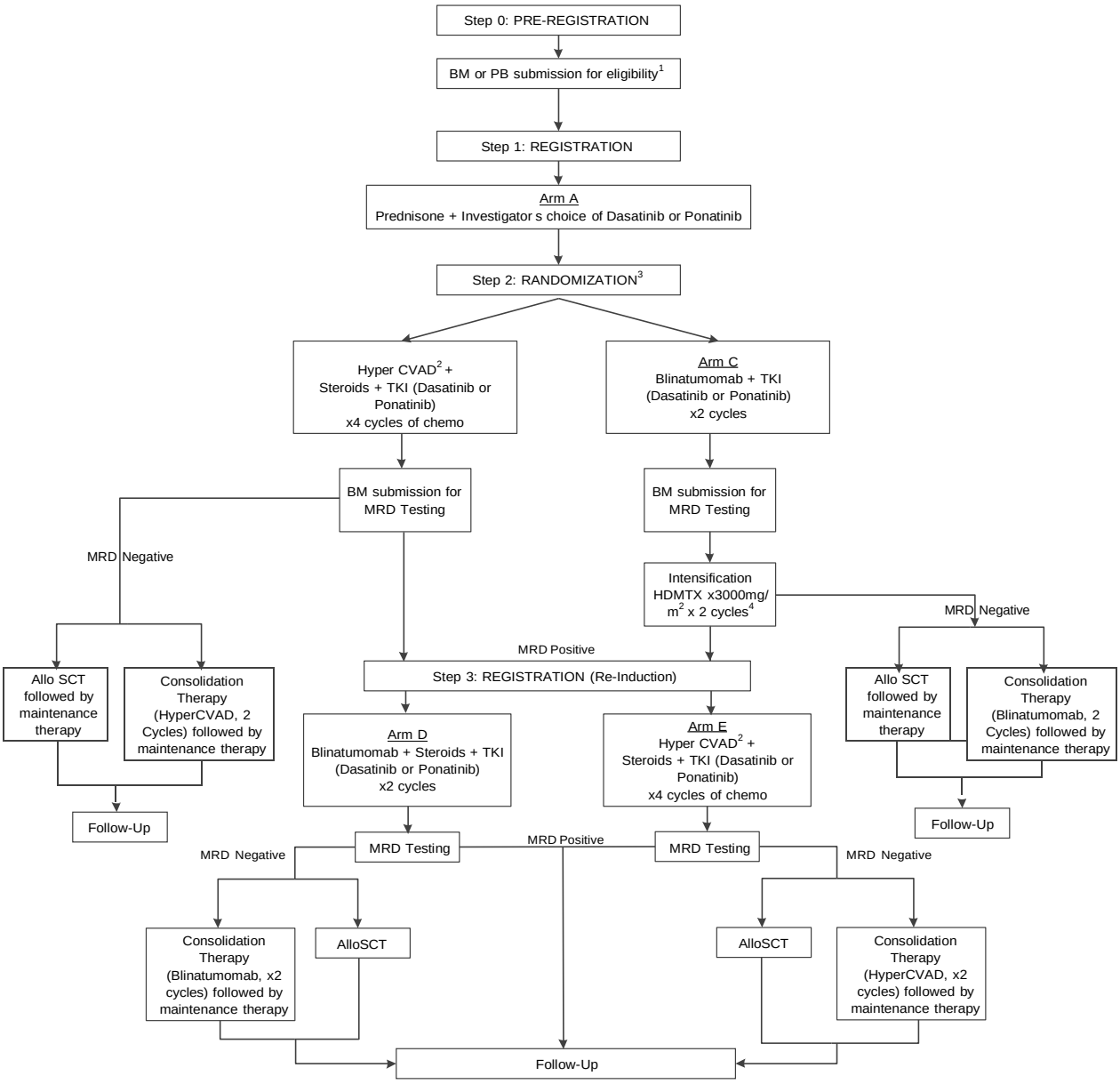
Schema



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 outline in Section 10.2. 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 unfit 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.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: This study involves preregistration during which specimens must be submitted for centralized BCR/ABL testing and results will determine the patient's Step 1 eligibility.

3.1 Preregistration (Step 0) Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 and ≤ 75 years of age.

_____ 3.1.2 Patient must be newly diagnosed with B-ALL or is suspected to have ALL

_____ 3.1.2.1 Patient must have BCR-ABL1 positive disease. The diagnosis of ALL and the presence of BCR-ABL translocation must be confirmed centrally. Please see Section 10, for central determination of BCR-ABL1 status. Patients can be registered and begin Step 1 therapy while awaiting central laboratory eligibility confirmation.

NOTE: Bone marrow and/or peripheral blood specimen must be submitted to the ECOG-ACRIN Leukemia Laboratory at MD Anderson Cancer Center to determine patient's eligbility for registration to Step 1 or confirm patient evaluability. Centrally FACS analysis will be performed to determine B-ALL and to exclude

acute myeloid leukemia (AML) or acute bi-phenotypic leukemia and baseline BCR-ABL status will be determined by fluorescent in situ hybridization (FISH). The ECOG-ACRIN Leukemia Laboratory will forward results within 48 hours of receipt of the specimen to the submitting institution.

Bone marrow is to be from first pull (initial or re-direct). Specimens must contain sufficient blast cells.

In cases where the bone marrow aspiration may be inadequate, or the bone marrow examination has already been performed prior to study consent and enrollment on Step 0, peripheral blood may be submitted, given that adequate circulating blasts are present (>10%).

If a diagnosis of BCR-ABL positive B-ALL has already been established by local CLIA certified laboratories, the patient may be registered to Step 1 without waiting for central confirmation.

_____3.1.3 Patient must not have received chemotherapy for B-ALL. Patients who received up to five days of hydroxyurea or steroids of any kind with the aim to reduce disease burden prior to study registration are eligible.

_____3.1.4 Patients who started any kind of TKI prior to study registration are allowed to proceed on the study if they received no more than 14 days of TKI.

_____3.1.5 Patient must not have unstable epilepsy that requires treatment.

3.2 Step 1 Registration Eligibility Criteria

_____3.2.1 The diagnosis of Ph+ ALL has been determined locally, and bone marrow and/or peripheral blood was sent for central confirmation or determined centrally by the ECOG-ACRIN Leukemia Laboratory at MD Anderson Cancer Center.

_____3.2.2 Women must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All females of childbearing potential must have a blood test or urine study within 14 days prior to registration to rule out pregnancy.

A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential?_____(Yes or No)

Date of blood test or urine study: _____

_____3.2.3 Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse from the time of registration, while on study treatment, and until at least six months after the last dose of study treatment.

_____3.2.4 Patient must not have known significant organ dysfunction as defined below:

3.2.4.1 Patients must have total bilirubin ≤ 3 mg/dL (unless related to Gilbert's syndrome in which case total bilirubin must be ≤ 5mg/dL) and AST(SGOT)/ALT(SGPT) ≤ 2.5X the instutional ULN and estimated creatinine clearance > 45mg/min (based on Cockcroft-Gault Equation:

$$\frac{\text{(140 - Pt. age) x (Pt. weight in kg) (for females, multiply the result by 0.85)}}{\text{72 x patient's serum creatinine}}$$

Total bilirubin:_____Date of Test: _____

Gilbert's Syndrome? _(Yes or No)

AST(SGOT):_____ULN: _____

Date of Test: _____

ALT(SGPT):_____ULN: _____

Date of Test: _____

Estimated creatinine clearance level: _____

Date of Test: _____

——— 3.2.4.2 Patients with acute organ dysfunction at registration, which may be attributed to leukemia can be registered regardless of lab results at presentation. Such patients will be allowed to register and can start Arm A steroid + TKI therapy but will only be allowed to proceed to Step 2 randomization if the eligibility criteria outlined in Section 3.3 is met.

_____3.2.5 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

_____ 3.2.6 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable or on suppressive therapy, if indicated.

_____3.2.7 Patients with a history of hepatitis C virus (HCV) infection must have an undetectable HCV viral load and if indicated, on treatment.

_____3.2.8 Patients with a prior malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

_____3.2.9 Patient must not have active concomitant malignancy. Patients on chronic hormonal therapy for breast or prostate cancer or patients

treated with maintenance with targeted agents but are in remission with no evidence for the primary malignancies can be included.

_____3.2.10 Patients must not have complaints of symptoms and/or have clinical and/or radiological signs that indicate an uncontrolled infection or any other concurrent medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol.

_____3.2.11 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients must be class 2B or better.

_____3.2.12 Investigators must confirm which TKI patient is to receive.

Ponatinib_____Dasatinib_____(please check the selected TKI)

NOTE: Patients with known T315I mutation status should receive ponatinib treatment.

NOTE: In situations due to insurance coverage issues and the pre-selected TKI is not immediately available, patients can receive dasatinib or imatinib during Step 1. The investigator must re-specify dasatinib or ponatinib prior to Step 2 randomization and from then on patients must receive the pre-selected TKI only.

3.3 Step 2: Randomization - Eligibility Criteria

_____3.3.1 Patient must have completed at least 7 of 21 days of protocol-treatment on Arm A prior to randomization.

NOTE: First day of steroids prescription after registration will be considered as the first day of study therapy. The selected TKI should be initiated prior to randomization.

_____ 3.3.2 Patients who presented with acute organ dysfunction at Step 1 must have their total bilirubin and AST (SGOT) /ALT(SGPT) reduce to <2x institutional ULN and have an estimated creatinine clearance >45mg/min (based on Cockcroft-Gault Equation:

$$\frac{(140 - \text{Pt. age}) \times (\text{Pt. weight in kg}) \text{ (for females, multiply the result by 0.85)}}{72 \times \text{patient's serum creatinine}}$$

Total bilirubin:_____ULN:_____

Date of Test:_____

AST(SGOT):_____ULN:_____

Date of Test:_____

ALT(SGPT):_____ULN:_____

Date of Test:_____

Estimated creatinine clearance:_____

Date of Test: _____

_____ 3.3.3 Investigators must confirm which TKI patient is to receive.

Ponatinib_____Dasatinib_____(please check the selected TKI)

NOTE: Patients with known T315I mutation status should receive ponatinib treatment.

_____3.3.4 For patients under age 70, intended chemotherapy regimen must have been determined prior to randomization:

Fit for full doses____Reduce doses____(Please check your selection)

_____ 3.3.5 Patient must not have active CNS involvement by leukemic blasts. Patients with signs of CNS involvement at presentation are eligible for randomization if clearance of blasts from the CSF is demonstrated.

3.4 Step 3: Registration (Re- Induction) – Eligibility Criteria

_____3.4.1 Institution has received centralized MRD results confirming positive status.

_____3.4.2 Patients who presented with acute organ dysfunction must have their total bilirubin and AST (SGOT) /ALT(SGPT) reduce to < 2x institutional ULN and have an estimated creatinine clearance > 45mg/min (based on Cockcroft-Gault Equation:

$$\frac{(140 - \text{Pt. age}) \times (\text{Pt. weight in kg}) \text{ (for females, multiply the result by 0.85)}}{72 \times \text{patient's serum creatinine}}$$

Total bilirubin:_____ULN:_____

Date of Test:_____

AST(SGOT):_____ULN:_____

Date of Test:_____

ALT(SGPT):_____ULN:_____

Date of Test:_____

Estimated creatinine clearance:_____

Date of Test: _____

_____ 3.4.3 Investigators must confirm which TKI patient is to receive.

Ponatinib_____Dasatinib_____(please check the selected TKI)

NOTE: Patients with known T315I mutation status should receive ponatinib treatment.

_____ 3.4.4 For patients under age 70 and previously assigned to Arm C, intended chemotherapy regimen must have been determined:

Fit for full doses____Reduced doses___(Please check your selection)

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.