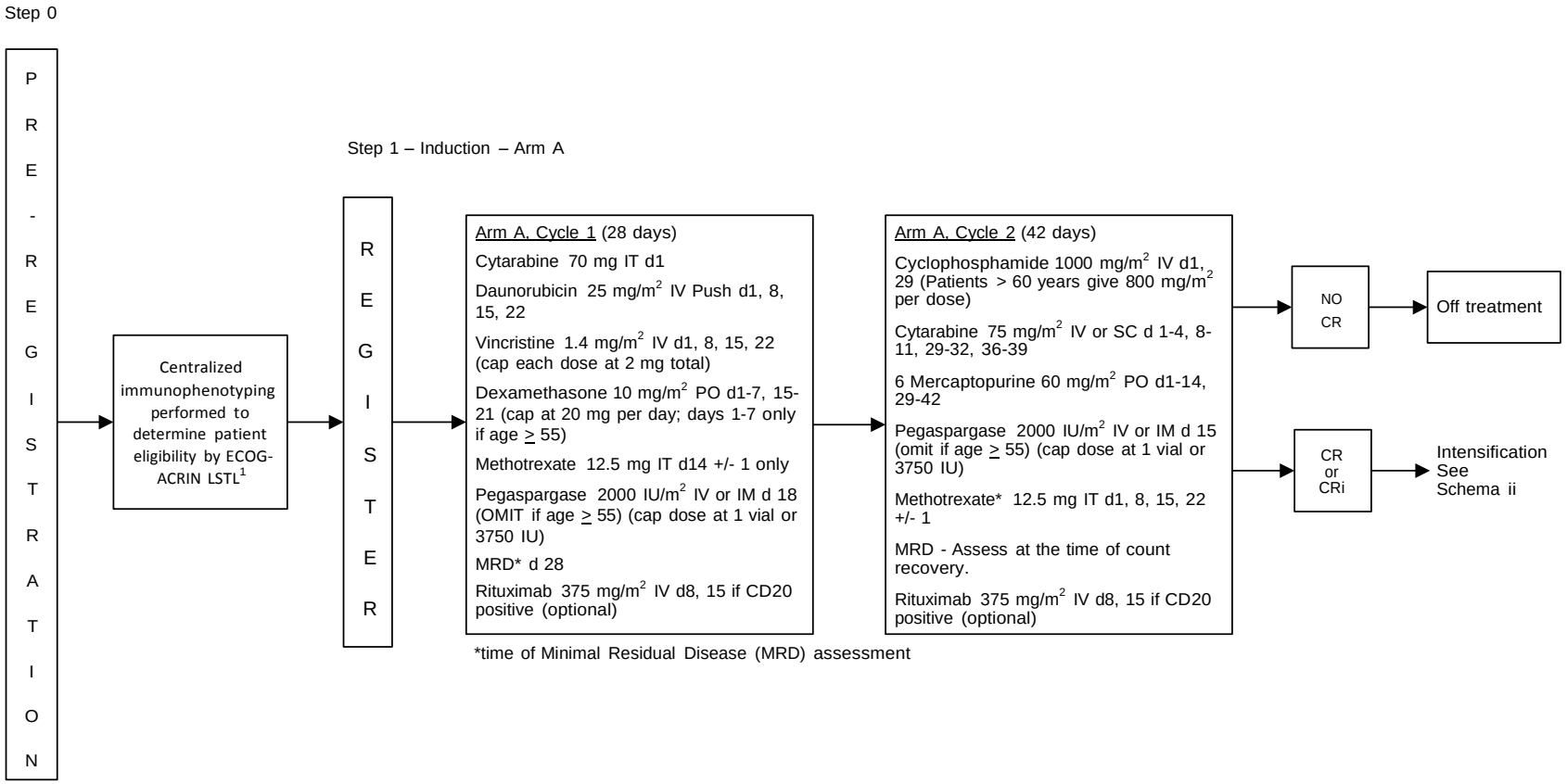
Rev. 7/14, 6/16, 8/17

Schema



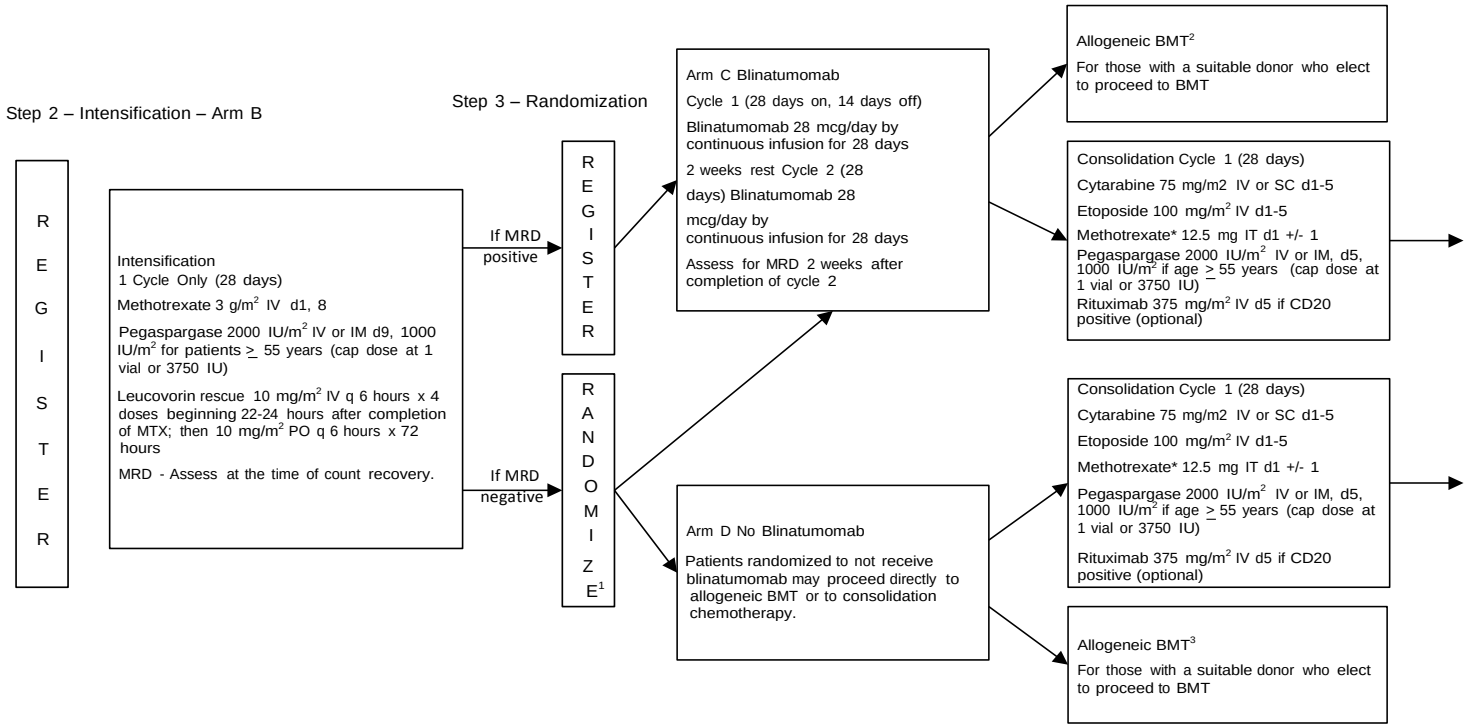
Total Accrual: 488

i

1. Bone Marrow and peripheral blood specimens must be submitted for mandatory testing for participation in this study.
* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Rev.7/14,3/15, 6/16, 8/17

Schema



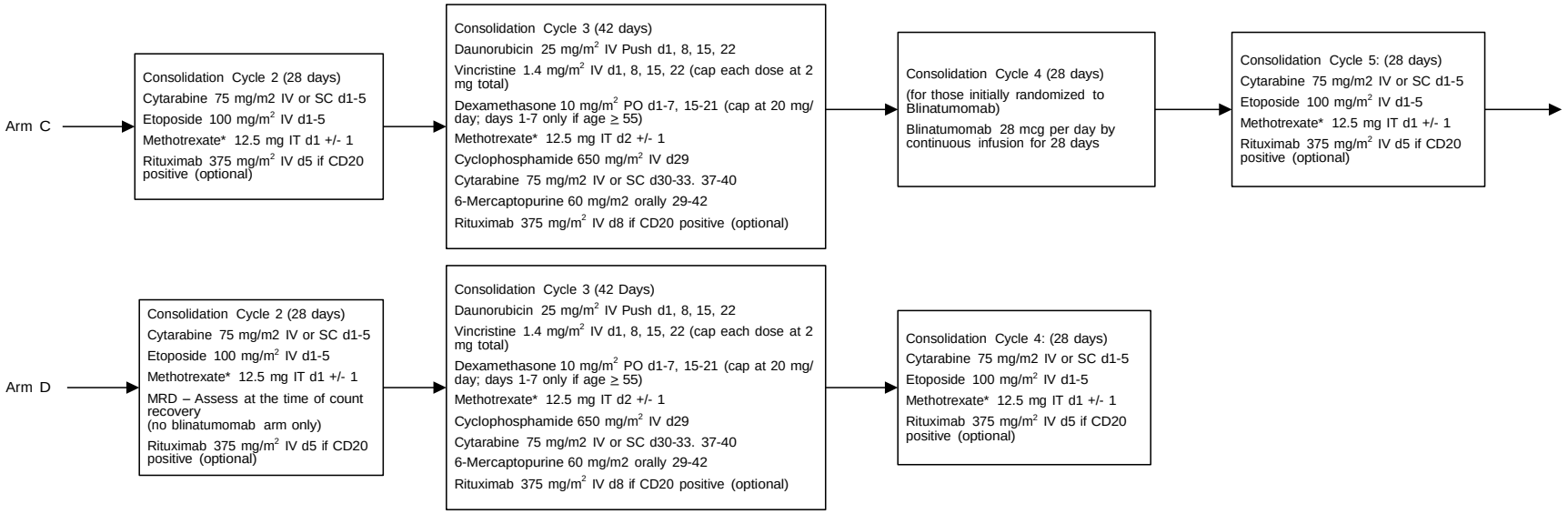
ii

1. Stratification:
   - < 55 yrs. vs ≥ 55 years
   - CD20 status positive vs. negative
   - rituximab use yes or no
   - Intent to receive allogeneic SCT or not
2. Patients may receive up to 2 cycles of consolidation chemotherapy prior to transplant.
   NOTE: Only submit bone marrow aspirates from the FIRST PULL for MRD.
3. Patients may receive up to 3 cycles of consolidation chemotherapy prior to transplant.
   NOTE: Only submit bone marrow aspirates from the FIRST PULL for MRD.

* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Rev.6/16, 8/17

Schema

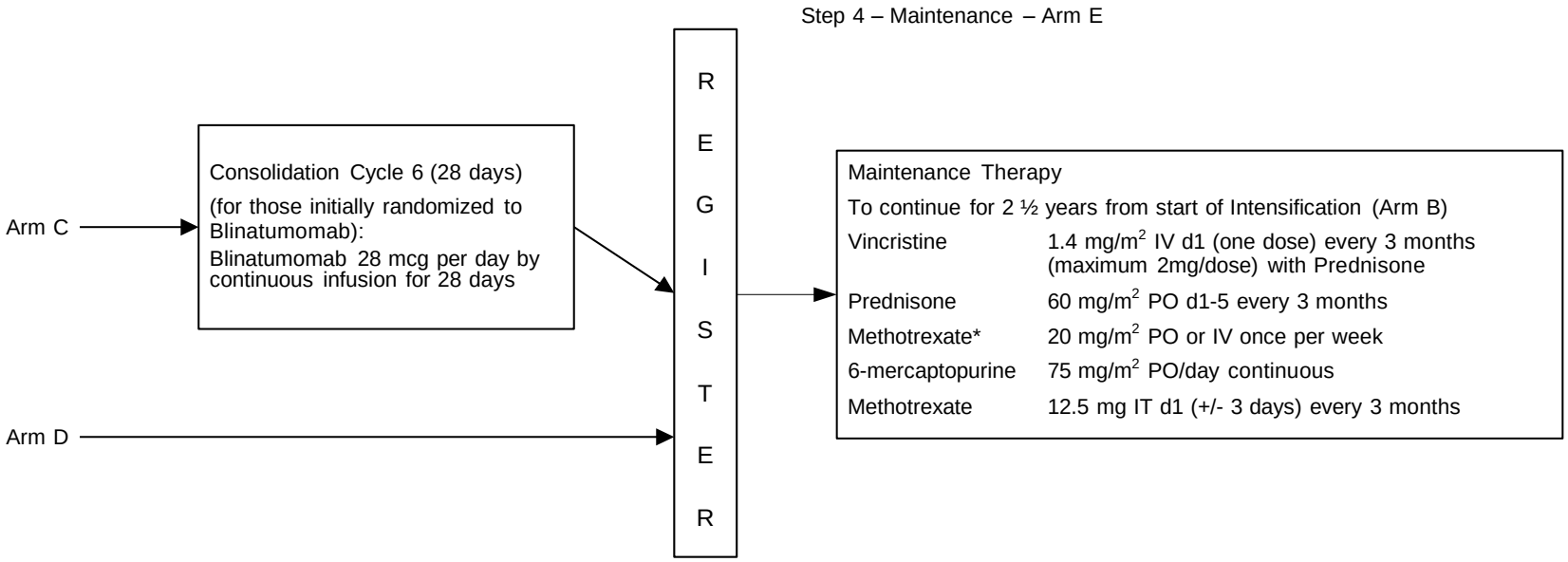


iii

* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Rev.6/16, 1/17, 8/17

Schema



* During a shortage of preservative-free methotrexate, institutions without a sufficient supply of preservative-free methotrexate for intrathecal use can switch to using cytarabine intrathecally. The suggested dose of IT cytarabine is 100 mg (or per local institutional standard) and is to be administered following the IT methotrexate schedule for the given cycle. The cytarabine can optionally be combined with 50 mg of hydrocortisone if desired.

Rev. 7/14

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: All questions regarding eligibility should be directed to the study chair or study chair liaison.

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 pre-registration (see Section 4). Bone marrow and peripheral blood specimens must be submitted for centralized immunophenotyping.

Rev. 6/16

Rev. 7/14

3.1 Pre-Registration

Rev.6/16

_____Diagnostic bone marrow and/or peripheral blood specimens **must be submitted** for immunophenotyping and selected molecular testing, and the establishment of BCR/ABL status. Testing will be performed by the ECOG-ACRIN Leukemia Translational Research Laboratory (LTRL) and reported to the institution.

NOTE: IT IS ESSENTIAL THAT A SAMPLE CONTAINING SUFFICIENT BLAST CELLS BE SUBMITTED TO THE ECOG-ACRIN LTRL AT BASELINE SO THAT SUBSEQUENT BONE MARROW ASSESSMENTS OF MRD CAN BE DONE. IN ADDITION TO ALLOWING THE LTRL TO CONFIRM ELIGIBILITY BASED ON BLAST CELL IMMUNOPHENOTYPE AND BCR/ABL STATUS, IT IS ALSO IMPERATIVE THAT AN ADEQUATE NUMBER OF BLASTS BE BANKED FOR ANALYSIS BY DRS MULLIGHAN/WILLMAN. WITHOUT ADEQUATE BASELINE SAMPLES, PATIENTS WILL NOT BE ABLE TO BE TREATED AND RANDOMIZED ON THIS PROTOCOL. IF A BONE MARROW ASPIRATE IS NOT AVAILABLE FOR LTRL SUBMISSION AT BASELINE, IT IS IMPERATIVE THAT DR PAIETTA FROM THE LTRL IS CALLED TO DISCUSS THE PERIPHERAL BLOOD WBC AND BLAST COUNT BEFORE BLOOD ONLY IS SUBMITTED.

Rev. 6/16

Rev. 2/18

NOTE: Hydroxyurea can be given for up to 5 days prior to initiation of protocol therapy for control of leukocyte count and/or other symptoms or signs. Corticosteroids can be given after pre-registration to the protocol and submission of baseline marrow and blood samples for control of leukocyte count and/or other symptoms or signs prior to

initiation of protocol therapy if needed. If corticosteroids are given prior to pre-registration, contact the study chair as the patient may still be eligible to participate.

3.2 Induction Eligibility Criteria – Step 1

Rev. 7/14 _____3.2.1 Age ≥ 30 years and ≤ 70 years.

New diagnosis of B lineage ALL must be made upon bone marrow or peripheral blood immunophenotyping. Cases with myeloid antigen expression, but unequivocal lymphoid immunophenotype, are eligible.

_____ 3.2.2 Mature B ALL (Burkitt's-like leukemia) is excluded from enrollment in this trial.

Rev. 2/18 Pre-study bone marrow biopsy and aspirate must be completed ≤ 1 week prior to registration.

_____3.2.3 Negativity for the Philadelphia chromosome must be established by conventional cytogenetics, FISH and/or PCR. Patients who are negative for the Philadelphia chromosome by conventional cytogenetics must have FISH or PCR performed for BCR/ABL to exclude occult translocations.

_____3.2.4 Cytogenetic analysis must be performed from diagnostic bone marrow (preferred) or if adequate number of circulating blasts from peripheral blood. FISH testing for common B-lineage ALL abnormalities including t(9;22) (*BCR/ABL1)*, t(12;21) (*ETV6/RUNX1)*, t(1;19) (*PBX1/TCF3),* +4,+10,+17, (Cen4/Cen10/Cen17), t(11q23;var), *(MLL)*, del(9p) (*CDKN2A*/Cen9), and t(14;var) (*IGH* is encouraged. If there are few or no circulating blasts and an adequate marrow sample cannot be obtained for cytogenetic analysis, the patient may still enroll on the trial.

Rev. 6/16

_____ 3.2.5 Patient must not have a concurrent active malignancy for which they are receiving treatment.

Rev. 6/15 _____3.2.6 Have lab values obtained ≤ 48 hours prior to registration. Serum direct bilirubin < 2 mg/dl **or** serum total bilirubin ≤ 3, and serum creatinine < 2 mg/dl.

Rev. 6/16

Serum direct bilirubin: _____ Serum creatinine: _____

Serum total bilirubin: _____

Date of tests: _____

NOTE: The above stipulation for normal hepatic function does not apply if liver dysfunction is due to leukemia infiltration.

_____3.2.7 Patient should be HLA typed (A, B, C, DR and DQ) during induction therapy phase or a written explanation for not undergoing HLA typing on the flow sheet.

_____3.2.8 Patient must not have intercurrent organ damage or medical problems that will jeopardize the outcome of therapy (i.e., psychiatric disorder, drug abuse, pregnancy).

Rev. 12/14, 8/17

_____ 3.2.9 Patients with known HIV infection are eligible If they meet all of the following criteria:

3.2.9.1 No history of AIDS-related complications other than a history of low CD4+ T-cell count (< 200/mm3) prior to initiation of combination antiretroviral therapy. On study CD4+ T-cell count may not be informative due to leukemia and should not be used as an exclusion criterion if low.

3.2.9.2 Patient must be healthy on the basis of HIV disease with high likelihood of near normal life span were it not for the leukemia.

3.2.9.3 Patient must have serum HIV viral load of < 200 copies/mm^3.

3.2.9.4 Patient must be on combination antiretroviral therapy with minimal pharmacokinetic interactions with study therapy and minimal overlapping clinical toxicity with protocol therapy.

Rev. 2/18

3.2.9.5 Patient must not be receiving protease inhibitors or once daily formulations containing cobicistat, stavudine, or on regimens containing stauvidine or zidovudine.

3.2.9.6 It is recommended to utilize a regimen of the integrase inhibitor, dolutegravir, combined with either disoproxil fumarate/emtricitabine or dolutegravir combined with tenofovir alafenamide/emtricitabine.

_____3.2.10 Patient must not have an antecedent hematologic disorder.

_____3.2.11 Patient must have no history of recent myocardial infarction (within three months), uncontrolled congestive heart failure, or uncontrolled cardiac arrhythmia.

_____3.2.12 Patient must not have a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, or other significant CNS abnormalities.

Rev. 7/14

_____3.2.13 Patient must have a normal cardiac ejection fraction by pretreatment MUGA or echocardiogram within 4 weeks prior to registration (resting ejection fraction ≥ 40% or ≥ 5% increase with exercise), shortening fraction by echocardiogram ≥ 24%, or to within the normal range of values for the institution.

_____3.2.14 Patient must not have an active uncontrolled infection.

_____3.2.15 Women must not be pregnant or breast-feeding due to administration of teratogenic chemotherapy and must not become pregnant or breastfeed during protocol therapy and for at least 3 months after protocol therapy. Woman of childbrearing potential must abstain from sexual activity or be willing to use 2 highly effective forms of contraception throughout protocol therapy and for at least an additional 3 months after the last dose of protocol-specified therapy.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____(Yes or No)

Date of blood test or urine study: _____

_____3.2.16 Men who have a female partner of childbearing potential must be willing to use 2 highly effective forms of contraception throughout protocol therapy and for at least an additional 3 months after the last dose of protocol-specified therapy.

Men who have a pregnant partner must be willing to use a condom during sexual activity throughout protocol therapy and for 3 months after the last dose of protocol-specified therapy.

_____3.2.17 ECOG performance score 0-3.

_____3.2.18 Patient must have given written informed consent.

3.3 Post-Induction Therapy Eligibility Criteria (prior to Intensification – Step 2)

_____3.3.1 ECOG performance status 0-2.

_____3.3.2 Patients must have achieved a CR or CRi as defined in Section 6.

_____3.3.3 Patients who have achieved a CR or CRi must have maintained peripheral blood evidence of a CR or CRi as defined in Section 6.

_____3.3.4 Patient must be CNS (CSF) negative for leukemia.

_____ 3.3.5 Patients must have resolved any serious infectious complications related to induction.

_____3.3.6 Any significant medical complications related to induction must have resolved.

Rev. 7/14
Rev. 12/14

_____3.3.7 Have lab values obtained ≤ 48 hours prior to registration. Patients must have serum creatinine ≤ 2.0 mg/dl.

Serum creatinine: _____

Date of tests: _____

Serum direct bilirubin < 2 mg/dL **or** serum total bilirubin ≤ 3, and AST and ALT < 3x upper limit of normal (ULN).

Serum direct or total bilirubin:_____

AST: _____

ALT: _____

Rev. Add14

3.4 Randomization or Assignment to Blinatumomab or No Blinatumomab – Step 3

_____3.4.1 Patients must have an ECOG performance status of 0-2.

_____ 3.4.2 Patients must have maintained peripheral blood evidence of a remission as defined in Section 6 and must have a CR or CRi, confirmed on restaging BM aspirate and biopsy.

_____3.4.3 Patients must have resolved any serious infectious complications related to therapy.

_____ 3.4.4 Any significant medical complications related to therapy must have resolved.

Rev. 7/14
Rev. 6/16

_____ 3.4.5 Patients must have a direct or total bilirubin < 1.5xULN (unless related to Gilbert's or Meulengracht's syndrome, and a serum creatinine < 1.5 x ULN. The values must be obtained within 48 hours prior to randomization.

Rev. 7/14

_____ 3.4.6 **Bone marrow aspirates must be submitted as outlined in Section 10 for centralized minimal residual disease (MRD) assessment performed by the ECOG-ACRIN Leukemia Translational Research Laboratory.**

Rev. 3/15

_____ 3.4.7 **MRD results will be reported to the submitting institution.**

NOTE: FOR MRD ASSESSMENTS, AN ASPIRATE FROM A SEPARATE BONE MARROW ASPIRATION SITE MUST BE SUBMITTED (THE NEEDLE CAN BE RE-DIRECTED THROUGH THE SAME SKIN PUNCTURE SITE). ONLY SUBMIT ASPIRATES FROM THE FIRST PULL OF AN ASPIRATION SITE FOR MRD TESTING. DO NOT SUBMIT SAMPLES FROM THE SECOND OR THIRD PULL OF THE SAME ASPIRATION SITE.

In B-lineage ALL, MRD levels in peripheral blood or from a dilute marrow aspiration can be 300% lower, on average, than those in bone marrow at a given time point. Submitting a first pull from a separate aspiration site will ensure that MRD determinations used in randomization and trial interpretation are accurate.

NOTE: Failure to submit bone marrow aspirates will result in a major violation at the time of an audit.

3.5 Criteria for Allogeneic Transplantation

_____ 3.5.1 A suitable donor must be identified. There are no restrictions on donor type and can include a matched sibling, a matched or mismatched unrelated donor, a family haplotype matched donor or a cord blood donor (single or double).

Rev. 8/17

_____ 3.5.2 Patients should meet the eligibility criteria in Section 3.4.

_____3.5.3 Patients must be considered reliable enough to comply with the medication regimen and follow-up, and have social support necessary to allow this compliance.

3.6 Criteria for Maintenance Therapy – Step 4

_____3.6.1 Patients must have an ECOG performance status of 0 -3.

Rev. 8/17

_____ 3.6.2 Patients must have maintained peripheral blood evidence of a remission as defined in Section 6 and must have a CR or CRi, confirmed on restaging BM aspirate and biopsy.

_____3.6.3 Patients must have resolved any serious infectious complications related to therapy.

_____ 3.6.4 Any significant medical complications related to therapy must have resolved.

_____ _____

Physician Signature Date

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