethasone, doxorubicin, dexrazoxane<br>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

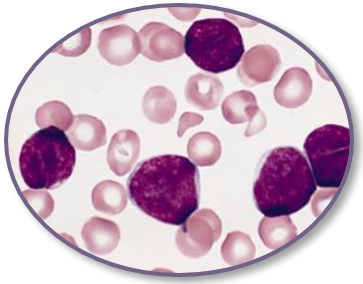
Using an intensive pediatric regimen for AYAs with ALL is feasible.

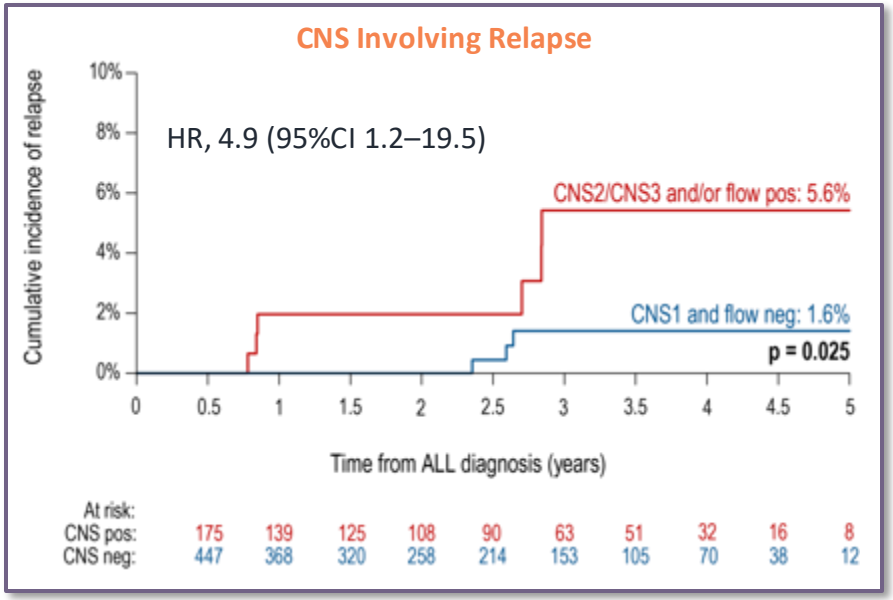
High rates of event-free survival (EFS) and overall survival (OS) were seen compared with controls.

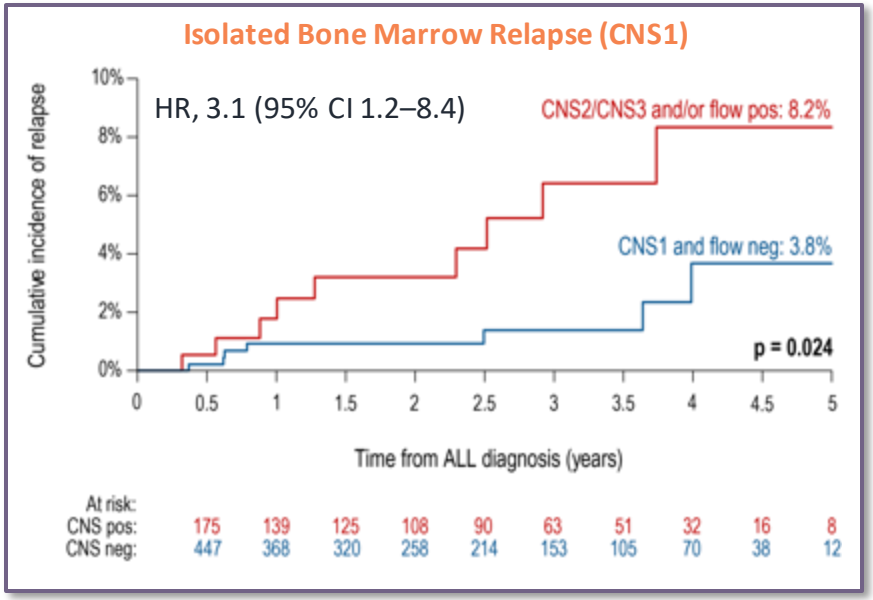
Stock W, et al. *Blood.* 2019;133(14):1548–1559.

# 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.

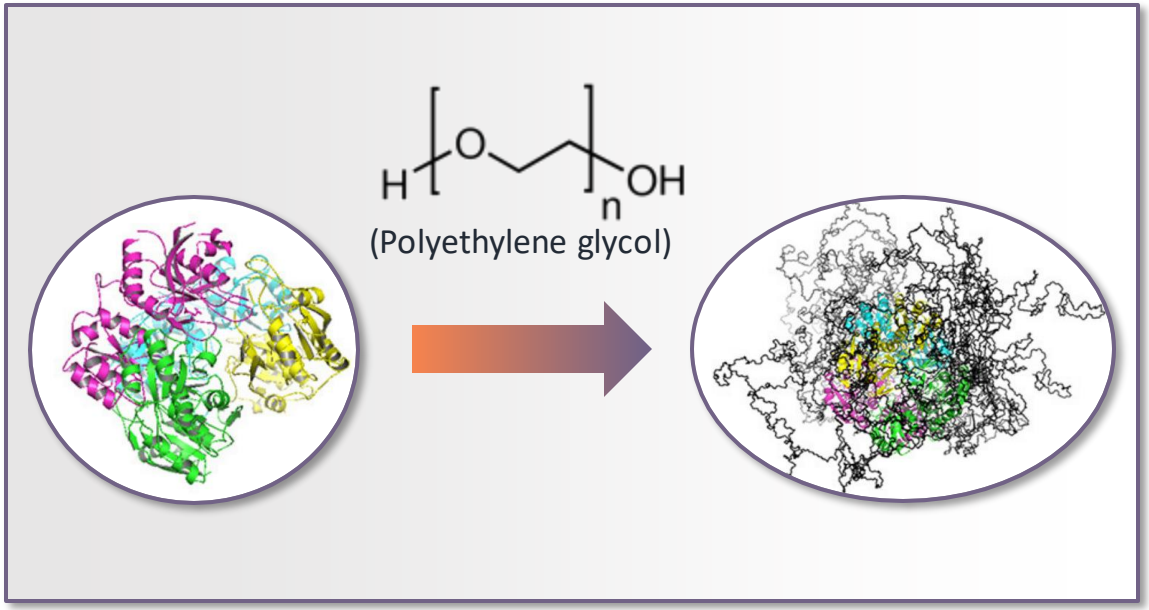
# CNS Leukemia

- 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

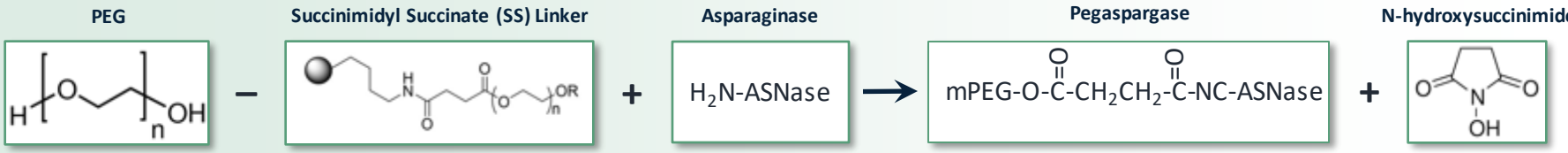
| Formulation | Derived from *E. coli* | FDA-approved Indication | Half-life | Administration |
|---|---|---|---|---|
| Pegylated asparaginase (pegaspargase) | Yes | As a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with<br>• First-line ALL<br>•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

IM, intramuscular; IV, intravenous.

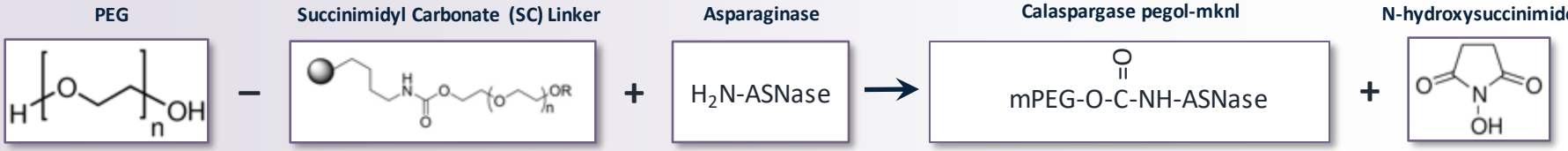
Vrooman LM, et al. *J Clin Oncol*. 2021;39(31):3496–3505. Juluri KR, et al. *Blood Lymphat Cancer*. 2022;12:55–79.
FDA-approved drug: pegaspargase. Revised December 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/103411s5205lbl.pdf.
FDA-approved drug: calaspargase pegol-mknl. Revised 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<br>• 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)<br>• 16 hours (IM) | • Derived from Erwinia chrysanthemi<br>• Identical products<br>• 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<br>• Approved under FDA real-time oncology review program on June 30, 2021<br>• New dosing regimen approved November 18, 2022 |

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

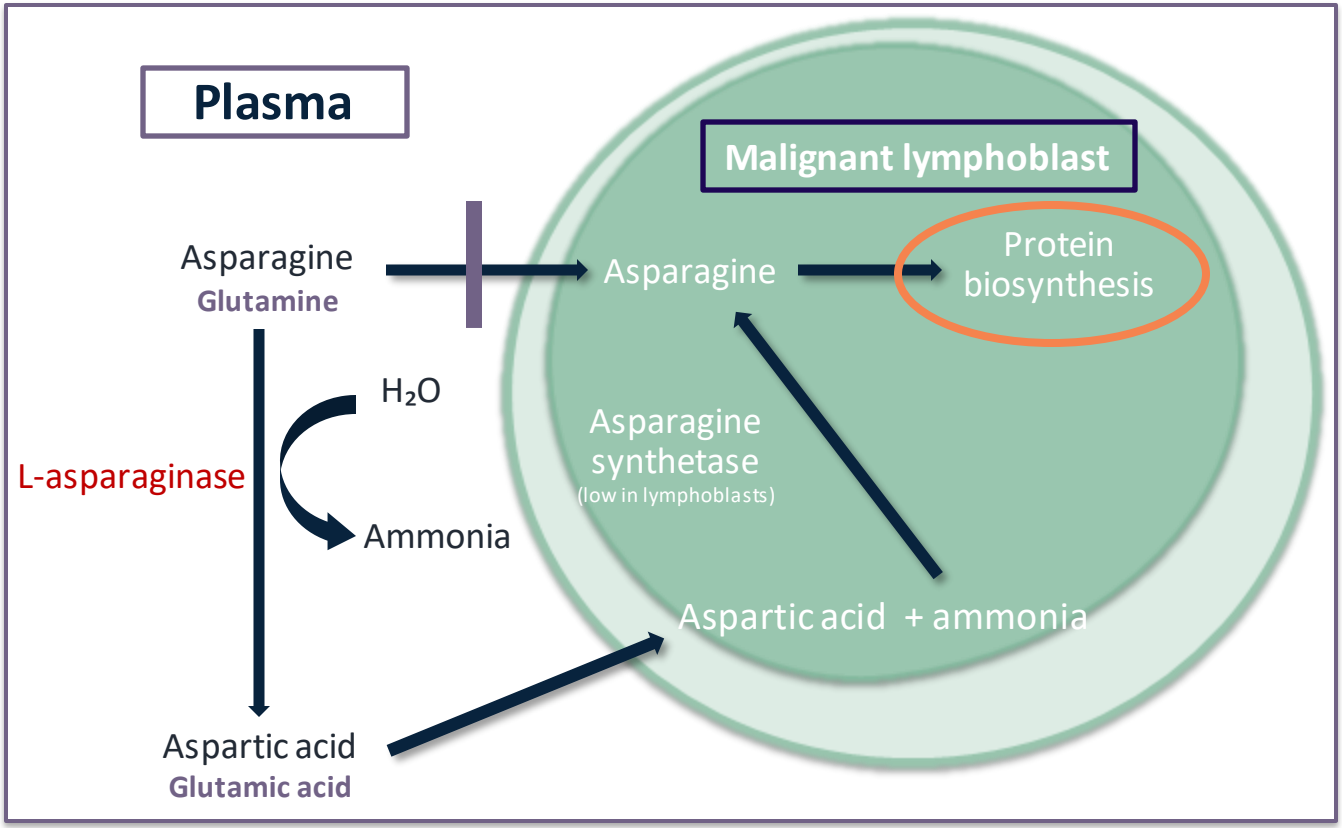
*As component of multiagent chemotherapeutic regimen. ****Non-recombinant asparaginase *Erwinia chrysanthemi* no longer available in United States.**

[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*

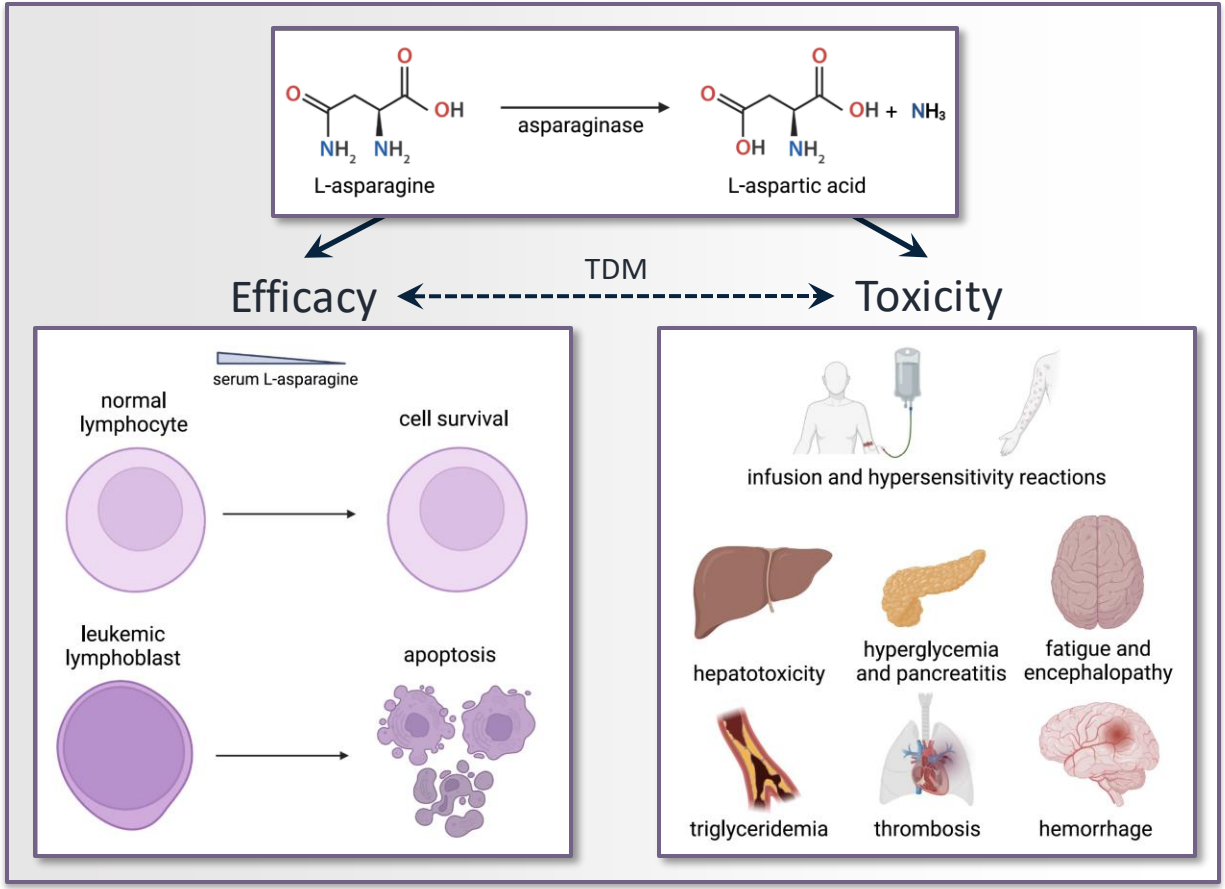



**All proteins affected**

**...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<br>• Silent inactivation | 2–10 |
| **Hepatotoxicity** | • Hyperbilirubinemia<br>• Transaminitis | 25–40<br>>50 |
| **Thrombosis** | • DVT/PE<br>• Cavernous sinus thrombosis | 7–27 |
| **Pancreatitis** | • Laboratory finding<br>• Clinical | 2–18 |
| **Hypertriglyceridemia** | • Laboratory finding | 7–51 |
| **CNS toxicity** | • Fatigue<br>• Encephalopathy | 2–14 |

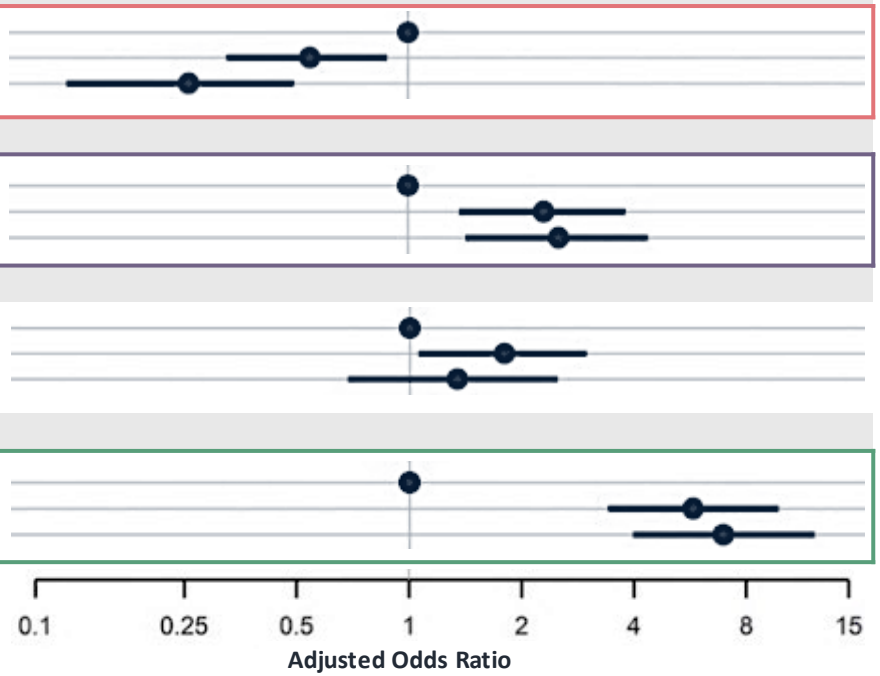
AE, adverse event; DVT, deep vein thrombosis; PE, pulmonary embolism.

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.

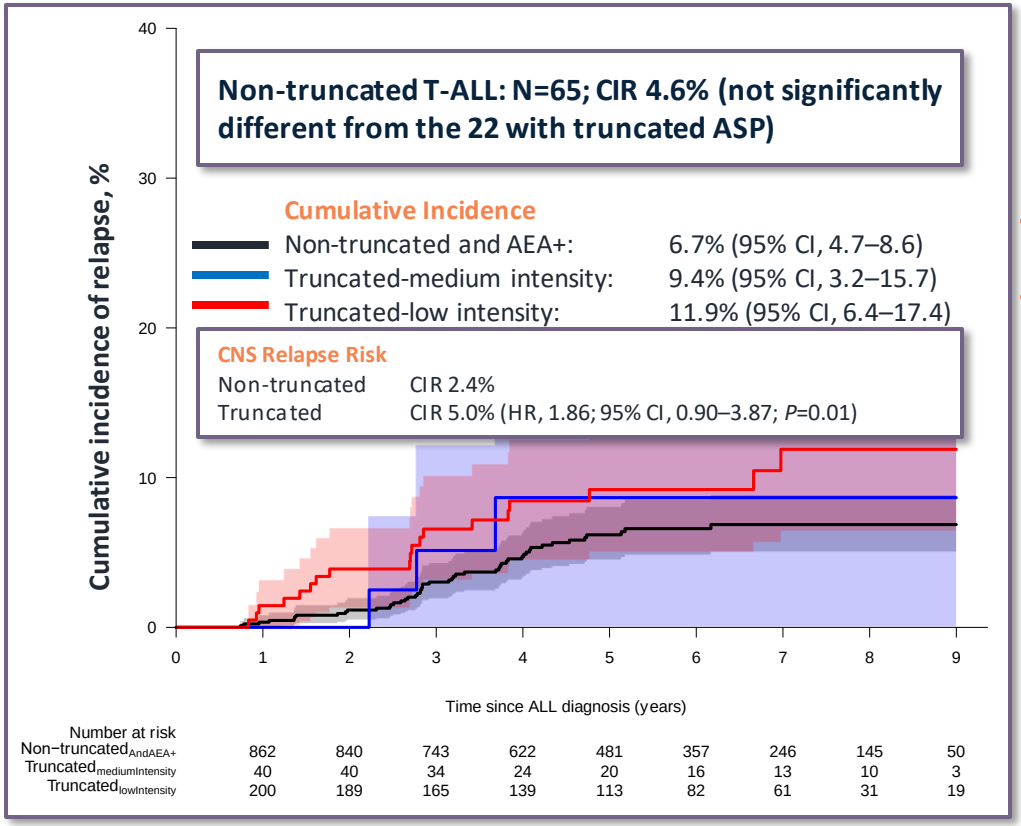
# Reasons for Discontinuation of ASNase in Children Aged 1–17 Years on NOPHO ALL2008

| 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<br>*HLA-DRB1* *04:05<br>*HLA-DRB1* *04:08<br>*HLA-DQA1*<br>*NFATC2* | Alterations in binding pocket of HLA-DR |
| **Hepatotoxicity**[4,5] | *SOD2* rs4880 CC<br>*PNPLA3* rs738409 | Fatty liver disease? |
| **Pancreatitis**[6–9] | *1 asparaginase synthetase<br>*CPA2*<br>*ULK2* rs281366<br>*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.

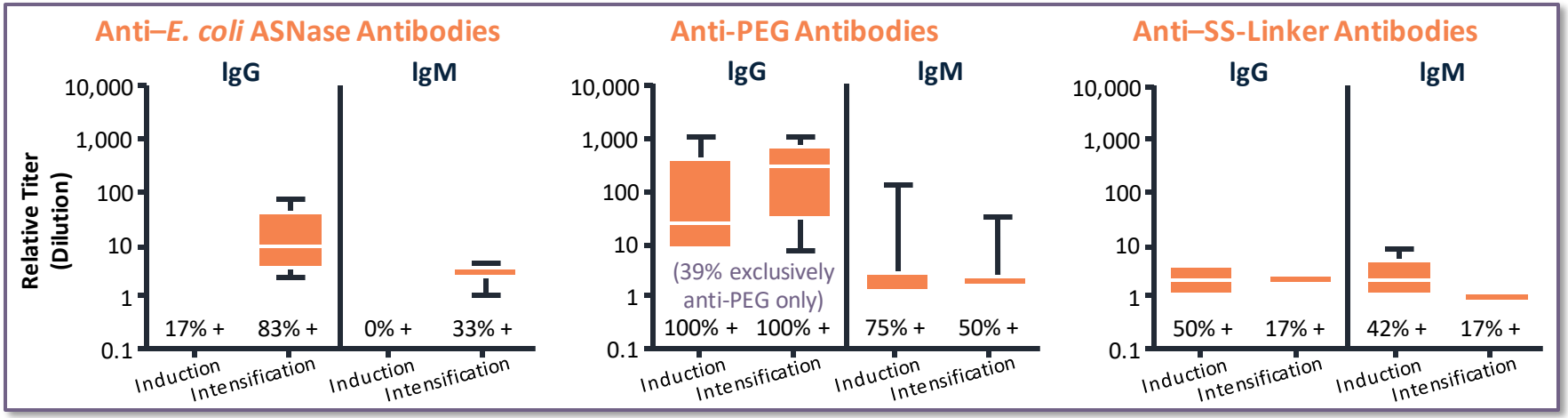
# Option

## *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.

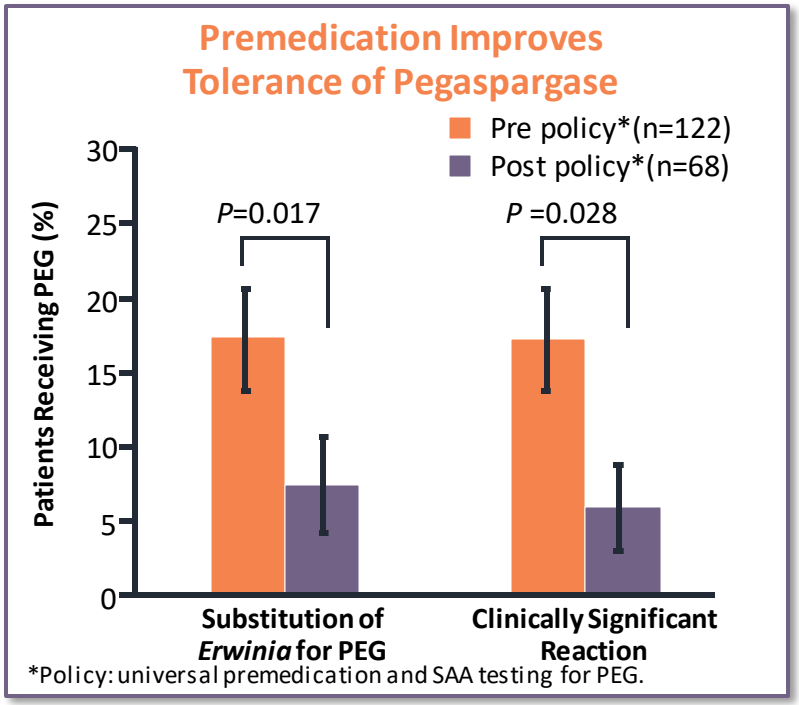
# Option

***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

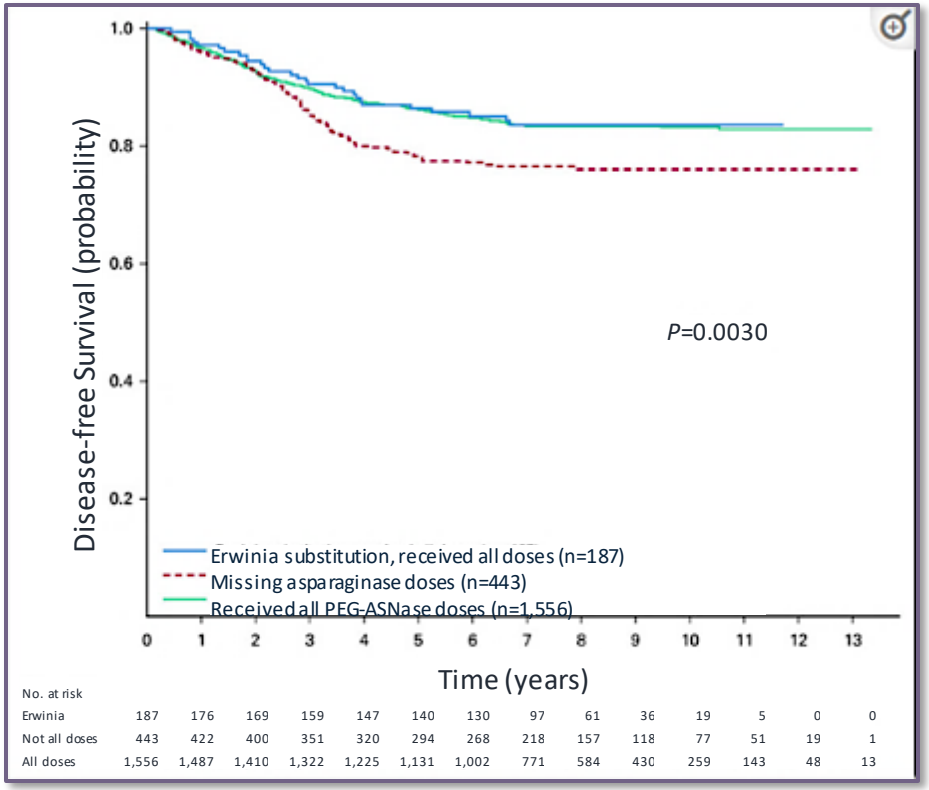
## *Switch to Non–cross-reactive ASNase Formulation*

*(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

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