COG-AALL1521: A Phase 2 Study of the JAK1/JAK2 Inhibitor Ruxolitinib With Chemotherapy in Children With De Novo High-Risk CRLF2-Rearranged and/or JAK Pathway–Mutant Acute Lymphoblastic Leukemia

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.
A subject who meets all of the following criteria may be included in the study:

___1. Age ≥ 1 year and ≤ 21 years at time of leukemia diagnosis.

___2. Newly diagnosed (*de novo)* HR Ph-like B-ALL defined as meeting any one or more of these criteria:
   a. Age ≥ 10 years at diagnosis
   b. WBC ≥ $50 \times 10^3/\mu L$.
   c. CNS3 leukemia at diagnosis
   d. Systemic steroid pretreatment without presteroid WBC documentation (consistent with criteria described in Protocol AALL1131)

   Note: Standard risk B-ALL that becomes HR due to end-Induction MRD+ status does not meet this criterion)

___3. Diagnostic bone marrow or peripheral blood sample must have genetic and gene expression profiling (performed by low density microarray [LDA] testing at COG ALL Reference Laboratory) that demonstrates a Ph-like expression profile (LDA-positive) and contains 1 of the following genetic lesions:
   a. CRLF2 rearrangement with confirmed JAK1 or JAK2 mutation (JAK+).
   b. CRLF2 rearrangement without JAK mutation.
   c. Other JAK pathway alterations (eg, JAK2 fusions, EPOR fusions, SH2B3 deletions, IL7RA mutations) with or without CRLF2-R, or CRLF2-R with unknown JAK status* as determined by a COG ALL Reference Laboratory.

   * Note: Cases of unknown status must be approved by the sponsor in the case of assay failure or inadequate and unrecoverable sample for mutation analysis (approval should be sought when other attempts at procuring the data have been exhausted).

___4. Has completed a 4-drug regimen Induction therapy (modified aBFM regimen or equivalent) on Study AALL1131 or per the institutional standard of care for HR B-ALL.

___5. Minimal residual disease must have been assessed from bone marrow by flow cytometry at end Induction (the result determines cohort assignment):
   a. End-Induction MRD+ status for subjects in Cohorts A, B, and C.
   b. End-Induction MRD(-) status for subjects in Cohort D.

___6. Male and female subjects must be of nonchildbearing potential or willing to take appropriate precautions to avoid pregnancy or fathering a child for the duration of study participation, by meeting 1 of the following criteria:
   a. Female of nonchildbearing potential (ie, prepubescent or surgically sterile with a hysterectomy and/or bilateral oophorectomy).
   b. Female of childbearing potential who has a negative serum pregnancy test at screening and before the first dose of study drug on Day 1 and who agrees to take appropriate precautions to avoid pregnancy from screening through safety follow-up.*
   c. Male who is prepubescent.
   d. Male who agrees to take appropriate precautions to avoid fathering children from screening through safety follow-up.*

   * For Criterion 6b or 6d, permitted prophylactic methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated, and the subject's understanding should be confirmed.

EXCLUSION CRITERIA:

A subject who meets any of the following criteria will be excluded from the study:

___1. Receipt of any other cytotoxic chemotherapy before Induction therapy (except pre-Induction hydroxyurea or steroid pretreatment).
___2. BCR-ABL1–rearranged ALL.
___3. Trisomy 21 (Down syndrome).
___4. Other malignancy in addition to ALL, or secondary ALL.
___5. Need for concurrent treatment with other anticancer therapy in addition to the Protocol-defined regimen.
___6. Has a significant concurrent, uncontrolled medical condition, including but not limited to the following:
   a. Renal
      – Calculated creatinine clearance or radioisotope glomerular filtration rate < 70 mL/min/1.73 m^2.
   b. Hepatic
      – Alanine aminotransferase ≥ 5 × upper limit of normal (ULN) for age.
      – Direct bilirubin ≥ 1.5 × ULN (may be assumed if total bilirubin is below ULN).
      – History or evidence of cirrhosis.
   c. Hematologic
      – Platelet count < 75 × 10^3/μL.
      – Absolute neutrophil count < 750/μL.
___7. Chronic or current active infectious disease requiring systemic antibiotics, antifungal treatment, or antiviral treatment that is not well-controlled or resolving.
___8. Hepatitis: Positivity for either hepatitis C virus (HCV) antibody, anti–hepatitis B core (anti-HBc) immunoglobulin G or immunoglobulin M, or hepatitis B surface antigen (HBsAg).
___9. Known human immunodeficiency virus infection.
___10. Prior treatment with a JAK inhibitor for any indication.
___11. Unwillingness to undergo transfusion with blood components.
___12. Current use of prohibited medication as described in Section 5.7.1.
___13. Use of any potent cytochrome P450 (CYP) 3A4 inhibitor or inducer (Appendix E) or fluconazole within 5 half-lives before the first dose of study drug. (Note: Potent CYP3A4 inhibitors are discouraged but permitted during the study with adjustment of study drug dose; see Section 5.5.3).
___14. Known hypersensitivity or severe reaction to ruxolitinib or its excipients (see IB) or to the components or excipients of components of the chemotherapeutic regimen.
___15. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
___16. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
___17. Currently breastfeeding.
___18. Inability to swallow and retain oral medication (use of nasogastric or gastrostomy tube is permitted if used for feeding).
___19. Inability or unwillingness of subject (or parent, guardian, or legally authorized representative) to comprehend or sign the informed consent form (ICF).
___20. Any condition that would, in the investigator's judgment, interfere with full participation in the study (including administration of study drug and attending required study visits), pose a significant risk to the subject, or interfere with interpretation of study data.

REQUIRED OBSERVATIONS:

- CBC with diff CMP, LDH, Mg, Phos, serum preg. PT, PTT, PT-1NR. Fasting if able. Lipase Amylase, Lipid Panel
- HBsAg
- HBsAg antibody
- HBc antibody
- HCV antibody – Results of antibody tests are required prior to enrollment.

PCR testing

- HBV-DNA
- HCV-RNA

Results of PCR test required prior to enrollment IF there is any question as to hepatitis status.

TREATMENT PLAN:
The study is a nonrandomized Phase 2 study with a pilot (safety) part to determine safety of combining ruxolitinib with standard post-Induction multi-agent chemotherapy and to determine the dose of ruxolitinib for subsequent efficacy testing in combination with chemotherapy. The backbone multi-agent therapy is a modified aBFM regimen that is used in the COG Study AALL1131 (control arm) for newly diagnosed patients with B-ALL. This chemotherapy backbone is the current leading standard of care for patients with HR B-ALL in the United States and Canada. Once the RP2D has been identified for ruxolitinib in combination with cytotoxic chemotherapy, Part 2 will then be enrolled. Both Part 1 and Part 2 will enroll all cohorts (Section 4.1.1); however, the primary endpoint will be evaluated using only those subjects in Cohorts A and B who began treatment at the RP2D.

TOXICITIES AND DOSAGE MODIFICATIONS:
Modifications of the multi-agent chemo regimen will be performed in accordance with the standard of care, and are addressed in Section 7.

For dose-limiting toxicity guidelines for Ruxolitinib see Section 5.4.3

SPECIMEN REQUIREMENTS:
Timed PD & PK samples on Day 1 at predose, hour 1, hour 2 and hour 4.