COG-ACCL1931: A Randomized Trial of Levocarnitine Prophylaxis to Prevent Asparaginase-Associated Hepatotoxicity in Adolescents and Young Adults Receiving Acute Lymphoblastic Leukemia Therapy

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. Timing
Patients will be enrolled and randomized following and as close to initial diagnosis of ALL, LLy, or MPAL as feasible but must be enrolled, randomized, and receive first levocarnitine dose (for those randomized to treatment Arm A levocarnitine prophylaxis) prior to the first dose of pegaspargase or calaspargase pegol.

___2. PRO/QOL Timing
Immediately upon study consent, participants must complete the Quality of Life Contact Information Form found in Appendix III. The information collected in this form is required for administration of assessments by the PRO/QOL team via planned electronic data capture. **We strongly encourage sites to scan and upload this form to Medidata Rave within 24 hours of enrollment to ensure timely completion of the baseline instruments.** See Section 13.1 for complete PRO/QOL administration and timing details.

___3. **Laboratory Studies**
All laboratory studies to determine eligibility must be performed within 7 days prior to *enrollment* unless otherwise indicated.

The following laboratory studies must be repeated prior to the *start of protocol therapy* if >7 days have elapsed from their most recent prior assessment: CBC with differential, total and conjugated bilirubin, AST (SGOT), ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.

If the result of a laboratory study that is repeated at any time *post-enrollment* and prior to the *start of protocol therapy* is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

___4. Age
Age: ≥15 and <40 years at time of diagnosis

___5. Diagnosis
Diagnosis: Newly Diagnosed B-ALL, T-ALL, Lymphoblastic Lymphoma (LLy), or Mixed-Phenotype Acute Leukemia/Lymphoma (MPAL)
Note: *PH+ and PH-like acute leukemia are eligible (use of TKI or CRLF2-targeted concomitant medication must be documented, if used)*

___6. Organ Function Requirements
- Adequate liver function defined as:
  - Conjugated bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, regardless of baseline bilirubin, and
  - SGPT (ALT) ≤ 225 U/L (≤5x ULN)*, and
  - SGOT (AST) ≤250 U/L (≤5x ULN)*
    * **Note:** For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L and SGOT (AST) to 50 U/L regardless of baseline.

For patients receiving ursodiol prior to enrollment, laboratory values must meet above criteria off ursodiol for 7 days.

- Adequate renal function defined as:

A. For pediatric patients (age 15-17 years):

A 24-hour urine Creatinine clearance ≥ 30 mL/min/1.73 m^2 OR

A GFR ≥ 30 mL/min/1.73 m^2. GFR must be performed using one of the following methods:

1. Estimated GFR (eGFR) ≥ 30 mL/min/1.73 m^2

"Bedside" Schwartz formula (2009):
eGFR = 0.413 x (height/Scr)
An online calculator is available through the National Kidney Foundation at
https://www.kidney.org/professionals/kdoqi/gfr_calculatorped

2. Measured GFR ≥ 30 mL/min/1.73 m^2 (any age). If *measured GFR is used, it must be performed using direct measurement with a nuclear blood sampling method or small molecule clearance method (iothalamate or other molecule per institutional standard).*

B. For adult patients (age 18 years or older):
Creatinine clearance ≥ 30 mL/min, as estimated by the Cockcroft and Gault formula or a 24-hour urine collection. Estimated creatinine clearance is based on actual body weight.

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg}\ \dagger}{72 \times \text{creatinine (mg/dl)}}$$

Multiply this number by 0.85 if the participant is a female.
† The kilogram weight is the participant weight with an upper limit of 140% of the ideal body weight (IBW).

An online calculator is available through the National Kidney Foundation at
https://www.kidney.org/professionals/kdoqi/gfr_calculatorcoc

___7. Treatment Plan

- BFM, COG, or C10403-based Induction regimen and must be inclusive of ≥1 dose of pegaspargase or calaspargase pegol, and
- First dose of asparaginase must be planned within the first week of Induction therapy, and
- Dose of pegaspargase or calaspargase pegol must be ≥1,000 IU/ m^2 (dose-capping permitted per primary regimen)

Note*: Co-enrollment on a therapeutic consortia trial is not required.*

The CIRB determined that assent of children age 15 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA

___1. Patients with the following conditions are not eligible
   a) Down Syndrome
   b) Known inherited or autoimmune liver disease impacting conjugated bilirubin (e.g., Alagille Syndrome, primary sclerosing cholangitis, other)
   c) Known biopsy (or imaging) proven severe liver fibrosis (Batts-Ludwig ≥Stage 3)
   d) Unable to tolerate oral formulation of study drug at enrollment

___2. Prior Therapy

Patients who received chemotherapy or treatment for a prior malignancy are not eligible.

The following are permitted: *steroid prophase, hydroxyurea, or other cytoreduction prior to initiation of Induction chemotherapy (must be documented) and chemotherapy for current diagnosis (i.e. initiation of Induction therapy within enrollment window). Chemotherapy prior to enrollment for treatment of a non-malignancy (e.g., steroid or methotrexate for autoimmune disease) is also permitted and must be documented.*

Please see Section 4.1 for the concomitant therapy restrictions for patients during treatment.

___3. Pregnancy and Breastfeeding

- Female patients who are pregnant since fetal toxicities and teratogenic effects in humans are unknown for study drug. A pregnancy test is required for female patients of childbearing potential.
- Lactating females who plan to breastfeed their infants.
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

REQUIRED OBSERVATIONS:

All baseline studies must be performed prior to starting protocol therapy. Study time points after Baseline are calculated from the first day of Induction chemotherapy.

Observation	Induction Phase					End of Consolidation
	Baseline	Days 8±3	Days 15±3	Days 22±3	End of Induction Days 29-35	
Demographics & Treatment	X				X	
Height, Weight	X				X	
CBC with diff/platelets	X				X	
CSF cell count and cytospin	X					
FISH/Cytogenetics/ Molecular	X					
AST, ALT, Total bilirubin, & **Direct (Conjugated) bilirubin**	X	X	X	X	X	
MRD, %					X	X (if EOI MRD ≥0.01%)[2]
FACT/GOG-NTX[1]	X				X	
Self-reported adherence[1]		X	X	X	X	
Pill Count[1]					X	

[1]See **Section 13.0** for additional details on PRO and adherence measures.
[2] Patients who have MRD ≥0.01% at EOI may be routinely assessed for MRD at end of Consolidation (EOC); if available, EOC MRD will be reported.

TREATMENT PLAN:
This is a Phase 3 open-label trial, with patients randomized 1:1, to: **(Arm A)** levocarnitine prophylaxis prior to initial pegaspargase or calaspargase pegol exposure through end of Induction; or **(Arm B)** standard of care without levocarnitine prophylaxis. Randomized participants will be followed from randomization until end of Induction (approximately Day 35) to capture development of the primary outcome.

A rescue arm (Arm C) will be open to participants in Arm B who develop conjugated hyperbilirubinemia > 3 mg/dL during Induction and wish to start levocarnitine supplementation. Sites must complete a Callback form to transition patients from Arm B to Arm C (see Section 4.4 for additional requirements). Participants in Arm A who develop conjugated hyperbilirubinemia > 3 mg/dL may continue with levocarnitine supplementation. Patients on Arms A and C will therefore have the option to receive post-toxicity levocarnitine rescue on protocol therapy until resolution of conjugated hyperbilirubinemia ≤ 3 mg/dL (or start of Consolidation or the next treatment phase, whichever occurs first).

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.

BIOLOGY REQUIREMENTS:
Six (6) blood samples baseline through days 29-35.
First sample prior to **ANTHRACYCLINE (IF DRAWN ON THE SAME DAY)**