# A Phase I/II Study of Bosutinib in Combination with Inotuzumab Ozogamicin in CD22-positive Philadelphia-Chromosome Positive Acute Lymphoblastic Leukemia and Chronic Myeloid Leukemia Lymphoid Blast Phase

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# 1.0 OBJECTIVES

## 1.1 Primary Objectives:

Phase I:

1. To determine the safety and MTD of bosutinib in combination with inotuzumab ozogamicin in patients with Ph+ ALL and CML in lymphoid blast phase that express CD22

Phase II:

1. To determine the efficacy of bosutinib in combination with inotuzumab ozogamicin in patients with Ph+ ALL and CML in lymphoid blast phase that express CD22

## 1.2 Secondary Objectives:

Phase I:

1. To determine the efficacy of bosutinib in combination with inotuzumab ozogamicin in patients with Ph+ ALL and CML in lymphoid blast phase that express CD22
2. To determine the duration of response of patients treated with this combination
3. To determine the overall survival of patients treated with this combination
4. To determine the effect of the level of pre-treatment expression of CD22 with response to this combination
5. To determine the efficacy of this combination according to pre-treatment mutation status in the abl kinase domain
6. To determine the minimal residual disease after treatment with this combination and its impact in long-term outcome

Phase II:

1. To determine the safety bosutinib in combination with inotuzumab ozogamicin in patients with Ph+ ALL and CML in lymphoid blast phase that express CD22
2. To determine the duration of response of patients treated with this combination
3. To determine the overall survival of patients treated with this combination
4. To determine the effect of the level of pre-treatment expression of CD22 with response to this combination
5. To determine the efficacy of this combination according to pre-treatment mutation status in the abl kinase domain
6. To determine the minimal residual disease after treatment with this combination and its impact in long-term outcome

# 2.0 BACKGROUND AND RATIONALE

The Philadelphia chromosome [t(9;22)(q34;q11)] (Ph+), is the most common cytogenetic abnormality in acute lymphoblastic leukemia (ALL) in adults.[1,2] Up to 40-50% of ALL patients older than 60 years will be Ph+. Before the introduction of molecularly targeted therapy, Ph+ ALL was associated with lower remission rates and a very poor prognosis with a median survival of less than one year.[3]

With the introduction of therapy using ABL-tyrosine kinase inhibitors (TKIs) targeted to the aberrant BCR-ABL protein, the outcome of Ph-positive ALL has improved substantially and has been the major treatment advance for adults with ALL in the past two decades.[4] Imatinib, the first TKI developed for use in Ph+ leukemias, has been combined with combination chemotherapy by various groups and this has substantially improved both complete remission (CR) and disease-free survival (DFS) rates.[5,6] The MD Anderson group was the first to report on the combination of imatinib with chemotherapy.[5,6] The 3 year CR duration and OS rates were significantly improved with hyper-CVAD-imatinib therapy compared to historical controls treated with hyper-CVAD alone (68% vs. 24% and 54% vs. 15%, respectively, $p < 0.001$). Second generation TKI dasatinib has also been combined with hyper-CVAD chemotherapy with improved outcomes.[7] In a report of 35 patients treated with hyper-CVAD + dasatinib, the CR rate of 94% was achieved with estimated 2-year OS of 64%.[7] Similar results have been reported by other groups and early TKI therapy is now established as the standard treatment of Ph+ ALL.[1,2,4,8] Ponatinib is a novel TKI with single-agent activity in patients with T315I mutations.[9] Cortes and colleagues reported activity of ponatinib monotherapy in patients with Ph+ leukemias.[9] The primary endpoint for the Ph+ ALL and CML in lymphoid blast phase disease phase was major hematologic response (MaHR), and was achieved in 31% of patients with CML in lymphoid blast crisis and 41% of patients with Ph+ ALL.

Bosutinib is a second generation TKI and is a dual Abl and Src kinase inhibitor. Bosutinib was recently approved for the treatment of adult patients with chronic, accelerated, or blast phase CML with resistance/ intolerance to prior therapy.[10-12] In a phase I/II study in advanced Ph+ leukemia with resistance/ intolerance to imatinib, patients received single-agent bosutinib (500 mg daily).[13] One hundred thirty four patients were enrolled (63 accelerated phase [AP], 48 blast phase [BP], 23 ALL). Non-hematologic treatment-related adverse events occurring in ≥10% of pts were diarrhea (67%), vomiting (40%), nausea (37%), rash (20%), and fatigue (10%). Grade 3/4 adverse events of any causality occurring in ≥5% of pts were diarrhea (6%), pneumonia (6%), elevated ALT (6%), vomiting (5%), and dyspnea (5%). Grade 3/4 hematologic toxicity of any causality were anemia (37%), neutropenia (46%), and thrombocytopenia (65%). For the evaluable patients with BP and ALL, major cytogenetic response and major molecular response occurred in 57% and 34% patients, respectively. Thus, bosutinib is an active agent for treatment of patients with advanced Ph+ leukemia.

CD22 expression occurs in >90% of patients with ALL. Inotuzumab ozogamicin (IO) is a CD22 monoclonal antibody bound to a toxin, calecheamicin, and has shown single-agent activity in

relapsed/refractory ALL.[14] In a phase II study, patients were given IO at 1.8 mg/m2 intravenously every 3-4 weeks. Forty-nine patients were treated. The median number of courses administered were 2 (range 1-5) and the median time between courses was 3 weeks (range 3-6). The overall response rate was 57% (CR 18%, marrow CR 39%). There were 7 patients with Ph+ ALL of which 3 (43%) had a response. Twenty-four percent patients had grade 1–2 and 4% had grade 3 increases in bilirubin. Grade 1–2 elevations of serum aminotransferase were noted in 55% patients and grade 3 elevations in 2% patients. Based on higher in vitro efficacy with more frequent exposure, a weekly schedule (0.8 mg/m2 day 1, 0.5 mg/m2 days 8 and 15, every 3-4 weeks) has been developed.[15] With the weekly schedule (n=34), overall response rate was 53% (similar to 57% noted with the every 3 weeks schedule). With the weekly schedule, reversible grade 1–2 and 3–4 bilirubin elevations were observed in 3% and 0% patients, respectively. Reversible grade 1–2 and 3–4 liver enzyme elevations were observed in 21% and 6%, respectively on the weekly dose. Thus, weekly schedule has similar efficacy as every 3 week schedule with improved toxicity profile.

Despite these advances with the introduction of TKI therapy and of the monoclonal antibodies such as IO, relapses are still major challenges in patients with ALL and long-term survival remains poor. As both TKIs and IO have shown independent clinical activity in patients with Ph+ ALL (and CML lymphoid blast phase), we hypothesize that combination strategy ('chemo-free' approach) would lead to improved clinical outcomes. We propose a phase I/II clinical trial with combination therapy with bosutinib and IO. If successful, this would represent a major advance in the management of patients with Ph+ ALL.

The present study will include patients with either Ph+ ALL or CML in lymphoid blast phase (CML-LBC). Both these disorders are characterized by increased number of lymphoid blasts in the marrow and the presence of the Philadelphia chromosome.[16,17] The disease biology, clinical outcomes and management of patients with CML-LBC and Ph+ ALL is identical [NCCN guidelines (version 4.2013)]. The presence of Philadelphia chromosome defines these disease subgroups which are many times impossible to differentiate from each other (e.g., de-novo blast phase versus Ph+ ALL) and therefore, it is not surprising that many pivotal clinical trials of TKI therapy have included both these groups of patients.[9,18,19]

Frontline Ph+ ALL Cohort: Outcomes of older patients with ALL remain suboptimal with long-term disease free control of <20% at 5 years.[20] One of the major reasons for inferior outcomes in older patients is the risk of infection with standard chemotherapy. In analysis reported by O'Brien and colleagues, the risk of death in CR due to infections was 34%.[21] Similar data have been reported by the UK ALL study group.[22]

Low-intensity regimens have been reported to be effective and safe in patients with ALL. Use of antibody-drug conjugate inotuzumab and lower-intensity chemotherapy has been shown to be very effective in patients with Ph negative ALL (Jabbour et al. ASH 2015). Given suboptimal results with standard chemotherapy in older patients with ALL, and poor tolerability of chemotherapy in

older patients, there is a need to develop better therapy with non-chemotherapy approaches for this group of patients. We plan to include older patients with Ph+ ALL or CML-LBC for frontline treatment.

## 3.0 STUDY POPULATION

To be eligible for this study, patients must meet all criteria outlined below in Section 3.1 and Section 3.2.

### 3.1 Inclusion Criteria

1. Relapsed or refractory B-cell ALL or CML in lymphoid blast phase. Philadelphia chromosome must be present at screening (as determined by cytogenetic analysis, FISH, or PCR [i.e., BCR-ABL positive]). Note: patients with CML who have received treatment with tyrosine kinase inhibitors for their CML, and have progressed to lymphoid blast phase are eligible for frontline treatment.

   Frontline Ph+ ALL or CML-LBC Cohort: Patients with newly-diagnosed Ph+ ALL or CML-LBC, who have received no or minimal treatment (minimal treatment is defined as treatment with steroids/hydroxyurea of ≤2 week duration; vincristine ≤ 2 doses; tyrosine kinase inhibitor of ≤4 week duration; ≤2 doses of cytarabine) and are ≥60 years or older are eligible. Patients must have bone marrow blasts >5% at the time of screening.

2. Expression of CD-22 in ≥20% blasts

3. Age 18 years or older (For Frontline Ph+ ALL or CML-LBC Cohort: Age 60 years or older)

4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤2

5. The following baseline laboratory data:
   - Serum bilirubin ≤2.0 mg/dl
   - Serum creatinine ≤2.0 mg/dl
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN)

6. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (β-hCG) pregnancy test result within 14 days prior to the first dose of study drugs and must agree to use one of the following effective contraception methods during the study and for 30 days following the last dose of study drug.
Effective methods of birth control include:

- birth control pills, shots, implants (placed under the skin by a health care provider) or patches (placed on the skin)
- Intrauterine devices (IUDs)
- condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicide

Females of non- childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.

7. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 30 days following the last dose of study drug

8. Patients or their legally authorized representative must provide written informed consent

### 3.2 Exclusion Criteria

1 History of another primary invasive malignancy that has not been definitively treated or in remission for at least 2 years. Patients with non-melanoma skin cancers or with carcinomas in situ are eligible regardless of the time from diagnosis (including concomitant diagnoses).

2 Patients with active unstable angina, concomitant clinically significant active arrhythmias, myocardial infarction within 6 months, or congestive heart failure New York Heart Association Class III-IV. Patients with a cardiac ejection fraction (as measured by either MUGA or echocardiogram) <40% are excluded.

3 Known evidence of active cerebral/meningeal disease. Patients may have history of CNS leukemic involvement if definitively treated with prior therapy and no evidence of active disease (defined as ≥2 consecutive spinal fluid assessments with no evidence of disease) at the time of consent.

4 Previous treatment with any anti-CD22 directed therapy

5 Patients with previous allogeneic stem cell transplant (SCT) if they meet either of the following criteria:

- <100 days from allogeneic SCT
- Active acute or chronic graft-versus-host disease (GvHD), or
- Receiving immunosuppressive therapy as treatment for GvHD within the last 7 days

6. Patients with uncontrolled active infections (viral, bacterial, or fungal) are not eligible

7. Active hepatitis B or C infection, or known seropositivity for HIV

8. Patients with liver cirrhosis or other serious active liver disease or with suspected alcohol abuse

9. History of autoimmune diseases (such as systemic lupus erythematosus (SLE), Wegener's, Wegener's granulomatosis, polyarteritis nodosa). Note: Prior autoimmune diseases are allowed as long as clinically stable.

10. Prior chemotherapy/radiotherapy/investigational therapy within 2 weeks before the start of study drugs with the following exceptions:
    a. To reduce the circulating lymphoblast count or palliation: steroids, hydroxyurea. No washout necessary for these agents.
    b. For ALL maintenance/CML treatment: mercaptopurine, methotrexate, vincristine, single-agent, single-dose of cytarabine and/or tyrosine kinase inhibitors. These agents should be discontinued at least 48 hours prior to start of study drugs. (Note: the interval of time from last dose of any approved TKI to start of protocol treatment is 48 hours regardless of the indication for treatment with the TKI.)

11. Patients who have not recovered from acute non hematologic toxicity (to ≤ Grade 1) of all previous therapy prior to enrollment

12. Females who are pregnant or lactating

13. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.
14. Patients previously exposed to bosutinib are eligible unless they carry T315I
15. Patients with T315I mutations will be excluded (This criteria is not applicable for the frontline Ph+ ALL or CML-LBC cohort)

### 3.3 Discontinuation of Study Drug

A patient's treatment with study drug may be discontinued for any of the following reasons:

- Clinically significant progressive disease
- Adverse events that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the investigator, pose an unacceptable risk for the patient.
- Investigator decision

- Patient decision (e.g., withdrawal of consent)
- Study termination by Sponsor

Patients who discontinue from the study for disease progression or initiation of new therapy are considered to have completed the study per protocol. Patients who discontinue study treatment will be contacted about every 12 weeks (for up to one year) and asked about any anti-cancer therapy they may be receiving.

## 4.0 TREATMENT PLAN

### 4.1 Study Design

The study will consist of two phases-

**4.1.1** **Phase I dose-escalation Phase** for relapsed or refractory B-cell ALL or CML in lymphoid blast phase patients will start therapy with bosutinib at 300 mg orally once daily (which is 40% lower than the FDA approved dose of 500 mg orally once daily). Bosutinib will be dose-escalated in subsequent cohorts in a standard 3+3 study design. Patients will receive inotuzumab ozogamicin as an intravenous infusion over approximately one hour on a weekly schedule (0.8 mg/m$^2$ IV day 1, 0.5 mg/m$^2$ day 8 (±3 days), and 0.5 mg/m$^2$ day 15 (±3 days). A minimum of 6 days should be maintained between subsequent doses.

A cycle is defined as 28 days, however, start of cycle 2 may be delayed if the patient achieves a CR or CRi and/or to allow toxicity recovery.

| **Dose Level** | **Bosutinib (mg/day) orally once daily** | **Inotuzumab ozogamicin IV (mg/m$^2$), repeat cycles every 3-4 weeks** |
|---|---|---|
| -1 | 200 | Day 1 - 0.8 mg/m$^2$<br>Day 8 - 0.5 mg/m$^2$<br>Day 15 - 0.5 mg/m$^2$ |
| 1 (starting dose) | 300 | Day 1 - 0.8 mg/m$^2$<br>Day 8 - 0.5 mg/m$^2$<br>Day 15 - 0.5 mg/m$^2$ |
| 2 | 400 | Day 1 - 0.8 mg/m$^2$<br>Day 8 - 0.5 mg/m$^2$<br>Day 15 - 0.5 mg/m$^2$ |
| 3 | 500 | Day 1 - 0.8 mg/m$^2$<br>Day 8 - 0.5 mg/m$^2$<br>Day 15 - 0.5 mg/m$^2$ |

**4.1.1.1** For Cycles 2 to 6, if there are no peripheral blood blasts, the inotuzumab ozogamicin dose is reduced to 1.5 mg/m$^2$ total but continues on a weekly

schedule (0.5 mg/m$^2$ days 1, 8 (±3 days) and 15 (±3 days). The rationale for this is that, based on prior experience at our institution, the number of circulating blast cells is a significant covariant affecting inotuzumab clearance and therefore, once the peripheral blood blasts clear, the dose may be reduced maintaining efficacy. This will also reduce the risk of toxicity for subsequent cycles.

**4.1.1.2** A minimum of 6 days should be maintained between the doses.

**4.1.1.3** For patients who have achieved CR/CRi – the next cycle (cycle 2 and onwards) will begin when ANC ≥1.0, and platelet count ≥75. These count recovery guidelines could be modified based on treating physician assessment if determined to be in the best interest of the patient after discussion with study PI (e.g., if there is evidence of minimal residual disease).

**4.1.1.4** **Transition to the every 4-weekly schedule –** In order to decrease the toxicity of the subsequent cycles, once a response is confirmed (CR, CRi, or whenever CCyR and/or absence of MRD by flow cytometry is documented), subsequent cycles will be administered at a dose of 1.0 mg/m$^2$ once every 4 weeks. Note: Patients who have been switched to every 4 weeks schedule may return to the weekly schedule if there is concern about recurrence of the disease.

**4.1.1.5** Patients who experience a clinical benefit (CR/CRi/PR) with acceptable toxicity can receive up to a total of 6 cycles of inotuzumab ozogamicin. Treatment with bosutinib should continue indefinitely as long as patient is tolerating it well and responding to it.

**4.1.1.6** Bosutinib will be dose-escalated in subsequent cohorts in a standard 3+3 study design (see Section 11.2).

**4.1.1.7** **Dosing for the Frontline** Ph+ ALL or CML-LBC Cohort

**Phase I dose-escalation Phase:** in the phase I portion of the study, frontline Ph+ ALL or CML-LBC patients will start therapy with bosutinib at 300 mg orally once daily. This dose has already been shown to be safe in the relapsed cohort (we have treated 3 patients with R/R ALL, and no DLT was noted at the 300mg dose level). Bosutinib will be dose-escalated in subsequent cohorts in a standard 3+3 study design.

Patients will receive inotuzumab ozogamicin as an intravenous infusion over approximately one hour on a weekly schedule (0.8 mg/m$^2$ IV day 1, 0.5 mg/m$^2$ day 8 (±3 days), and 0.5 mg/m$^2$ day 15 (±3 days). A minimum of 6 days should be maintained between subsequent doses.

A cycle is defined as 28 days, however, start of cycle 2 may be delayed if the patient achieves a CR or CRi and/or to allow toxicity recovery.

| Dose Level | Bosutinib (mg/day) orally once daily | Inotuzumab ozogamicin IV ($mg/m^2$), repeat cycles every 3-4 weeks |
|---|---|---|
| -1 | 200 | Day 1 - 0.8 $mg/m^2$<br>Day 8 - 0.5 $mg/m^2$<br>Day 15 - 0.5 $mg/m^2$ |
| 1 (starting dose) | 300 | Day 1 - 0.8 $mg/m^2$<br>Day 8 - 0.5 $mg/m^2$<br>Day 15 - 0.5 $mg/m^2$ |
| 2 | 400 | Day 1 - 0.8 $mg/m^2$<br>Day 8 - 0.5 $mg/m^2$<br>Day 15 - 0.5 $mg/m^2$ |
| 3 | 500 | Day 1 - 0.8 $mg/m^2$<br>Day 8 - 0.5 $mg/m^2$<br>Day 15 - 0.5 $mg/m^2$ |

For Cycles 2 to 6, if there are no peripheral blood blasts, the inotuzumab ozogamicin dose is reduced to 1.5 $mg/m^2$ total but continues on a weekly schedule (0.5 $mg/m^2$ days 1, 8 (±3 days) and 15 (±3 days). A minimum of 6 days should be maintained between the doses. For patients who have achieved CR/CRi – the next cycle (cycle 2 and onwards) will begin when ANC ≥1.0, and platelet count ≥75. These count recovery guidelines could be modified based on treating physician assessment if determined to be in the best interest of the patient after discussion with study PI (e.g., if there is evidence of minimal residual disease).

**Transition to the every 4-weekly schedule –** In order to decrease the toxicity of the subsequent cycles, once a response is confirmed (CR, CRi, or whenever CCyR and/or absence of MRD by flow cytometry is documented), subsequent cycles will be administered at a dose of 1.0 $mg/m^2$ once every 4 weeks. Note: Patients who have been switched to every 4 weeks schedule may return to the weekly schedule if there is concern about recurrence of the disease.

Patients who experience a clinical benefit (CR/CRi/PR) with acceptable toxicity can receive up to a total of 6 cycles of inotuzumab ozogamicin. Treatment with bosutinib should continue indefinitely as long as patient is tolerating it well and responding to it.

NOTE: For all patients included in this trial, inotuzumab doses may be omitted if deemed in the best interest of the patient (for e.g. patients with plans of undergoing stem cell transplant) by the treating physician (after discussion with the study PI). The reason for omission will be noted in the medical record.

Patients who achieve MRD negative remission may have further doses of inotuzumab omitted, if deemed in the best interest of the patient by the treating physician (in discussion with the study PI).

### 4.1.2 Evaluation of dose limiting toxicity (DLT)

**4.1.2.1** Prior to advancing/changing cohorts a cohort summary will be completed and submitted to the Medical Monitor in the IND Office.

**4.1.2.2** DLT is defined as clinically significant non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle of therapy that meets any of the following criteria:

- CTCAE Grade 3 or 4 AST (SGOT) or ALT (SGPT) for ≥ 14 days
- All other clinically significant non-hematological adverse event possibly related to study drugs that is Grade 3 or 4 according to the NCI common terminology criteria version 4.0. with the following exceptions:
  - Grade 3 or 4 nausea, vomiting and diarrhea will be considered DLT only if not controlled by optimal therapy.
  - Grade 3 biochemical abnormalities (e.g., lipase or bilirubin elevation) will only be considered DLT if accompanied by clinical consequences. Grade 3 or 4 electrolyte abnormalities will only be considered DLT if possibly related to study drug and not corrected by optimal replacement therapy.
- Hematologic DLT is defined as absolute neutrophil count (ANC) <0.5 $x10^9$/L or platelet count <25 $x10^9$/L with a hypocellular bone marrow lasting for 6 weeks or more after the start of a course in the absence of residual leukemia (i.e., with less than 5% blasts). (In case of a normocellular bone marrow with <5% blasts, 8 weeks with pancytopenia will be considered DLT). Anemia will not be considered for the definition of DLT.
- The last patient enrolled in each cohort will be observed for toxicity for 28 days (1 cycle) prior to advancing to the next dose level.

**4.1.2.3** Patients that are removed from study during cycle 1 for any reason other than toxicity and have not experienced DLT will be replaced.

**4.1.2.4** For the purpose of defining DLT, the first cycle will be considered; however information on observed toxicities during subsequent cycles will be collected from all patients.

**4.1.3** Cycle 1 is a 4 week cycle. However, cycle 2 may be started up to 1 week early if the patient has not achieved a CR or CRi and/or has persistent disease or rapidly proliferating disease, provided all drug-related toxicity has recovered to grade 1 or less. All subsequent cycles are 4 week cycles. Note: Subsequent cycles may start early if there is recovery of all toxicity related to the study drugs to grade 1 or less, but not earlier than day 21.

**4.1.3.1** Subsequent cycles may be delayed for recovery of toxicity. Delays in start of subsequent cycles greater than 8 weeks should be discussed with the principal investigator.

**4.1.3.2** If the peripheral counts do not recover (ANC <1 $x10^9$/L and/or platelets <75 $x10^9$/L) but there is evidence of residual leukemia in the bone marrow, subsequent cycles can be administered at the discretion of the treating physician.

**4.1.4** **Phase II Phase:** Once the MTD (or bosutinib 500 mg dose level, if MTD not exceeded at this level) is established in each cohort separately, a phase II portion will commence respectively for each cohort. For each cohort, the 6 patients at MTD from the phase I dose part will be enrolled in the phase II portion of the study.

Patients will receive bosutinib per the MTD established in the Phase I study. Patients will receive inotuzumab ozogamicin at the same dose and schedule as for the Phase I part of the study. For each cohort, a maximum of 28 patients (including the 6 patients at MTD from the phase I dose part) will be enrolled in the phase II portion of the study.

## 5.0 TREATMENTS ADMINISTERED

**5.1 Inotuzumab ozogamicin**, the investigational agent under study in this protocol, is an ADC comprised of a humanized IgG4 monoclonal antibody (G5/44) that recognizes CD22 antigen and is covalently linked via an acetyl butyrate linker to N-acetyl-γ-calecheamicin dimethyl hydrazide (CalichDMH), a semisynthetic derivative of calecheamicin.

Detailed information describing the preparation, administration, and storage of inotuzumab ozogamicin is located in the Pharmacy Manual.

### 5.1.1 Description

Inotuzumab ozogamicin is a white to off-white powder or cake, lyophilized, unpreserved 4-mg protein equivalent powder for intravenous injection in an amber vial supplied by Pfizer.

### 5.1.2 Dose and Administration

Inotuzumab ozogamicin must not be administered as an IV push or bolus. Inotuzumab ozogamicin should not be mixed with other medications. Dosing is based on patient

weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Please refer to the Dosage and Administration Instructions in the Pharmacy Manual for inotuzumab ozogamicin intravenous solution. Reconstituted inotuzumab ozogamicin will be administered over 1 hour ± 15 minutes by intravenous infusion unless the subject requires temporary interruption of the administration. A minimum of 6 days should be maintained between the doses.

### 5.1.3 Required Premedication

Recommended premedication before inotuzumab ozogamicin: acetaminophen 650 mg orally, diphenhydramine 10-25 mg IV, hydrocortisone 25 mg IV. Modifications to this premedication are also allowed.

### 5.1.4 Drug Preparation, Storage and Handling

Detailed drug preparation instructions are provided in the Investigator Brochure. Unused portions of the study drug will be discarded properly as per the institutional policies.

**5.2 Bosutinib (BOSULIF®)** is a kinase inhibitor FDA approved for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy. The recommended dose is 500mg once daily with food. Bosutinib will be provided by Pfizer. Bosutinib inhibits the abnormal Bcr-Abl kinase that promotes CML. Modeling studies indicate that bosutinib binds the kinase domain of Bcr-Abl. Bosutinib is also an inhibitor of Src family kinases including Src, Lyn and Hck. Bosutinib minimally inhibits PDGF receptor and c-Kit.

### 5.2.1 Method of Administration

Bosutinib tablets are available containing bosutinib monohydrate equivalent to either 100 or 500 mg of bosutinib. The recommended dose of Bosutinib for the treatment of leukemia is 500 mg by mouth once daily with food. If a dose is missed, the patient should not take an additional dose, but take the usual prescribed dose on the following day. Unused portions of the study drug will be discarded properly as per the institutional policies.

## 6.0 DOSE MODIFICATIONS

**6.1** Intrapatient dose reduction will be allowed depending on the type and severity of toxicity. Dose interruption may occur within a cycle until adequate recovery or omission of a dose during a given treatment cycle. While doses given within a treatment cycle (i.e., Days 8 and/or 15) need not be delayed due to neutropenia or thrombocytopenia, dose delays

within a cycle are required for drug-related non hematologic toxicity. The start of the next cycle may be delayed if additional time is required for the patient to recover from study treatment-related toxicity experienced during the current cycle. Delays in start of subsequent cycles greater than 8 weeks should be discussed with the principal investigator. Doses reduced for treatment-related toxicity should not be re-escalated without discussion with the principal investigator.

### 6.2 Recommended dose modifications for inotuzumab ozogamicin-related toxicity

Dose reductions may be required based on the worst toxicity experienced in the previous cycle. Patients experiencing a treatment interruption due to inotuzumab ozogamicin-related toxicity (such as grade 3-4 thrombocytopenia, grade 3-4 transaminitis) ≥14 days will be dose reduced as per the Table below. Inotuzumab will be resumed once the toxicity recovers to grade 2 or less. Once a patient has a dose reduction for a drug-related toxicity, the dose will not be re-escalated.

Patients who are unable to tolerate dose level -2 will be withdrawn from treatment unless the PI thinks it is in the best interest of the patient. In that situation, a further 25% dose reduction will be performed.

**Dose Modification table for inotuzumab ozogamicin**

| **Dose Level** | **Cycles 1-6 (in mg/m$^2$)** | **Cycles 2 to 6 # (in mg/m$^2$)** | **Cycles 2 to 6 * (in mg/m$^2$)** |
|---|---|---|---|
| **-2** | Day 1 – 0.6<br>Day 8 – Skip<br>Day 15 – 0.375 | Day 1 – 0.375<br>Day 8 – Skip<br>Day 15 – 0.375 | Day 1 – 0.5 |
| **-1** | Day 1 – 0.6<br>Day 8 – 0.375<br>Day 15 – 0.375 | Day 1 – 0.375<br>Day 8 – 0.375<br>Day 15 – 0.375 | Day 1 – 0.75 |
| **1 (starting dose level)** | Day 1 – 0.8<br>Day 8 – 0.5<br>Day 15 – 0.5 | Day 1 – 0.5<br>Day 8 – 0.5<br>Day 15 – 0.5 | Day 1 – 1.0 |

# if no peripheral blood blasts; * once a response is confirmed (CR, CRi, CCyR, and/or absence of MRD by flow cytometry)

### 6.3 Recommended dose modifications for bosutinib-related toxicity

If the toxicities experienced by the patient are thought to be related to bosutinib, the following dose modification criteria will be used-

**Non-Hematologic Bosutinib-related toxicity**

| Adverse Event | Action# |
|---|---|
| **Grade I** | Remain on current dose level |
| **Grade II** | For persistent, clinically relevant toxicity not responding to optimal management: Interrupt bosutinib, then reintroduce at the same dose or reduce dose by one level upon recovery to grade ≤ 1 |
| **Grade III** | For persistent, clinically relevant toxicity not responding to optimal management: Interrupt bosutinib, then dose reduce by 1 level upon recovery to grade ≤ 1 |
| **Grade IV** | Interrupt bosutinib. Discuss with PI about resuming bosutinib with appropriate dose reduction. Resumption should happen only upon recovery to grade ≤ 1 |

# For subjects who have required a dose reduction due to toxicity, but then have been free of the specific toxicity (grade ≤ 1) for at least 1 month and are otherwise tolerating bosutinib well, the investigator may choose to re-escalate the dose by one dose level each month (i.e. increase the daily dose by 100 mg/month) until the subject is back to the starting or previous dose (whichever is higher).

NOTE: Cytopenias are common in the patient population studied in this trial. Inotuzumab ozogamicin can cause low platelet count. Therefore, dose modification for bosutinib for hematologic toxicities would be considered only if the investigator and PI strongly feel that the cytopenias were related to bosutinib.

**Dose Modification table for bosutinib**

| Dose Level | Bosutinib (mg/day) orally once daily |
|---|---|
| **-1** | 200 |
| **1** | 300 |
| **2** | 400 |
| **3** | 500 |

**6.4** For patients with adverse events that are due to one of the two agents, dose adjustments to only one of the study drugs may be adjusted as per the guidelines mentioned above.

**6.5** Dose reductions different than dose described above are acceptable after discussion with the principal investigator and documentation of the rationale for such action.

## 7.0 CONCOMITANT THERAPY

All concomitant medications will be noted in the medical record. All supportive measures consistent with optimal patient care should be provided throughout the study according to the institutional standards.

### 7.1 Allowed Concomitant Therapy

Prophylactic intrathecal therapy is allowed. The use of hematopoietic growth factors or transfusions is allowed. The use of hydroxyurea and/or steroids is permitted for the first 2 weeks of the study period for cytoreduction. Note: Patients with isolated CNS relapse while on the study can continue on the study if deemed in the best interest of the patient. These patients can receive intrathecal chemotherapy to clear the CNS leukemia.

### 7.2 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications (excluding therapy as described in Section 7.1), radiotherapy, or systemic anti-neoplastic therapy during the study. Herbal supplements, including St. John's Wort and grapefruit juice are prohibited.

### 7.3 Concomitant Use With CYP3A Inhibitors

Avoid the concomitant use of strong or moderate CYP3A and/or P-gp inhibitors with bosutinib as an increase in bosutinib plasma concentration is expected. Strong CYP3A inhibitors include ritonavir, indinavir, nelfinavir, saquinavir, ketoconazole, boceprevir, telaprevir, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and conivaptan. Moderate CYP3A inhibitors include fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products and ciprofloxacin.

### 7.4 Concomitant Use With CYP3A Inducers

Avoid the concomitant use of strong or moderate CYP3A inducers with bosutinib as a reduction in exposure is expected. Strong CYP3A inducers include rifampin, phenytoin, carbamazepine, St. John's Wort, rifabutin and phenobarbital. Moderate CYP3A inducers include bosentan, nafcillin, efavirenz, modafinil and etravirine.

### 7.5 Concomitant Use with Proton Pump Inhibitors

Proton Pump Inhibitors decrease bosutinib plasma concentration. Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H2 blocker dosing and bosutinib dosing by more than 2 hours.

## 8.0 STUDY CALENDAR

| | | | | | |
|---|---|---|---|---|---|
| | | **Cycle 1** | **At the start of each subsequent cycle, Day 1 of each cycle (±3 days), Cycle 2-6** | **At the start of each subsequent cycle, Day 1 of each cycle (±3** | |

| | | | | | | days), Cycle 7 onwards | |
|---|---|---|---|---|---|---|---|
| **Study Assessments[1]** | **Screen[2]** | **Day 1[2]** | **Day 8 (±3 days)** | **Day 15 (±3 days)** | **Continuation[3]** | **Continuation[3]** | **End of Treatment Visit[10]** |
| Informed Consent | X | | | | | | |
| Baseline Demographics | X | | | | | | |
| Medical History | X | | | | | | X |
| Concomitant Medications | X | Continuous | | | | | X |
| Physical Exam | X | X | | X | X | X | X |
| ECOG Performance Status | X | X | | | X | X | X |
| Vital Signs | X | X | X | X | X | X | X |
| Weight | X | X | | | X | X | X |
| Height | X | | | | | | |
| Hematology, Clinical Chemistry[4,5] | X | X | X | X | X | X | X |
| Screening for Hepatitis B, Hepatitis C and HIV | X[7] | | | | | | |
| Pregnancy Test[6] | X | | | | | | |
| 12-Lead ECG | X[7] | | | | | | |
| ECHO or MUGA | X[7] | | | | | | |
| Disease Assessment[8] | X[7] | | | | X[8] | X[8] | X[11] |
| CD22 immunophenotyping | X[9] | | | | X[9] | X[9] | X[11] |
| Inotuzumab | | X | X | X | X[12] | | |
| Bosutinib | | Continuous daily | | | | | |
| Adverse Events | | Continuous | | | | | |

1. Assessments scheduled on days of dosing should be done prior to administration of study drug(s), unless otherwise specified.
2. Within 14 days before first dose. Screening assessments can be used as day 1 assessments if done within 72 hrs.
3. If clinically indicated, assessments during Continuation period can occur more frequently.
4. Hematology (WBC with differential, unless WBC <0.5 $x10^9$/L in which case differential not needed), Hemoglobin, Platelet count); Clinical Chemistry (Alanine aminotransferase (ALT), Bilirubin total, Creatinine, uric acid).
5. Hematology and Clinical Chemistry will be performed 1 to 3 times weekly during the cycle 1 and at least weekly during the cycles 2-6. For patients who continue bosutinib as maintenance therapy, at least monthly labs are required. Outside labs will be permitted and the PI/treating physician will review the labs for clinical significance, and sign/date the results.
6. Perform only in women of child-bearing potential. Pregnancy test can be done in either serum or urine.
7. Within 30 days of start of treatment
8. Disease assessment by bone marrow samples (aspirate and/or biopsy) should be done at screening, end of cycle 1 (before start of cycle 2), and then before of start cycles 3-6. Note: Once CR/CRi is achieved, bone marrow will repeated every 2 cycles, or as clinically indicated. For patients who continue bosutinib as monotherapy (after completing all 6 cycles of inotuzumab or if inotuzumab is discounted early), bone marrow will be repeated every 3 months. ABL-kinase domain mutation analysis will be performed at baseline (except in patients on the Frontline Ph+ ALL or CML-LBC cohort) and may be repeated after starting treatment, as clinically indicated. Peripheral blood (or bone marrow) PCR for BCR-ABL would be obtained at baseline and prior to start of each cycle.
9. CD22 immunophenotyping performed at screening on peripheral blood or bone marrow aspirate. CD22 immunophenotyping will be performed in follow-up bone marrow to assess for minimal residual disease.
10. End of Treatment Visit should occur 28 days (±10 days) after last dose of study drugs. For patients who cannot come for the clinic visit, a phone call to assess for any side-effects will be done. Final study visit assessments will be performed before any other therapeutic intervention, if possible.
11. These procedures will not be performed on patients who cannot come to MD Anderson for their final study visit.
12. The schedule of Inotuzumab could be days 1, 8, and 15 OR once every 4-weeks (please see Section 4.1 for details)

## 9.0 CRITERIA FOR RESPONSE

**Major hematologic response (MaHR):** The detailed definition of MaHR is listed below.

| **Major hematologic response (MaHR)** defined as either: | |
|---|---|
| **Complete Hematologic Response (CHR)** | **No Evidence of Leukemia (NEL)** |
| ▪ White blood count (WBC) ≤ institutional upper limit of normal (ULN)<br>▪ Absolute neutrophil count (ANC) ≥1000/mm³<br>▪ Platelets ≥100,000/ mm³<br>▪ No blasts or promyelocytes in peripheral blood<br>▪ Bone marrow blasts ≤5%<br>▪ <5% myelocytes plus metamyelocytes in peripheral blood<br>▪ Basophils <5% in peripheral blood<br>▪ No extramedullary involvement (including no hepatomegaly or splenomegaly) | ▪ WBC ≤ institutional ULN<br>▪ No blasts or promyelocytes in peripheral blood<br>▪ Bone marrow blasts ≤5%<br>▪ <5 % myelocytes plus metamyelocytes in peripheral blood<br>▪ Basophils <5% in peripheral blood<br>▪ No extramedullary involvement (including no hepatomegaly or splenomegaly)<br>▪ At least one of the following:<br>(i) 20,000/mm³ ≤ platelets < 100,000/mm³<br>(ii) 500/mm³ ≤ ANC < 1000/mm³ |

**Complete Response (CR):**

Disappearance of all clinical and/or radiologic evidence of disease

Neutrophil count ≥ 1.0 x $10^9$/L

Platelet count ≥ 100 x $10^9$/L

Normal bone marrow differential (≤ 5% blasts)

No extra-medullary leukemia

**Complete Remission without Incomplete Blood Count Recovery (CRi):**

CR except for ANC < 1.0 x $10^9$/L and/or platelets < 100 x $10^9$/L

**Partial Remission (PR):**

Blood count recovery as for CR, but with a decrease of at least 50% in the percentage of marrow blasts to >5% to 25% in the bone marrow.

## 10.0 ADVERSE EVENT REPORTING

### 10.1 Leukemia-specific Adverse Event Recording and Reporting Guidelines

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events-definition of expected AE-"

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

**10.1.1** PDMS/CORe will be used as the electronic case report form for this protocol. Adverse events will be documented in the medical record and entered into PDMS/CORe.

**10.1.2** Adverse Events (AEs) will be evaluated according to the CTCAE version 4.0 and documented in medical record. All AE's regardless of grade and attribution will be collected on toxicity logs; however, unexpected and related AE's of all grades will be entered into CORe. Only unexpected AEs, any grade, will be recorded in the Case Report Form (CRF). Expected events during leukemia therapy are:

**10.1.2.1** Myelosuppression related events (due to disease or leukemia therapy)

**10.1.2.1.1** Febrile or infection episodes not requiring management in the intensive care unit

**10.1.2.1.2** Epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage

**10.1.2.1.3** Anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia

**10.1.2.2** Disease related events

**10.1.2.2.1** Symptoms associated with anemia (fatigue, weakness, shortness of breath)

**10.1.2.2.2** Electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)

**10.1.2.2.3** Chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)

**10.1.2.2.4** Coagulation abnormalities

**10.1.2.2.5** Disease specific therapy (induction, maintenance, salvage, or stem cell therapy)

**10.1.2.2.6** Alopecia

**10.1.2.2.7** Bone, joint, or muscle pain

**10.1.2.2.8** Liver function test abnormalities associated with infection or disease progression

**10.1.2.2.9** Disease progression

**10.1.2.2.10** Abnormal hematologic values

**10.1.2.3** General therapy related events

**10.1.2.3.1** Catheter related events

**10.1.2.3.2** Renal failure related to tumor lysis syndrome or antibiotic/ antifungal therapy

**10.1.2.3.3** Rash related to antibiotic use

**10.1.2.4** Hospitalization for the management of any of the above expected events

**10.1.3** Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

**10.1.4** All events that are not listed as expected in section 10.1.2 will be collected for the purpose of grading, and determining attribution to study drug by the PI.

**10.1.5** Serious Adverse Event Reporting (SAE)
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB and IND Office in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

**"Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols":**

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

**Reporting to FDA:**

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

**It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

**Investigator Communication with Supporting Companies:**

Any individual expedited SAE reports required by the FDA will be reported to Pfizer within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigator will report to Pfizer by facsimile any Serious Adverse Event as soon as it is determined to meet the definition. Principal Investigator will report SAEs using one of the following forms: (1) an FDA MEDWATCH form, (2) a CIOMS form, (3) an Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, or (4) any other form prospectively approved by Pfizer. The *Reportable Event Fax Cover Sheet* provided by Pfizer must also be included with each SAE submitted.

## 11.0 STATISTICAL CONSIDERATIONS

## 11.1 Endpoints

### 11.1.1 Primary Endpoints:

Phase I:

1. MTD of bosutinib in combination with inotuzumab ozogamicin in patients with Ph+ ALL and CML in lymphoid blast phase that express CD22

Phase II:

2. Major hematologic response (MaHR) for relapsed ph+ALL and CR/CRi for newly diagnosed Ph+ ALL or CML-LBC with age≥60.

### 11.1.2 Secondary Endpoints:

Phase I:

1. Overall MaHR
2. Duration of response and overall survival

Phase II:

3. Incidence and severity of adverse events
4. Duration of response and overall survival

## 11.2 Sample size

This will be a single arm, single center, open label study of bosutinib in combination with inotuzumab ozogamicin in patients with Ph+ ALL and CML in lymphoid blast phase that express CD22. There are two parallel cohorts of patients: relapsed ph+ALL and newly diagnosed Ph+ ALL or CML-LBC with age≥60.

Sample size – Up to 18 patients will be enrolled in phase I part of the study for each cohort. Therefore, there will be a maximum of 36 patients, 18 patients per cohort in phase I part. A total of 56 patients will be enrolled in phase II with 28 patients for each patient cohort: relapsed ph+ALL and newly diagnosed Ph+ ALL or CML-LBC with age ≥60. The 6 patients treated at the MTD from the phase I dose cohort will be included in the phase 2 part for each cohort. Therefore, the maximum sample size is 36 in phase I + 44 in phase II = 80.

*Phase I*

Bosutinib will be dose-escalated in a standard 3+3 study design separately for two cohorts (relapsed ph+ALL and newly diagnosed Ph+ ALL or CML-LBC with age ≥60). Patients will be entered sequentially to each dose level. Three combination dose levels are defined. The starting dose is dose 1. If none of the first 3 patients at a dose level experience first cycle dose-limiting toxicity (DLT), new patients may be entered at the next higher dose level. If 1 of 3 patients experience first cycle DLT, up to 3 more patients are started at that same dose level. If 1of 6 experience DLT, then new patients may be entered at the next higher dose level. If 2 or more

experience first cycle DLT, no further patients are started at that dose. The MTD is the highest dose level in which <2 patients of 6 develop first cycle DLT. Detailed dose escalation rules are described in the following section. A maximum of 18 patients will enroll in the phase I study. DLT definition is provided in Section 4.1.2.

Table 11.1 Dose-Escalation Decision Rules for 3+3 Escalation Schema is provided below:

| **Number of Patients with DLT at a Dose Level** | **Decision** |
|---|---|
| 0 of 3 | Escalate and evaluate in 3 subsequent patients. |
| 1 of 3 | Enroll 3 additional subjects at this dose level. |
| >/=2 of 3 | The MTD has been exceeded. Dose escalation will stop and this level will be declared the maximum administered dose. Evaluate 3 additional patients at the prior dose level if only three were treated at that dose previously.<br>An interim dose may be explored if the increments between maximally administered dose and the next lower dose is >50%. |
| 1 of 6 | Escalate dose and evaluate in 3 subsequent patients. |
| </=1 out of 6 at the Highest Dose Below the Maximum Administered Dose | This is the MTD. |
| >/=2 of 6 | The MTD has been exceeded. Dose escalation will stop and this level will be declared the maximum administered dose. Evaluate 3 additional patients at the prior dose level if only three were treated at that dose previously.<br>An interim dose may be explored if the increments between maximally administered dose and the next lower dose is >50%. |

*Phase II*

Cohort 1: relapsed ph+ALL

Once the MTD (bosutinib 500mg dose level or lower,) is established, a phase II portion will commence. Patients will receive bosutinib per the dose established in the Phase I study. Patients will receive inotuzumab ozogamicin at the same dose and schedule as for the Phase I part of the study.

A total of 28 patients (including the 6 patients treated at the MTD from the phase I dose cohort) will be enrolled in the phase II portion of the study. The primary efficacy endpoint is MaHR during the study period of 4 cycles. We will employ Simon MinMax two-stage design.[23] The target response rate will be 50% and a response rate of 30% or lower will be considered as not

having desired efficacy. With alpha of 0.1 and beta of 0.2, the first stage will require 12 patients. If there are 3 or fewer patients responded, the trial will be stopped. If 4 or more out of the first 12 patients respond, accrual will continue until a total of 28 patients have been enrolled. At the end of the study, if 12 or more patients out of 28 patients respond, the regimen will be considered active. With this design, the probability of early termination is 49% if the true response rate is only 30%.

The method of Thall, Simon, and Estey will be used to perform interim safety monitoring.[24] We will assume a Beta (0.6, 1.4) prior distribution for the toxicity rate which in particular has mean of 30%. The toxicity is defined as any DLT at least possibly attributed to the study drug during the treatment period.

The following decision criteria will be applied continuously up to the 28 patient. The trial will be stopped early according to the following monitoring rule.

$$\Pr\{\text{toxicity rate} > 30\% | \text{ data}\} > 0.93$$

That is, if at any time during the study we determine that there is more than a 93% chance that the toxicity rate is more than 30% we will stop the study. The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the toxicity stopping boundaries and the OC table. The stopping rule boundary is shown in table 12.2.

Table 11.2: Safety monitoring boundary

| #patient | Stop the trial if there are this many toxicities total: |
|---|---|
| 6 | 4-6 |
| 7-8 | 5-8 |
| 9-11 | 6-11 |
| 12-13 | 7-13 |
| 14-16 | 8-16 |
| 17-19 | 9-19 |
| 20-21 | 10-21 |
| 22-24 | 11-24 |
| 25-27 | 12-27 |
| 28 | 13-28 |

Table 11.3: the operating characteristics for safety monitoring

| True toxicity | Early Stopping Probability | Average number of patients treated |
|---|---|---|

| | | |
|---|---|---|
| 0.2 | 0.03 | 27.4 |
| 0.25 | 0.09 | 26.5 |
| 0.3 | 0.19 | 25 |
| 0.35 | 0.34 | 22.7 |
| 0.4 | 0.53 | 19.8 |

Cohort 2: newly diagnosed Ph+ ALL or CML-LBC with age ≥60

Patients in this cohort will be given the dosage of bosutinib in combination with inotuzumab ozogamicin that has been found to be safe in the relapsed patients. A total of 28 patients will be enrolled. The primary efficacy endpoint is CR/CRi during the study period of 4 cycles. Similar to the relapse cohort, we will employ Simon MinMax two-stage design.[23] The target response rate will be 50% and a response rate of 30% or lower will be considered as not having desired efficacy. With alpha of 0.1 and beta of 0.2, the first stage will require 12 patients. If there are 3 or fewer patients responded, the trial will be stopped. If 4 or more out of the first 12 patients respond, accrual will continue until a total of 28 patients have been enrolled. At the end of the study, if 12 or more patients out of 28 patients respond, the regimen will be considered active. With this design, the probability of early termination is 49% if the true response rate is only 30%.

The method of Thall, Simon, and Estey will be used to perform interim safety monitoring.[24] We will assume a Beta (0.6, 1.4) prior distribution for the toxicity rate which in particular has mean of 30%. The toxicity is defined as any DLT at least possibly attributed to the study drug during the treatment period.

The following decision criteria will be applied continuously up to the 28 patient. The trial will be stopped early according to the following monitoring rule.

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| | |
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| 7-8 | 5-8 |
| 9-11 | 6-11 |
| 12-13 | 7-13 |
| 14-16 | 8-16 |
| 17-19 | 9-19 |
| 20-21 | 10-21 |
| 22-24 | 11-24 |
| 25-27 | 12-27 |
| 28 | 13-28 |

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|---|---|---|
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| 0.25 | 0.09 | 26.5 |
| 0.3 | 0.19 | 25 |
| 0.35 | 0.34 | 22.7 |
| 0.4 | 0.53 | 19.8 |

### 11.3 Statistical Analysis Plan

The primary end-point is major hematologic response. The response will be evaluated along with its 95% confidence interval. Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drugs and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency.

Analysis of secondary endpoints will be predominantly descriptive statistics and will be interpreted as being exploratory and hypothesis generating. The duration of response and overall survival (OS) will be estimated using the method of Kaplan-Meier. Cox regression models will be used to determine the relationship with the time-to-events (e.g. OS) and the potential prognostic factors.

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