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Protocol Page

An open-label phase II dose optimization study of bosutinib at a starting dose of 300 mg daily for adult patients with chronic myeloid leukemia (CML) in chronic phase post frontline TKI failure

2016-0081

Core Protocol Information

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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

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Protocol 2016-0081. An open-label phase II dose optimization study of bosutinib for adult patients with chronic myeloid leukemia (CML) in chronic phase post frontline TKI failure

Contents

1.0 OBJECTIVES

Primary:

To assess the response rate within 24 weeks in patients in chronic phase receiving bosutinib with the starting dose of 300 mg per day, with potential escalation to 400mg, 500 mg and 600mg per day.

Response is defined as follows:

1. For patients who do not currently have a partial cytogenetic response (PCyR), achievement of major cytogenetic response (MCyR) is considered a response.
2. For patients who are currently in PCyR, achievement of complete cytogenetic response (CCyR), CCyR is considered a response.

Secondary:

- Safety of dosing schedule.
- Frequency of treatment interruptions and dose reductions.
- Determine the rate of BCR-ABL/ABL <10% at 3 months and <1% at 6 months, reported on the international scale, and the rate of complete cytogenetic response (CCyR) at 6 months after the start of treatment.
- Determine the cumulative rate of CCyR.
- Determine the rate of major molecular response, MR4, MR4.5 and complete molecular response.
- Determine long-term outcomes, including progression-free survival, event-free survival, and overall survival.
- Investigate the correlation between ABL kinase domain mutations, if present at the time of enrollment, with outcome.

- Determine the rate of development and type of ABL kinase domain mutations during therapy with bosutinib.

2.0 STUDY DESIGN

The study is an open-label phase II trial in patients with CML in chronic phase who have experienced resistance or intolerance to frontline TKI therapy. The starting dose of bosutinib is 300 mg per day. Patients will have the opportunity to dose escalate to 400mg, 500mg and subsequently to 600mg if therapeutic targets are not met and toxicity does not preclude such dose escalation.

Toxicity will be monitored continuously, throughout the duration of the study.

3.0 CHRONIC MYELOID LEUKEMIA

3.1 Disease Overview

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1-2 cases per 100,000 adults, and accounts for approximately 15% of newly diagnosed cases of leukemia in adults.(1) Central to the pathogenesis of CML is the fusion of the Abelson murine leukemia (ABL) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22, which results in expression of an oncoprotein, termed BCR-ABL.2 BCR-ABL is a constitutively active tyrosine kinase that promotes growth and replication through downstream pathways such as RAS, RAF, JUN kinase, MYC and STAT.(3-9) This influences leukemogenesis by creating a cytokine-independent cell cycle with aberrant apoptotic signals in response to cytokine withdrawal.

Until approximately a decade ago, drug therapy for CML was limited to non-specific agents such as busulfan, hydroxyurea, and interferon-alfa (INF-a).(10) INF-a led to regression of the disease and improved survival but was hindered by a multitude of toxicities. Allogeneic stem cell transplantation (AlloSCT) was a curative intervention, but carried with it a high risk of

morbidity and mortality. Further, alloSCT is only an option for patients with excellent performance status and an appropriate stem cell donor.

The landscape changed dramatically with the development of small molecule tyrosine kinase inhibitors (TKIs) that were shown to potently interfere with the interaction between the BCR-ABL protein and adenosine triphosphate (ATP), blocking cellular proliferation of the malignant clone.(11) This “targeted” approach was found to dramatically alter the natural history of the disease, improving 10-year overall survival from approximately 20% to 80 – 90%.(1,12)

3.2 Frontline management

Three TKIs have received regulatory approval for the frontline treatment of CML: imatinib, dasatinib, and nilotinib. Current guidelines endorse all three as excellent options for the initial management of CML in the chronic phase (CML-CP). Imatinib mesylate (Gleevec, Novartis Pharmaceutical Corporation, NJ, USA), was the first TKI to receive approval by the Food and Drug Administration (FDA) for the treatment of patients with CML-CP. It acts via competitive inhibition at the ATP-binding site of the Bcr-Abl oncoprotein, which results in the inhibition of phosphorylation of proteins involved in cell signal transduction. It efficiently inhibits the Bcr-Abl kinase activity, but also blocks the platelet-derived growth factor receptor (PGDFR), and the C-KIT tyrosine kinase.(11-12)

The International Randomized Study of IFN-a and STI571 (IRIS) study is considered a landmark clinical trial for TKIs and CML.(13) Investigators randomized 1,106 patients to receive imatinib 400 mg/day or IFN plus subcutaneous low-dose cytarabine. After a median follow-up of 19 months, relevant outcomes for patients receiving imatinib were significantly better than for those treated with IFN plus cytarabine, notably the rate of CCyR (74% vs. 9%, $P < .001$), and freedom from progression to accelerated phase (AP) or blast phase (BP) at 12 months (99% vs. 93%, $P < 0.001$). The responses to imatinib were also durable, as shown in an 8-year follow up of the IRIS study;(12) the estimated event-free survival rate was 81%; the overall survival (OS) rate was 93% when only CML-related deaths were considered.

While the results using imatinib were impressive, only 55% of patients enrolled remained on therapy at the 8-year follow up time. This underscores the need for additional options for patients who had failed or were intolerant to imatinib, and led to the rational development of second generation TKIs.

Dasatinib (Sprycel, Bristol-Myers Squibb) is an oral, second generation TKI, which is 350 times more potent than imatinib in vitro.(14-16) It also inhibits the Src family of kinases, which may also be important in blunting critical cell signaling pathways.(17) Following the positive results in the salvage setting post imatinib failure, dasatinib was evaluated as frontline CML therapy.

The DASISION trial was a randomized, phase III, international study comparing imatinib 400 mg daily versus dasatinib 100 mg daily in newly diagnosed patients with CML-CP.(18) The primary endpoint of the study was confirmed CCyR at 12 months, which was achieved in a higher percentage of patients randomized to dasatinib (77% vs. 66%, P = 0.007). Dasatinib was also able to induce higher rates of major molecular response (MMR) compared with imatinib.(19)

Nilotinib (Tasigna, Novartis Pharmaceutical Corporation, NJ, USA) is a structural analog of imatinib, though Its affinity for the ATP binding site on Bcr-Abl is 50 times more potent in vitro.(20) Like dasatinib, nilotinib initially demonstrated the ability to induce hematologic and cytogenetic responses in patients with CML post imatinib failure, leading to nilotinib therapy in the frontline setting.

ENESTnd was a randomized, phase III, international study comparing two doses of nilotinib (300 mg or 400 mg twice daily) to imatinib 400 mg once daily.(21) The primary study endpoint was the rate of MMR at 12 months, which was achieved at higher rates on the nilotinib arms compared with imatinib (44% and 43% vs. 22%, P <0.001). There were also fewer cases of progression to AP or BP noted with nilotinib.(22)

3.3 Management of TKI resistance

A problem that may increase due to the widespread use of all of the commercially available TKIs for CML is increased drug resistance. One of the most common mechanisms of resistance involves point mutations in the kinase domain of BCR-ABL, which impair the activity of the available TKIs. Second generation TKIs are able to overcome most of the mutations that confer resistance to imatinib, though novel mutations rendering the leukemia resistant to dasatinib and/or nilotinib have emerged. One important mutation, the T315I, is known as the “gatekeeper” mutation, as it confers resistance to all currently available TKIs except ponatinib.

Before their approval to treat first-line CML in chronic phase (CML-CP), both nilotinib and dasatinib were approved for use in second-line CML-CP following prior therapy, including imatinib.(23-24) Based on these clinical studies, several noteworthy ideas have emerged. First, second-line treatment can yield high rates of response in patients who have inadequate response to imatinib, including high rates of MMR. Second, dose escalation of imatinib can improve response rates in patients with inadequate response to standard-dose imatinib, but switching to second-line TKIs can be more effective.(25) In addition, earlier switch to second-line TKI may be more effective than later switch.(26)

3.4. Bosutinib

Bosutinib was initially studied in patients that were resistant to or intolerant of imatinib.(27) After a dose escalation period, 500 mg once daily was selected to go forward as the phase II dose, with the potential for dose escalation to 600 mg once daily for patients not meeting pre-specified benchmarks. There were 288 patients enrolled in the pivotal phase II trial, with more than two thirds of the patients documented as having imatinib-resistant disease. The primary endpoint was MCyR at 6 months, and this was achieved in 31% of the patients treated. At any point during follow up, 41% achieved a CCyR. Bosutinib appeared to retain activity across most known mutations that confer imatinib resistance, except for the T315I. Responses were independent of whether patients were resistant to or intolerant of imatinib. The most common toxicities noted were diarrhea, nausea, vomiting, and rash. Diarrhea occurred in 84% of the patients overall, with 9% experiencing an event classified as grade 3

(there were no grade 4 events documented). Other notable adverse events included myelosuppression and liver function test abnormalities.

Bosutinib was assessed in the frontline therapy of patients with newly diagnosed CML.(28) In the phase 3 BELA study, which evaluated the effect of treatment in a first-line setting, bosutinib at 500 mg did not achieve the primary efficacy end point of a superior rate of CCyR at 12 months versus imatinib. However, bosutinib did demonstrate superiority across many other efficacy end points including MMR at 12 months, and importantly for patients, the percentage of patients with transformation to AP or BP was lower for bosutinib than imatinib.(28)

In addition, the safety profile of bosutinib was distinct from that of imatinib in terms of increased gastrointestinal (GI) toxicity, especially diarrhea, and increased values for liver function tests (LFTs). Compared with imatinib, bosutinib was associated with higher incidences of Grade 3-4 GI toxicities, including diarrhea (12% vs. 1%), vomiting (3% vs. 0%) and abdominal pain (1% vs. <1%), although these AEs were usually transient and manageable. Notably, diarrhea occurred mostly in the first 1-2 months of therapy and improved or subsided spontaneously over time. Conversely, there were fewer patients with hematologic toxicity in the bosutinib arm compared to imatinib.

Subsequently, the BFORE study was designed, which compared bosutinib at a lower dose of 400mg/d to imatinib 400mg/d. There remained a significant incidence of grade 3-4 AEs with bosutinib, especially elevated ALT (19%) and diarrhea (8%). Although somewhat lower in incidence than in the BELA study of 500mg/d, these were associated with a significant incidence of treatment interruptions and reductions (56%, overall). Median duration of dose interruption was 23 days. MMR rate at 12 months was 47% in BFORE, compared to 41% in BELA, indicating that the lower dose of bosutinib did not compromise efficacy.(1)

3.5. Rationale for the starting dose of 300 mg per day of bosutinib

The first studies in 2nd line and first line therapy used 500mg/d. In both studies, a substantial number of patients reported toxicities. The incidence of treatment emergent AEs (TEAEs)

overall as well as unique TEAEs were lower following dose reduction from 500 mg to 400 mg, while the efficacy of bosutinib in patients who received dose reductions to 400 mg remained favorable.

Therefore, it was concluded that a starting dose of 400 mg daily would be used in this phase II study in patients post frontline TKI failure, with potential escalation to 500 mg daily and subsequently to 600mg daily, if therapeutic targets at pre-specified timepoints are not met and toxicity is within acceptable limits. By starting at a lower dose and dose-escalating as tolerated/necessary, we will minimize dose interruptions, which may compromise efficacy. We hypothesize that such a dosing strategy will result in better tolerability and similar, if not superior, efficacy as a starting dose of 500 mg daily.

Recently, results of the BFORE study were published, demonstrating favorable efficacy (higher rate of MMR at 12 months with a dose of 400mg bosutinib than when starting with 500mg in the BELA study), confirming the above hypothesis. However, there was still a significant incidence of grade 3-4 toxicity and dose interruptions/reductions, which may have a greater impact on efficacy than receiving a lower, consistent dosing schedule. Additionally, in the first 8 patients treated on this study, we have had 3 patients with grade 3-4 toxicity (elevated LFTs in 2 patients and diarrhea in 1 patient). Therefore, we subsequently amended the study to commence dosing at 300mg per day, with the option to escalate doses if therapeutic targets are not met during treatment.

4.0 NUMBER OF PATIENTS

42 patients will be enrolled in this open-labeled phase II trial.

5.0 STUDY ENTRY CRITERIA

5.1 Inclusion criteria:

1. Patients with CML in chronic phase who have resistance and/or intolerance to frontline TKI therapy. Resistance is defined as lack (lack defined as response not achieved or lost by the given dates mentioned hereafter) of CHR within 3 months, lack of MCyR within 6 months, and lack of CCyR within 12 months of therapy with

frontline TKIs. In addition, loss of MCyR or CCyR at any time during the course of therapy is also considered resistance to therapy. Intolerance is defined as persistent or severe toxicity that is unacceptable to the patient.

2. Chronic phase is defined as:
   a. <15% blasts in peripheral blood and bone marrow;
   b. <30% blasts plus promyelocytes in peripheral blood and bone marrow;
   c. <20% basophils in peripheral blood;
   d. > or =100 x 10^9/L platelets (> or =100,000/mm3);
   e. No evidence of extramedullary disease except hepatosplenomegaly; and
   f. No prior diagnosis of AP or BP-CML. Patients with clonal evolution but no other criteria for accelerated phase are eligible.
3. ECOG performance status of 0, 1, or 2.
4. Age 18 years or older.
5. Adequate organ function with creatinine less than or equal to 2.0 mg/dl, bilirubin less than or equal to 3.5 mg/dl and ALT less than or equal to 2.5 times institutional upper limit of normal
6. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (beta-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: a. birth control pills, shots or implants (placed under the skin by a health care provider) or patches (placed on the skin); b. Intrauterine devices (IUDs); c. 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.

5.2 Exclusion criteria:

1. Women that are pregnant or lactating
2. Known to be HIV+
3. Active and uncontrolled disease/infection that in the opinion of the treating physician and principal investigator may affect the ability to participate in the trial or put the patient at unduly high risk
4. Unable or unwilling to sign the informed consent document
5. Received other investigational therapy within the past 14 days
6. Presence of T315I mutation on ABL1 sequencing
7. Patient is currently in complete cytogenetic remission (CCyR)

6.0 TREATMENT PLAN

Bosutinib will be commenced at 300mg/d. Subsequent dose changes may be made in the event of inadequate response or toxicity, according to the dose levels in table 2.

Table 2. Bosutinib dose levels

Dose level	Bosutinib (mg)
+3	600
+2	500
+1	400
Starting dose	300
-1	200
-2	100

6.1 Management of bosutinib dosing.

Patients may have their dose increased by one dose level, at the 1, 3, 6 and 12 month assessments, if they do not achieve or subsequently lose the following therapeutic milestones:

i) month 1, complete hematologic response;

ii) month 3, BCR-ABL1 transcripts < or = 10% and/or Ph + metaphases < or = 35%;

iii) month 6 BCR-ABL1 transcripts < or = 1% and/or Ph + metaphases 0%);

iv) month 12, BCR-ABL1 transcripts <0.1%. All BCR-ABL targets refer to the international scale.

AND

They do not currently have grade >/= 3 hematologic or grade >/=2 non-hematologic toxicity.

6.1.1 Patients who had their dose reduced for any reason may have the dose re-escalated after at least 28 days at the lower dose provided they do not currently have grade >/= 3 hematologic or grade >/=2 non-hematologic toxicity.

6.1.2 At least 28 days should have elapsed from a prior dose escalation before a new dose escalation can be implemented, and the patient should not currently have grade >/= 3 hematologic or grade >/=2 non-hematologic toxicity. The highest dose level to be used in this study is 600 mg daily.

6.1.3 Dose escalations outside the above timepoints may be initiated by the treating physician if deemed to be in the best interests of the patient, with the approval of the PI.

6.2 Bosutinib dose reductions:

General guidelines include the following:

a) Non-Hematologic Toxicity

- **Grade 2:** Patients with persistent grade 2 toxicity that is unresponsive to appropriate therapy, may have treatment held until the toxicity has resolved to grade < or =1. Bosutinib may then be resumed at the same dose the patient was receiving at the time treatment was interrupted. If the grade 2 toxicity recurs, bosutinib may be held until the toxicity has resolved to grade 1. Treatment may then be resumed with a one dose level reduction.
- **Grade 3-4**: If a patient experiences Grade 3-4 toxicity that is related to bosutinib, therapy must be withheld until the toxicity has resolved to Grade < or = 1. Bosutinib

may then be resumed with a one dose level reduction.

b) Hematologic Toxicity

- If absolute neutrophil count is <1.0 x 10^9/L or platelets are <50 x 10^9/L, hold therapy until granulocytes are above 1 x 10^9/L and platelets are > or = 50 x 10^9/L, then resume therapy.
- If recovery takes more than 2 weeks, resume bosutinib at 1 dose level reduction from the dose the patient was receiving at the time therapy was interrupted.
- If recovery takes less than 2 weeks, resume bosutinib at the same dose the patient was receiving at the time treatment was interrupted. If myelosuppression recurs, resume bosutinib at one dose level reduction from the dose the patient was receiving at the time the treatment was interrupted.
- If a similar degree of toxicity returns, a further dose reduction by one dose level can be performed, using the above procedures.

c) Modifications of dose schedules other than the above will be allowed in the best interest of the patient, with the approval of the PI.

6.3 Missed doses.

Occasional missed doses will not be considered a deviation. Missed doses of > or = 2 weeks will be considered a protocol deviation unless treatment interrupted for medical reasons.

7.0 PRE-TREATMENT EVALUATION AND EVALUATION DURING TREATMENT

Table 3. Pre-treatment evaluation and evaluation during treatment.

Cycle	**Screening/ baseline(1)**	**1**	**1**	**2**	**3**	**6**	**9**	**12**	**18**	**24**	**At progression**
Day within cycle(2)	**-28 to 1**	**15(a)**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	
Informed consent(3)	**X**										
Medical history(4)	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**

Physical examination including vital signs(5)	X		X		X	X	X	X	X	X		X
Complete blood count with differential(6)	X	X	X	X	X	X	X	X	X	X		X
Biochemistry(7)	X	X	X	X	X	X	X	X	X	X		X
Bone marrow examination and conventional cytogenetics(8)	X					X						X
Cytogenetic analysis(9)	X				X	X	X	X	X	X		X
PCR testing for BCR-ABL1(10)	X				X	X	X	X	X	X		X
Kinase domain sequencing(11)	X											
Pregnancy test(12)	X											

(a) Evaluations on day 15 and 56 can either be performed in the context of a clinic visit at M.D. Anderson **or** patients can have labs drawn locally and the results provided to study staff. Additional evaluations may be ordered at the discretion of the treating physician, if deemed necessary.

(1) Screening period testing. All the above must be completed within 28 days of study enrollment, with the exception of bone marrow examination, cytogenetics and kinase domain sequencing, which must be completed within 42 days prior to study enrollment and pregnancy test, which must be performed within 14 days prior to study enrollment.

(2) Evaluations within the first month of therapy must take place within +/- 1 week of scheduled time. Evaluation at D56 must occur within +/-2 weeks. Subsequent evaluations must occur within 1 month of the scheduled time.

(3) Informed consent. All patients must take part in the informed consent process.

(4) Medical history. A complete medical history will be obtained at screening, and at the end-of-treatment visit. At all other visits, the medical history taking can be focused to the needs of the patient.

(5) Physical examination. Complete physical examination must be performed pre-treatment. Thereafter, it can be directed to the specific needs of the patient.

(6) Complete blood count with differential. CBC with differential is not required if WBC < or = 0.5 x 10^9/L

(7) Biochemistry. Assessment will include, ALT, bilirubin and creatinine levels. Others will be performed at treating physician discretion according to the needs of the patient.

(8) Bone marrow examination, with conventional cytogenetic analysis, will be performed at screening, at 6 months and at progression. Bone marrow obtained as part of standard of care prior to signing of informed consent form can be used at screening as long as it was collected within 42 days of commencing treatment.

(9) Cytogenetic analysis. This will be performed every 3 months, either by conventional karyotype analysis in bone marrow, or using FISH in peripheral blood or bone marrow, until complete cytogenetic remission is achieved. After achieving complete cytogenetic remission, cytogenetic analysis need only be repeated if clinically indicated (eg. in the event of a significant rise in BCR-ABL levels).

(10) RT-qPCR testing for BCR-ABL1 quantitation will be performed from peripheral blood or bone marrow at screening, then every 3 months (+/- 1 month) until achievement of MMR, then every 6 months or as clinically indicated.

(11) Kinase domain sequencing; this will be performed during the screening period and then as clinically indicated In patients where the reason for changing therapy is intolerance,

rather than progression/lack of response, this test may be omitted and this will not be considered a deviation.

(12) Pregnancy test. The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test, using either urine or serum. Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. If the test is deemed necessary, it must be performed within 14 days of commencement of study treatment and known to be negative prior to commencement of study treatment.

8.0 CRITERIA FOR RESPONSE

8.1 Hematologic response:

Complete hematologic response is defined as a white blood cell count <10 × 10^9/l, a platelet count <450 × 10^9/l, no blasts in the peripheral blood and disappearance of all signs and symptoms related to leukemia, including palpable splenomegaly.

8.2 Cytogenetic response:

Cytogenetic assessments are based on at least 20 metaphases or fluorescence in situ hybridization with at least 200 cells on peripheral blood or bone marrow Cytogenetic response can be categorized as:

- Complete: 0% Ph+ metaphases;
- Partial cytogenetic response: 1%-35%;
- Major cytogenetic response, 0%-35%;
- Minor cytogenetic response, 36%-65%;
- Minimal cytogenetic response, 66%-95%;
- No cytogenetic response, > 95%.

8.3 Molecular response:

Molecular assessments are based on quantitative reverse transcriptase polymerase chain reaction for Bcr-Abl in peripheral blood. Molecular response is categorized as MMR (Bcr-

Abl/Abl ratio of < or =0.1% in the International Scale), MR4 (Bcr-Abl/Abl < or =0.01%), and MR4.5 (BCR-ABL/ABL < or =0.0032%).

To convert M.D. Anderson BCR-ABL results to the international scale, multiply result by 0.35.

8.4 Survival:

- Overall survival: Overall survival is calculated from the start date of therapy to the date of death or last follow-up.
- Failure-free survival: Failure-free survival is measured from the start of study drug to the earliest date of the following: an event as defined for event-free survival, transformation to AP or BP, intolerance, treatment discontinuation for any reason (as assessed by investigator), or death from any cause while on bosutinib therapy.
- Event-free survival (EFS): EFS is defined as the time from treatment start until any of the following events that occur during study treatment: loss of complete hematologic response (CHR); loss of major cytogenetic response (MCyR); progression to AP/BP; death due to any cause.
- Transformation-free survival: Transformation-free survival is defined as the time from treatment initiation until either progression to AP/BP or death from any cause.

9.0 EVALUATION OF TOXICITY

Toxicities will be graded in the research nurse/PI dictations in the medical record, according to the NCI Expanded Common Toxicity Criteria version 4.03 or later.

10.0 CRITERIA FOR REMOVAL FROM THE STUDY

Criteria for removal from study include, but are not restricted to, the following:

1. Clinically significant progressive disease, defined as accelerated phase (except clonal evolution as the only criterion for accelerated phase) or blast phase, loss of complete
2. Recurrent non-compliance by the patient with protocol requirements.
3. Patient's request to be removed from the study.
4. Unacceptable toxicity.

5. Failure to respond at 3, 6, 12 months according to European LeukemiaNet (ELN) criteria for response to second line therapy (i.e. "Failure" category in table 6, below), despite recommended optimization of therapy

Table 4. ELN criteria for response in 2nd line therapy of CML.

	Optimal	Warning	Failure
3 months	BCR-ABL < or =10% and/or	BCR-ABL >10% or Ph+ 65-95%	Ph+ >95%.
6 months	BCR-ABL < or =10% and/or Ph+ <35% (i.e. MCyR)	Ph+ 35-65%	BCR-ABL >10% and/or Ph+ >65% and/or new mutations
12 months	BCR-ABL <1% and/or Ph+ 0 (i.e. CCyR)	BCR-ABL 1-10% and/or Ph+ 1-35%	BCR-ABL >10% and/or Ph+ >35% and/or new mutations

11.0 STATISTICAL CONSIDERATIONS

This is a single-arm open-label phase II study to assess the response rate achieved with bosutinib therapy in patients with chronic phase CML who have experienced resistance or intolerance to frontline TKI therapy. Patients will receive an escalating schedule of bosutinib with the starting dose of 400 mg per day. The primary endpoint is response rate, as defined in section 1.0, within the first 6 months therapy. The Simon's optimal two-stage design will be used for interim futility monitoring. The null hypothesis is that the response rate is 20% and our target rate under the alternative hypothesis is 35%. Under the design, we will enroll 20 patients in the first stage. If 4 or fewer patients achieve the primary endpoint, enrollment of future patients will be halted. If 5 or more out of the first 20 patients have met the primary endpoint, accrual will continue until a total of 42 patients are enrolled. If 12 or more out of these 42 patients achieve the primary endpoint, the treatment will be considered efficacious and is worth further investigation. Under this Simon's optimal two-stage design, the type I error is 0.101, the power is 79.8%, the probability of early

termination is 0.63 if the true hematologic remission rate is 20% and the expected sample size is 28.2 patients. After the first stage, if <5 responders are observed in the first 20 patients, we will temporarily suspend the accrual until a sufficient number of responders (i.e., >/=5) is reached.

We will also monitor treatment emergent toxicities using a Bayesian design by Thall, Simon and Estey, starting from the 6th patient and then in cohort size of 6. For monitoring purposes, toxicity is defined as the occurrence of grade 3-4 hematologic or non-hematologic toxicity leading to treatment discontinuation and the associated toxicity stopping rule is to stop the trial if Prob{p(TOX) > 0.35| data} > 0.90, where p(TOX) is the toxicity rate and a beta(0.7, 1.3) distribution was assumed for the prior. That is, if at any time during the trial we determine that there is more than 90% chance that the toxicity rate is more than 35%, we will stop the trial due to safety concern. The corresponding stopping boundaries are shown in Table 1 below and the operating characteristics of the toxicity monitoring are illustrated in Table 2. Multc Lean Desktop (v2.1.0) (https://biostatistics.mdanderson.org/SoftwareDownload/) was used for generating the stopping boundaries and the OC table. Toxicities will be monitored continuously over the two year duration of the study.

Table 5. Toxicity stopping boundaries in cohort size of 6.

Number of patients	Stop the trial if there are this many patients having toxicity
6	4-6
12	7-12
18	10-18
24	12-24
30	15-30
36	17-36

42	Always stop with this many patients	

Table 6: Operating characteristics for toxicity monitoring.

True Toxicity Rate	Early Stopping Probability	Average number of patients treated	25th, 75th percentile
0.25	0.050	40.4	42, 42
0.30	0.112	38.6	42, 42
0.35	0.227	35.6	42, 42
0.40	0.400	31.2	18, 42
0.50	0.789	20.6	6, 36
0.60	0.974	12.4	6, 18

Analysis Plan:

The response rate will be estimated along with the 95% credible interval. Data from all subjects who receive any study drug will be included in the safety analyses. 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 AE category, severity and frequency. The Frequency of treatment interruptions and dose reductions will be summarized. The rates of major molecular response, MR4, MR4.5 and complete molecular response will be estimated along with the exact 95% confidence intervals. Similarly, the rates of BCR-ABL/ABL <10% at 3 months and BCR-ABL/ABL <1% at 6 months since treatment start, on the international scale, will be estimated along with the exact 95% confidence intervals. Kaplan-Meier method will be used to assess the overall survival (OS), failure-free survival (FFS), failure-free survival (FFS) and transformation-free survival (TFS). Cox proportional hazards regression models will be fit to assess the association between patient characteristics including ABL kinase domain mutation status and each survival outcome. In addition, the change of ABL kinase domain mutation status

over time will be summarized and its association with survival outcomes will be analyzed through landmark analyses.

12.0 REPORTING REQUIREMENTS

Reporting Requirements

12.1 Reporting requirements will be as per institutional guidelines.

12.2 Adverse events related to study conditions

The SAE reporting period will begin with the initiation of bosutinib

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate.

12.3 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.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB 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”.
- All SAEs will also be reported in parallel to Pfizer. No individual SAE reports will be sent to Pfizer but SAEs will be reported as a cumulative line listing to BMS approximately every 12 months.
- 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.
- 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.

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14.0 ABBREVIATION LIST

ABL – Abelson tyrosine kinase.
AE – adverse event
alloSCT – allogeneic stem cell transplant.
ALT – alanine transaminase.
ANC – absolute neutrophil count
AP – accelerated phase.
AST – aspartate transaminase
ATP – adenosine triphosphate.
BCR – Breakpoint Cluster Region.

BELA – Bosutinib vs Imatinib in Newly Diagnosed Chronic Myeloid Leukemia.

BP – blast phase

BUN – blood urea nitrogen

CBA – chromosome banding analysis

CBC – complete blood count

CCyR – Complete Cytogenetic Response.

CHR – complete hematologic response.

C-KIT – KIT protooncogene

CML – Chronic Myeloid Leukemia.

CP – chronic phase.

CTCAE – Common Terminology Criteria for Adverse Events

DASISION – Dasatinib or Imatinib in Newly Diagnosed Chronic Myeloid Leukemia

EC – ethics committee

ECG – electrocardiogram

ECHO – echocardiogram

ENESTnd – Evaluating Nilotinib Efficacy and Safety in Clinical Trials – newly diagnosed patients

FDA – food and drug administration.

FFS – failure free survival

GI – gastrointestinal

hCG – human chorionic gonadotropin.

HIV – human immunodeficiency virus

INF-a – interferon-alpha.

IRB – institutional review board

IRIS – International Randomized Study of INF-a and STI571

IUD – intrauterine device.

JUN – JUN protocooncogene

LFTs – liver function tests

MCyR – major cytogenetic response

MDASI – M.D. Anderson Symptom Index

MMR – major molecular response

MR4 – Molecular Response with 4 log reduction from baseline BCR-ABL transcript level.

MR4.5 – Molecular Response with 4.5 log reduction from baseline BCR-ABL transcript level.

MUGA – multigated acquisition scan

MYC – MYC protooncogene

NCI – national cancer institute

NK – natural killer.

OS – overall survival.

PCR – Polymerase Chain Reaction

PDGFR – platelet-derived growth factor receptor

Ph – Philadelphia Chromosome

PI – primary investigator

RAF – Rapidly Activated Fibrosarcoma

RAS – Rat Sarcoma

RT-qPCR – real time quantitative polymerase chain reaction

SRC – SRC protooncogene

STAT – Signal Transducer and Activator of Transcription

SUSAR – serious unexpected adverse event

T315I – threonine-315-isoleucine mutation

TEAE – treatment emergent adverse event

TFS – transformation-free survival.

TranscriptionTKIs – tyrosine kinase inhibitors.

ULN – upper limit of normal

WBC – white blood cell