Patient Population
See Section 3 for Complete Eligibility Details

Eligibility Criteria for Pre-registration (Step 0):
• Age ≥ 18 and ≤ 75; ECOG PS 0-3
• Must be newly diagnosed with B-ALL or suspected to have ALL (must have BCR-ABL1 positive disease)
• Must not have a diagnosis of BCR/ABL T-ALL
• Must not have received chemotherapy for B-ALL
• Patients on TKI prior to registration to Step 1 are permitted if they received no more than 14 days of TKI
• Must not have unstable epilepsy that requires treatment
• Patients with lymphoid blast crisis CML are not eligible

Eligibility Criteria for Registration to Step 1:
• Must have a diagnosis of Ph+ ALL that has been determined locally, and bone marrow/peripheral blood sent and receipt confirmed for central confirmation
• Must not have known significant organ dysfunction defined per protocol (labs obtained ≤ 28 days prior to Step 1 registration; see protocol for details)
• Patients with HIV, HBV, HCV are eligible per protocol
• No active concomitant malignancy (see protocol)
• If applicable, patient must be NYHA class 2B or better
• Investigators must confirm which TKI the patient is to receive

Eligibility Criteria for Randomization to Step 2:
• Must have completed at least 7 and no more than 21 days of protocol treatment on Arm A prior to Step 2 randomization (see protocol for details)
• For patients under 70, intended chemotherapy regimen must be determined prior to randomization
• No active CNS involvement by leukemic blasts (see protocol for details)
• Must have resolved serious infectious/medical complications related to therapy

Eligibility Criteria for Registration to Step 3:
• Institution has received centralized MRD results confirming positive status

Treatment Plan
See Section 5 for Complete Treatment Details

Step 1 – Single Arm Steroid + TKI Pre-Induction:
• Arm A: Prednisone 60 mg/m² PO (max dose 140 mg) daily days 1-21 + TKI (dasatinib 140 mg PO or ponatinib 30 mg PO, days 1-21) daily
• Spinal fluid examination should be performed early during Step 1 (i.e., during first 3 days of therapy)

Step 2 Randomization – Induction Therapy:
• To be initiated within 7 days of Step 2 randomization
• Arm B: Chemotherapy arm (4 cycles + continuous therapy with TKI [dasatinib/ponatinib]); see protocol for fit patients ages 18-70 or patients > 70/unfit
• Arm C: Blinatumomab arm (2 cycles + continuous therapy with TKI)
      ◦ Dexamethasone 20 mg PO/IV day 1; Blinatumomab 9 mcg/day continuous IV days 1-7 followed by 28 mcg/day continuous IV days 8-28, followed by 14 day treatment-free interval
• Patients must have achieved CR or CRi in order to begin intensification therapy; high dose methotrexate is to be administered after MRD testing

Step 3 Registration – Re-induction:
• Arm D: Patients treated on Arm B who at the end of induction remain MRD positive will receive blinatumomab based re-induction (i.e., Arm C regimen)
• Arm E: Patients treated on Arm C who at the end of induction remain MRD positive will receive chemotherapy based re-induction (i.e., Arm B regimen)
• Patients who received induction and re-induction but remained with detectable disease will proceed to follow-up and are treated per investigator discretion (see protocol)

Patients with a MRD Negative Status:
• Following step 2 or 3, patients will proceed to follow-up treatment per physician discretion with recommendations for allo-HCT or consolidation followed by maintenance therapy (see protocol)

Study Chair:
Yishai Ofran, MD
Co-Chair:
Jacob M. Rowe, MD

Patient Enrollment
All Sites: Oncology Patient Enrollment Network (OPEN) https://open.ctsu.org/open

Protocol Information

Please Enroll Your Eligible Patients!
Schema

Step 0: PRE-REGISTRATION
BM or PB submission for eligibility

Step 1: REGISTRATION (Pre-Induction)
Arm A
Prednisone + Investigator’s choice of Dasatinib or Ponatinib

Step 2: RANDOMIZATION (Induction)
Arm B
Hyper CVAD® + Steroids + TKI (Dasatinib or Ponatinib)
x4 cycles of chemo

Arm C
Binatumumab + TKI (Dasatinib or Ponatinib)
x2 cycles

BM submission for MRD Testing

MRD Negative
AllSCT followed by maintenance therapy
Consolidation Therapy (HyperCVAD, 4 Cycles) followed by maintenance therapy
Follow-Up

MRD Positive
Follow-Up

Arm D
Binatumumab + Steroids + TKI (Dasatinib or Ponatinib)
x2 cycles

Arm E
Hyper CVAD® + Steroids + TKI (Dasatinib or Ponatinib)
x4 cycles of chemo

Intensification
HD MTX x200mg/m² (1 cycle)³

MRD Negative
AllSCT followed by maintenance therapy
Consolidation Therapy (Binatumumab, 2 Cycles) followed by maintenance therapy
Follow-Up

MRD Positive
MRD Testing

MRD Positive
MRD Testing

MRD Negative
Follow-Up

Consolidation Therapy (Binatumumab, x2 cycles) followed by maintenance therapy
AllSCT followed by maintenance therapy
Consolidation Therapy (HyperCVAD, x4 cycles) followed by maintenance therapy

Acruel: 346 patients

1. Bone marrow specimen must be submitted to ECOG-ACRIN Leukemia Bank at MD Anderson Cancer Center for the central establishment of BCR-ABL status to confirm patient’s eligibility for registration to Step 1 as outlined in Section 10.1. If a diagnosis of BCR-ABL positive ALL has been established locally, the patient may be registered to Step 1 without waiting for central confirmation. Peripheral Blood is only acceptable if there is circulating blasts.

2. Patients older than 70 and younger until patients are subject to modified Hyper-CVAD treatment only. All other patients will be treated with full Hyper-CVAD as outlined in Section 5. Type of planned Hyper-CVAD therapy is to be reported at time of registration.

3. At Step 2 Randomization, patients will be stratiﬁed by age (< 60 years vs 60-70 years vs > 70 years) of age, TKI intended to receive (Dasatinib vs Ponatinib) and for patient age < 70 years, if patient is randomized to chemotherapy, investigators declaration of full or modiﬁed Hyper-CVAD protocol.

4. Patients must have achieved CR or CRI in order to begin intensiﬁcation therapy.