THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Alternating or Combined Therapy with Axitinib and Bosutinib for Patients with Chronic Myeloid Leukemia in Chronic, Accelerated or Blastic Phases
2015-0787

Core Protocol Information

Short Title	Axitinib and Bosutinib in CML
Study Chair:	Prithviraj Bose
Additional Contact:	Andrea L. Booker Vicky H. Zoeller Leukemia Protocol Review Group
Additional Memo Recipients:	**Recipients List** **OPR Recipients** (for OPR use only) None **Study Staff Recipients** None
Department:	Leukemia
Phone:	713-792-7747
Unit:	428
Study Manager:	Carissa G. Jurisprudencia
Full Title:	Alternating or Combined Therapy with Axitinib and Bosutinib for Patients with Chronic Myeloid Leukemia in Chronic, Accelerated or Blastic Phases
Public Description:	N/A
Protocol Type:	Standard Protocol
Protocol Phase:	Phase I/Phase II
Version Status:	Activated -- Closed to new patient entry as of 09/23/2019
Version:	11
Document Status:	Saved as "Final"
Submitted by:	Andrea L. Booker--9/16/2019 12:25:43 PM
OPR Action:	Accepted by: Rosheta McCray -- 9/23/2019 11:51:49 AM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

Axitinib bosutinib protocol after SIV (02-07-17) amended 01-18-2018 Final.docx

Hidden Fields==========

Alternating or Combined Therapy with Axitinib and Bosutinib for Patients with Chronic Myeloid Leukemia in Chronic, Accelerated or Blastic Phases

PI: Prithviraj Bose, M.D.
Co-PI: Jorge Cortes, M.D.

Department of Leukemia

The University of Texas, MD Anderson Cancer Center

TABLE OF CONTENTS

1.0 Objectives and endpoints

1.1 Objectives

1.1.1 Primary:

- Chronic phase cohort: To assess the rate of major cytogenetic response (MCyR) of an alternating schedule of axitinib and bosutinib in patients with chronic myeloid leukemia – chronic phase (CML-CP) after failure of/intolerance to ≥3 tyrosine kinase inhibitors (TKIs) using standard response criteria[1].

- Advanced phase cohort – phase I portion: To determine the recommended phase II doses (RPTDs) of axitinib and bosutinib in combination in patients with CML in accelerated phase (CML-AP) or blast phase (CML-BP). (AP patients must have received ≥1 prior TKI).

- Advanced phase cohort - phase II portion: To evaluate the rate of major hematologic response (MaHR) of combined treatment with axitinib and bosutinib in patients with CML-AP or CML-BP using standard response criteria[1]. (AP patients must have received ≥1 prior TKI).

1.1.2 Secondary:

- Chronic phase cohort:
  - To determine the rate of complete cytogenetic response (CCyR), BCR-ABL/ABL ≤10% and ≤1%, major molecular response (MMR), molecular response 4-log (MR4), molecular response 4.5-log (MR4.5), and complete molecular response (CMR), overall and at different time points.

  - To determine the duration of response (DOR), event-free survival (EFS), transformation-free survival (TFS), failure-free survival (FFS) and overall survival (OS) for patients with CML-CP treated with alternating axitinib and bosutinib after failure of/intolerance to ≥3 TKIs.

  - To determine the safety and tolerability of alternating therapy with axitinib and bosutinib after failure of/intolerance to ≥3 TKIs.

- Advanced phase cohort – phase I portion: To establish the response rate of concurrent administration of axitinib and bosutinib to patients with CML-AP or CML-BP. (AP patients must have received ≥1 prior TKI).

- Advanced phase cohort - phase II portion:
  - To determine the rate of complete hematologic response (CHR), complete cytogenetic response (CCyR), BCR-ABL/ABL ≤10% and ≤1%, major molecular response (MMR), molecular response 4-log (MR4), molecular response 4.5-log (MR4.5), and complete molecular response (CMR), overall and at different time points of combined treatment with axitinib and bosutinib in patients with CML-AP or CML-BP. (AP patients must have received ≥1 prior TKI).

- To determine the DOR, EFS, TFS, FFS and OS for patients with CML-AP or –BP treated with combined axitinib and bosutinib. (AP patients must have received ≥1 prior TKI).
- To analyze differences in response rates, duration and survival according to pre-treatment mutations and patient characteristics in both the CP and AP/BP cohorts.
- To evaluate symptom burden in patients with CML receiving axitinib and bosutinib, whether alternating (CP) or in combination (AP/BP).

1.2 Endpoints

1.2.1 Primary:

- Chronic phase cohort: The rate of major cytogenetic response (MCyR) among patients with CML-CP s/p failure of/intolerance to ≥3 TKIs treated with alternating axitinib and bosutinib.

- Advanced phase cohort – phase I portion: The maximum tolerated doses (MTDs, up to the target doses) of the combination of axitinib and bosutinib among patients with CML-AP or –BP. (AP patients must have received ≥1 prior TKI).

- Advanced phase cohort - phase II portion: The major hematologic response (MaHR) rate to the combination of axitinib and bosutinib among patients with CML-AP or –BP. (AP patients must have received ≥1 prior TKI).

1.2.2 Secondary:

- Chronic phase cohort: The rates of CHR, CCyR, MMR, MR4, MR4.5, CMR, BCR-ABL/ABL ≤10% and ≤1%, DOR, EFS, TFS, FFS and OS among patients with CML-CP after resistance and/or intolerance to ≥3 TKIs treated with alternating axitinib and bosutinib.
- Advanced phase cohort – phase I portion: The nature, incidence and severity of adverse events (AEs), as determined by history and physical examination and laboratory assessment, seen with the combination of axitinib and bosutinib among patients with CML-AP or –BP. (AP patients must have received ≥1 prior TKI).
- Advanced phase cohort - phase II portion: The rates of CHR, CCyR, MMR, MR4, MR4.5, CMR, BCR-ABL/ABL ≤10% and ≤1%, DOR, EFS, TFS, FFS and OS among patients with CML-AP or –BP receiving combined therapy with axitinib and bosutinib. (AP patients must have received ≥1 prior TKI).
- Characterization of somatic mutations in *BCR-ABL* at baseline and throughout the study in all patients receiving study drugs.MDASI-CML scores in all patients receiving study drugs.

2.0 Background

2.1 Purpose

The basic hypothesis underlying our therapeutic programs in CML is to be able to achieve meaningful and sustained suppression of the Philadelphia chromosome and the resultant fusion protein, BCR-ABL. CCyRs have been associated with improved overall survival (OS) in CML, while MMRs are associated with improved event-free survival (EFS) and possibly more durable CCyRs[2]. Deeper molecular responses, e.g., MR4, MR4.5, or undetectable levels of BCR-ABL do not appear to further improve survival[3].

2.2 Overview of the disease

CML has an incidence of 1-2 cases per 100,000 people and accounts for 15% of leukemias in adults. The median age at presentation is 45-55 years, and most cases (85%) are diagnosed in CP. Untreated, CML-CP progresses to the accelerated and blastic phases (AP and BP) within 3-5 years[4]. The diagnostic and pathogenetic hallmark of CML is the Philadelphia chromosome (Ph, present in 95% of patients), a shortened chromosome 22 resulting from the t(9;22)(q34;q11) translocation, the molecular consequence of which is the creation of the BCR-ABL fusion protein, a constitutively active cytoplasmic tyrosine kinase (TK). Nearly all patients with typical CML-CP express a 210-kd-BCR-ABL protein[5].

CML-BP is defined by the presence of ≥30% leukemic cells in peripheral blood or marrow or the presence of extramedullary infiltrates of blast cells, apart from in the spleen[4]. In one-third of cases, the blasts have a lymphoid morphology, express lymphoid markers and respond to acute lymphoblastic leukemia (ALL)-like regimens, and in the remaining two-thirds of cases, express myeloid markers; the latter comprise a heterogeneous group. Criteria derived from multivariate analyses to define CML-AP include 15-29% circulating or marrow blasts, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30%[1], peripheral basophilia (≥20%), thrombocytopenia unrelated to therapy (<100,000/μL) and cytogenetic clonal evolution[4].

BCR-ABL signaling is causative in CML, activating numerous downstream signaling pathways, e.g., JAK-STAT, Ras/Raf/MAPK, JUN, MYC and PI3K/Akt, among others[4, 5]. Disease progression in CML and transformation to BP are accompanied by increased BCR-ABL levels, differentiation arrest, genomic instability, inhibition of DNA repair, inactivation of tumor suppressor genes and acquisition of additional chromosomal abnormalities, e.g., +8, i(17q) and duplicate Ph[6].

2.3 First and second generation tyrosine kinase inhibitor (TKI) therapy of CML

The development of small molecule inhibitors of the oncogenic kinase activity of BCR-ABL has revolutionized the treatment of CML[7], so much so that the rate of OS in newly diagnosed patients in CP in all age groups in the TKI era is only slightly lower than, and that in patients who achieve CCyR or better within 1 year of treatment is similar to that of the general population[8]. In marked contrast, however, median survival after diagnosis of CML-BP currently ranges between 7 and 11 months, compared with 3-4 months in the pre-TKI era[9].

Imatinib

Imatinib was the first small molecule BCR-ABL TKI to be widely used, being approved by the FDA for the treatment of CML in 2001. In addition to ABL and BCR-ABL, it also inhibits c-kit and platelet derived growth factor receptor (PDGFR) TKs[10]. In a large phase II study in late CP patients who had failed interferon alfa (IFN-α), it induced MCyRs in 60% and CHRs in 95%; 89% had not progressed and 95% were alive after a median follow-up of 18 months[11]. These promising findings led to the landmark International Randomized Study of Interferon (plus cytarabine) vs. STI571 (IRIS), a phase III, open-label trial in previously untreated CML-CP patients. The 6-year update of IRIS reported a cumulative best CCyR rate of 82%, an estimated EFS at 6 years of 83%, and an estimated rate of freedom from progression (FFP) to AP/BP of 93%. The estimated OS rate was 88% (95% when considering only CML-related deaths)[12].

In a phase II study in patients with CML-AP, imatinib led to sustained hematologic responses in 69% (34% CHRs) and MCyRs in 24% (17% CCyRs), with estimated 12-month progression-free survival (PFS) and OS rates of 59% and 74%, respectively[13]. Among patients with CML in myeloid BP, imatinib induced sustained hematologic responses (8% CHRs) in 31%, with a median duration of response (DOR) of 10 months, and MCyRs in 16% (7% CCyRs)[14]. Finally, in a smaller phase II trial in patients with relapsed/refractory Ph^+ ALL or CML in lymphoid BP, imatinib induced sustained CHRs and marrow CRs in 6%, with median estimated time to progression (TTP) and OS for the ALL patients being 2.2 and 4.9 months, respectively, while one of eight CML-BP patients had a sustained CHR[15].

Dasatinib

Dasatinib is a 2nd generation TKI with a two-log increased potency relative to imatinib against BCR-ABL that retains activity against many imatinib-resistant BCR-ABL mutants, but not T315I[16]. Additionally, dasatinib inhibits SRC-family kinases. It was approved by the FDA in 2006 for patients with CML or Ph^+ ALL resistant to or intolerant of prior therapy including imatinib, and in newly diagnosed CML-CP patients in 2010. In a large, phase 3 trial, 670 patients with CML-CP resistant/intolerant to imatinib were randomized to 4 different dose cohorts of dasatinib[17]. Estimated 6-year PFS and OS rates ranged from 40-51% and 70-77% across the 4 dose cohorts, respectively, and rates of survival without transformation ranged from 74-83%. MMR was achieved in 43% of patients in the approved 100 mg once daily cohort and 40% of the rest by 6 years[17]. Approval for newly diagnosed CML-CP patients was based on the DASISION trial, that compared dasatinib 100 mg/d to imatinib 400 mg/d[18]. At the final, 5-year analysis of this trial, the rates of CCyR (83% vs. 78%), MMR (76% vs. 64%), MR4.5 (42% vs. 33%) and transformation to AP/BP (4.6% vs. 7.3%) all significantly favored dasatinib, as did time to CCyR and MMR, although PFS and OS were not significantly different[19].

In a phase II trial in 174 imatinib resistant/intolerant patients with CML-AP receiving dasatinib 70 mg bid, CHRs were attained by 45%, and MCyRs and CCyRs by 39% and

32% of patients, respectively, at a median follow-up of 14.1 months. 12-month PFS and OS rates were 66% and 82%, respectively[20]. In another phase II trial in 157 CML-BP patients (109 myeloid, 48 lymphoid), major hematologic responses were achieved in 34% and 35% of myeloid and lymphoid BP patients, respectively, MCyRs in 33% and 52%, respectively, and CCyRs in 26% and 46%, respectively. Median PFS and OS were 6.7 and 3 months, and 11.8 and 5.3 months, respectively, in myeloid and lymphoid BP patients[21]. A phase III study in patients with imatinib-resistant/intolerant CML-BP that compared dasatinib 140 mg once daily to 70 mg bid found improved tolerability (with similar efficacy) for the once-daily regimen[22].

Nilotinib

Nilotinib is a 2nd generation, selective inhibitor of BCR-ABL which is significantly more potent than imatinib, and active against a number of imatinib-resistant Bcr-Abl mutants, with the exception of T315I[23]. It was initially FDA-approved in 2007 for the treatment of patients with CML-CP and –AP resistant to or intolerant of prior therapy including imatinib, and subsequently in 2010 for newly diagnosed patients with CML-CP. 48-month follow-up of a phase II study of nilotinib in CML-CP patients resistant to or intolerant of imatinib yielded a 59% MCyR rate with 45% CCyRs. The estimated rates of PFS and OS at 48 months were 57% and 78%, respectively[24]. The phase III ENESTnd trial compared nilotinib 300 or 400 mg bid to imatinib 400 mg/d and served as the basis for the approval of nilotinib for frontline use in CML-CP patients. After 1 and 2 years of treatment, nilotinib demonstrated significantly faster and higher rates of CCyR, MMR, MR4 and MR4.5, as well as significantly lower rates of progression to AP/BP and fewer CML-related deaths compared to imatinib[25, 26]. Estimated 3-year rates of EFS, PFS and OS were all higher for both nilotinib arms compared with imatinib[27]. Long-term (minimum 5 years) follow-up of this trial has continued to show significantly higher cumulative rates of MMR and MR4.5 in the nilotinib groups, as well as significantly fewer progressions to AP/BP[28].

Among 137 imatinib-resistant/intolerant patients with CML-AP, 31% attained CHR on nilotinib 400 mg bid, and 32% achieved MCyRs, with most being CCyRs. Responses were durable, with 66% of patients maintaining MCyR at 24 months. The estimated OS and PFS rates at 24 months were 70% and 33%, respectively[29]. Among 136 CML-BP patients (105 myeloid, 31 lymphoid), major hematologic responses were achieved in 60% and 59% of myeloid and lymphoid BP patients, respectively, MCyRs in 38% and 52%, respectively, and CCyRs in 30% and 32%, respectively. Median DOR (MCyR) and OS were 10.8 and 3.2 months, and 10.1 and 7.9 months, respectively, in myeloid and lymphoid BP patients[30].

Bosutinib

Bosutinib is a dual Src/Abl inhibitor that potently inhibits BCR-ABL TK activity in CML cells and blocks their proliferation, causing complete regression of tumor xenografts in nude mice upon once-daily administration[31]. It was approved by the FDA in 2012 for the treatment of patients with CML with resistance or intolerance to prior therapy. 2-year

(minimum) follow-up of a phase I/II trial of bosutinib as 2nd line therapy for 288 patients with imatinib-resistant/intolerant CML-CP showed 85% CHRs, 59% MCyRs and 35% MMRs. 2-year estimates of retaining response were >70%, and of PFS and OS were 81% and 91%, respectively[32]. Among 118 patients with CML-CP previously treated with imatinib followed by dasatinib and/or nilotinib in another phase I/II study, bosutinib produced/maintained MCyRs in 40% and CCyRs in 32% at 4 years of follow-up[33], while CHR was achieved/maintained in 73% at 2 years. At 2 years, estimated PFS was 73% and OS 83%[34]. Responses to bosutinib were seen across BCR-ABL mutants, with the exception of T315I[32, 34].

Bosutinib 500 mg/d was compared to imatinib 400 mg/d in 502 newly diagnosed CML-CP patients in the phase III BELA trial. The 12-month CCyR rate was not significantly different (70% for bosutinib vs. 68% for imatinib); however, the rate of MMR was significantly higher with bosutinib (41% vs. 27%). Both CCyR and MMR were reached significantly faster with bosutinib, and fewer patients had transformed to AP/BP (2% vs. 4%) or died (3 vs. 8) compared to imatinib[35]. Cumulative CCyR rates remained similar (79% vs. 80%) at the 24-month time point, while cumulative MMR rates were 59% for bosutinib and 49% for imatinib. No new disease progressions occurred between the 12- and 24-month analyses with bosutinib; 4 occurred with imatinib[36].

The safety of bosutinib has been assessed in both the frontline setting (BELA) and in the context of previous therapy. Among patients with 2nd line CML-CP (n=286), 3rd/4th line CML-CP (n=118) or advanced Ph+ leukemia (n=166) who received bosutinib for a median of 11.1 months, treatment-emergent adverse events (TEAEs) were primarily GI – diarrhea (74-86%), nausea (46-48%) and vomiting (37-43%). Diarrhea was grade 3 or 4 in 8%, and 6% required a dose reduction because of diarrhea. Grade 3/4 myelosuppression occurred in 41%, and was mostly manageable with treatment interruption (46%) or dose reduction (32%). ALT elevation occurred in 17% (grade 3/4 in 7%). Bosutinib re-challenge was successful in 74% of dose-interrupted patients[37]. In the BELA trial, the toxicity profiles of bosutinib and imatinib were distinct. Diarrhea (70% vs. 26%), vomiting (33% vs. 16%), ALT (33% vs. 9%) and AST (28% vs. 10%) elevations and pyrexia (19% vs. 12%) were significantly more common with bosutinib, while edema, musculoskeletal pain, increased CPK and neutropenia/leukopenia were significantly more common with imatinib[38].

2.4 Bcr-Abl kinase domain mutations and resistance to TKI therapy in CML

Mutations in the kinase domain (KD) of BCR-ABL are the most prevalent mechanism of acquired TKI resistance in patients with CML[39, 40], and their detection is strongly suggestive of the development of clinical resistance[41]. Amino acid substitutions at seven residues (M244V, G250E, Y253F/H, E255K/V, T315I, M351T, and F359V) account for 85% of all resistance-associated mutations, which are more common in patients with advanced phases of CML or Ph^+ ALL[40]. KD mutations are associated with a greater likelihood of progression to AP/BP and shorter survival, at least in imatinib-treated CML-CP patients[40, 42]. The T315I "gatekeeper" mutation[43] uniformly confers resistance to all first and second generation TKIs[44]. Although primary resistance to imatinib is very

uncommon[45], KD mutations are associated in 30% of cases[40] and the T315I mutation has been described at diagnosis of CML[46]. Mutations in the ATP-binding "P-loop" confer high level resistance to imatinib and a poor prognosis in imatinib-treated patients[40-42].

Both preclinical and clinical studies suggest that the spectra of mutations that confer resistance to imatinib, dasatinib and nilotinib are distinct, with cross-resistance being limited to T315I[44, 47, 48]. In one series, 43% of imatinib-treated patients had mutations predicting for reduced sensitivity to nilotinib/dasatinib at imatinib cessation or commencement of dasatinib/nilotinib, including 14% with T315I[48]. In another series, the prevalence of T315I at the start of 2nd line TKI therapy was 15%, and response rates to 2nd or 3rd line TKI were similar for patients with and without mutations, regardless of mutation site, except for T315I. In this cohort, 26% developed new KD mutations after 2nd or 3rd line TKI therapy, but only 4% developed T315I[49]. In general, analyses of the 2nd line nilotinib/dasatinib trials in CML-CP patients have shown that the Y253H, E255V/K, and F359V/C mutants may respond slightly less favorably to nilotinib[50], while high response rates and durable efficacy have been reported with dasatinib regardless of BCR-ABL mutation status, except T315I[51]. In these and other studies, the frequency of mutations among imatinib-resistant patients at initiation of nilotinib/dasatinib was 43-55%[40, 42, 50, 51]. Some studies have suggested reduced activity of dasatinib against the F317L and V299L mutants[48]. In the CA180-034 phase III trial that compared 4 doses/schedules of dasatinib in 670 imatinib resistant/intolerant CML-CP patients, the 3 mutations that persisted or developed in patients who discontinued dasatinib 100 mg/d due to loss of response were V299L, T315I and F317L[52].

Ponatinib is a rationally designed, multi-targeted TKI that potently inhibits the BCR-ABL T315I mutant, as well as retains activity against other mutants and wild type BCR-ABL (pan-BCR-ABL inhibitor)[53]. However, emergence of compound mutations in a BCR-ABL allele may confer ponatinib resistance[54]. 449 heavily pretreated patients with CML or Ph+ ALL with resistance or intolerance to dasatinib or nilotinib or who had the T315I mutation received ponatinib, initially at 45 mg/d in a phase II trial (PACE)[55]. Among 267 patients with CML-CP, 56%, 46% and 34% achieved MCyR, CCyR and MMR, respectively; rates were higher among those with the T315I mutation (70%, 66% and 56%, respectively). The estimated rate of a sustained (≥12 months) MCyR was 91%. Major hematologic response and MCyR rates among patients with CML-AP (n=83), CML-BP (n=62) and Ph+ ALL (n=32) were 55% and 39%, 31% and 23%, and 41% and 47%, respectively[55]. At a median follow-up of 27.9 months, 2-year rates of MCyR duration, estimated PFS and OS among CML-CP patients were 87%, 67% and 86%, respectively. For patients with CML-AP, CML-BP, and Ph^+ ALL, estimated OS and PFS at 2 years were 72% and 39%, 18% and 11%, and 18% and not available, respectively[56].

64% of patients in the PACE trial had ≥1 dose reduction within the first year to manage adverse events (AEs). Frequent (≥20%) TEAEs were thrombocytopenia (44%), abdominal pain (41%), rash (41%), constipation (37%), headache (37%), dry skin (35%), fatigue (29%), pyrexia (29%), nausea (28%), arthralgia (28%), hypertension (26%), neutropenia (25%), anemia (22%), myalgia (21%), diarrhea (21%), vomiting (21%), increased lipase (21%). The most common serious adverse events (SAEs) were

pneumonia (7%) and pancreatitis (6%). Arterial thrombotic events were observed in 19% (14% serious) patients and included 10% cardiovascular (7% serious), 7% cerebrovascular (5% serious) and 7% peripheral vascular (4% serious) events. Venous thromboembolic events were observed in 5% (3% serious) of patients[56]. Because of serious safety concerns, ponatinib is currently indicated for the treatment of patients with CML or Ph^+ ALL with T315I, and for those for whom no other TKI is indicated. The drug label carries a black box warning for arterial/venous thrombosis and occlusions (≥27%), heart failure (8%) and hepatotoxicity.

Omacetaxine mepesuccinate, a semi-synthetic derivative of homoharringtonine, is a protein synthesis inhibitor that is active in CML patients with the T315I mutation after TKI failure[57]. In a phase 2 trial, 77% of 62 CML-CP patients achieved CHR for a median of 9.1 months, and 23% MCyR (16% CCyR). Median PFS was 7.7 months. Grade 3/4 thrombocytopenia, neutropenia and anemia occurred in 76%, 44% and 39%, respectively[57]. The drug was approved by the FDA in 2012 for the treatment of patients with CML-CP or –AP after failure of or intolerance to ≥2 TKIs. In the phase II open-label registration trial, among 46 CML-CP patients who had all received imatinib + dasatinib and/or nilotinib, 67% achieved or maintained a hematologic response for a median of 7 months. 22% achieved MCyR (4% CCyRs) and median PFS was 7 months. Grade 3/4 thrombocytopenia, neutropenia and anemia occurred in 54%, 48% and 33%, respectively[58]. In the final analysis of this study, with 24 months of follow-up, the MCyR rate had come down to 18% with a median duration of 12.5 months; responses were maintained for at least a year in 3 of 14 responders, and median OS was 40.3 months[59]. MCyR was not achieved in AP patients, whose median OS was 14.3 months[59].

2.5 Rationale for alternating or concurrent therapy with axitinib and bosutinib

Options for the treatment of patients with CML bearing the T315I mutation remain unsatisfactory, given the high toxicity of ponatinib and the modest efficacy of omacetaxine. Additionally, omacetaxine is highly myelosupressive and requires twice daily administration by subcutaneous injection in a healthcare setting. The temporary withdrawal of ponatinib by the FDA in view of the high rate of vascular thrombotic/occlusive and other adverse events reported in the clinical trials of this agent have substantially reduced enthusiasm for its use. As noted above, outcomes for patients in CML-BP remain dismal[9]. Therapeutic options also remain limited for patients in CML-AP who exhibit resistance to TKI therapy, as well as for patients with CP disease who fail or are intolerant to ≥2 TKIs[60].

Axitinib is a potent and selective inhibitor of vascular endothelial growth factor receptors (VEGFRs) that is FDA-approved for the 2nd line therapy of advanced renal cell carcinoma at a dose of 5 mg bid. In a large, head-to-head phase III trial vs. sorafenib, it demonstrated a highly significant PFS benefit and was better tolerated, with diarrhea, hypertension and fatigue being the major AEs[61]. Very recently, axitinib has been found to be a selective and effective inhibitor of BCR-ABL T315I[62]. The T315I mutation shifts the conformational equilibrium of the kinase in favor of an active (DFG-in) A-loop conformation, which has more optimal binding interactions with axitinib. Furthermore, axitinib fills a different binding space than the 5 commercially available BCR-ABL TKIs.

Axitinib potently inhibited BCR-ABL T315I, at both biochemical and cellular levels (both in cell lines and in primary patient-derived cells), and treatment of a T315I-bearing CML patient with axitinib resulted in a rapid reduction of T315I-positive cells from the bone marrow. However, axitinib appears to be a selective gatekeeper-mutant inhibitor that is less active against BCR-ABL without T315I[62].

There has been considerable interest in using rational, noncross-resistant TKI combinations in the treatment of CML, particularly in advanced phases of the disease, given that the spectrum of resistance-conferring BCR-ABL KD mutations differs between individual TKIs, and because novel yet viable ones are unlikely to emerge (many mutations would not be viable due to kinase inactivation)[45]. Indeed, preclinical studies have demonstrated both the feasibility and high efficacy of TKI combinations[47, 63]. Finally, particularly in chronic phase disease, intermittent therapy with a potent TKI could be sufficient to induce apoptosis[64, 65].

In light of these considerations, we propose a clinical trial of axitinib and bosutinib in patients with CML in 2 cohorts: a phase II study in CP patients who have failed or are intolerant to ≥2 other TKIs employing the 2 drugs on an alternating schedule; and a phase I/II study in AP/BP patients of the 2 agents in combination. For BP patients, prior therapy will not be required, whereas AP patients must have failed or been intolerant to ≥1 TKI in order to be eligible. Apart from the mechanistic rationale discussed above, the combination of axitinib and bosutinib is a particularly appealing one because of their largely non-overlapping toxicity profiles, their excellent safety profiles when used alone, and because these 2 agents do not inhibit their own metabolism via CYP3A4[62].

2.6 MD Anderson Symptom inventory (MDASI)

Symptoms are subjective phenomena reported by patients that indicate a change in normal functioning, sensation, or appearance due to disease. Symptom burden is the combined impact of disease- and therapy-related symptoms on the ability of persons to function as they did prior to onset of their disease and/or therapy. The MDASI is a valid and reliable measure of symptom burden[66]. Recently a CML-specific version of the MDASI, the MDASI-CML, that assesses 7 CML-specific symptoms, i.e., diarrhea, swelling, rash/skin changes, muscle soreness/cramping, easy bruising/bleeding, malaise and headache, in addition to the 13 symptom items and 6 interference items of the core MDASI, has been validated[67]. Common symptoms of chronic myeloid leukemia (CML) and its treatment can significantly impair the daily functioning of patients. Symptoms such as fatigue, drowsiness, sleep disturbance, memory loss, nausea and vomiting, diarrhea, muscle cramps, skin changes, and headache add to the burden of CML[67]. Patients with serious illnesses often report that they would like to “return to a normal life”. Decreasing the symptom burden of CML and its treatments will allow patients to function as normally as possible. Currently, there is little research on symptoms and their impact on daily functioning experienced by patients with CML to direct interventions that may assist patients in returning to normal.

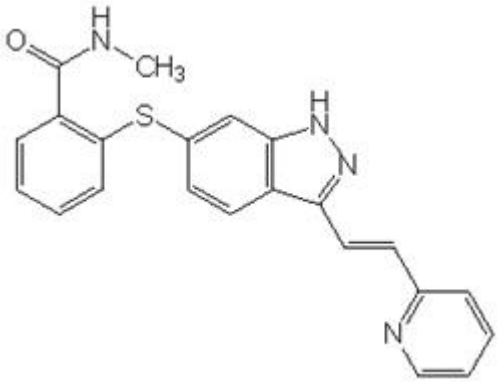
We have successfully developed IVR technology for the assessment of multiple symptoms using the MDASI in patients with cancer undergoing chemotherapy, radiation therapy, and surgery. We currently have one active study in a sample of patients with CML, many of whom are receiving kinase inhibitor therapies, using the MDASI-CML. Initial evaluation has shown this to be a feasible option for patient-reported symptom burden assessment in this group of patients and further evaluation is ongoing. The patient chooses the day and the time to receive the IVR system call; the system calls the patient three times if necessary to complete the assessment.

3.0 Background Drug Information

3.1 Axitinib (INLYTA®)

3.1.1 Product description

Axitinib is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. Axitinib has the chemical name N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide. The molecular formula is C22H18N4OS and the molecular weight is 386.47 Daltons. The chemical structure is:



Axitinib is a white to light-yellow powder with a pKa of 4.8. The solubility of axitinib in aqueous media over the range pH 1.1 to pH 7.8 is in excess of 0.2 µg/mL. The partition coefficient (n-octanol/water) is 3.5.

Axitinib is supplied as red, film-coated tablets containing either 1 mg or 5 mg of axitinib together with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and Opadry® II red 32K15441 as inactive ingredients. The Opadry II red 32K15441 film coating contains lactose monohydrate, HPMC 2910/Hypromellose 15cP, titanium dioxide, triacetin (glycerol triacetate), and red iron oxide.

3.1.2 Storage and handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

3.1.3 How supplied

Axitinib tablets are supplied as follows:

1 mg tablets are red film-coated, oval tablets debossed with "Pfizer" on one side and "1 XNB" on the other; available in bottles of 180: NDC 0069-0145-01.

5 mg tablets are red film-coated, triangular tablets debossed with "Pfizer" on one side and "5 XNB" on the other; available in bottles of 60: NDC 0069-0151-11.

3.1.4 Route of administration and pharmacokinetics

Oral.

Absorption and Distribution: Following single oral 5-mg dose administration, the median Tmax ranges from 2.5 to 4.1 hours. Based on the plasma half-life, steady state is expected within 2 to 3 days of dosing. Dosing of axitinib at 5 mg twice daily results in approximately 1.4-fold accumulation compared to administration of a single dose. At steady state, axitinib exhibits approximately linear pharmacokinetics within the 1-mg to 20-mg dose range. The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%.

Axitinib can be administered with or without food.

Axitinib is highly bound (>99%) to human plasma proteins with preferential binding to albumin and moderate binding to α1-acid glycoprotein.

Metabolism and Elimination: The plasma half-life of axitinib ranges from 2.5 to 6.1 hours. Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1 to carboxylic acid, N-glucuronide and sulfoxide metabolites. Unchanged axitinib is not detected in urine but is the major component identified in feces.

3.1.5 Availability

Axitinib tablets for this study will provided by Pfizer.

3.1.6 Agent Destruction and Return

Unused/expired drug will be disposed of onsite according to institutional guidelines.

3.1.7 Contraindications

None.

3.1.8 Drug Interactions

In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 Inhibitors

Co-administration of ketoconazole, a strong inhibitor of CYP3A4/5, increased the plasma exposure of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inhibitors should be avoided. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, the axitinib dose should be reduced.

CYP3A4/5 Inducers

Co-administration of rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

3.1.9 Warnings and Precautions

Hypertension and Hypertensive Crisis

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving axitinib and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving axitinib and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving axitinib and none of the patients receiving sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting axitinib. Hypertension was managed with standard antihypertensive therapy. Discontinuation of axitinib treatment due to hypertension occurred in 1/359 patients (<1%) receiving axitinib and none of the patients receiving sorafenib.

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the axitinib dose. Discontinue axitinib if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of axitinib, and discontinuation should be considered if there is evidence of hypertensive crisis. If axitinib is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Arterial Thromboembolic Events

In clinical trials, arterial thromboembolic events have been reported, including deaths. In a controlled clinical study with axitinib for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving axitinib and 4/355 patients (1%) receiving sorafenib. Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving axitinib and none of the patients receiving sorafenib.

In clinical trials with axitinib, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 17/715 patients (2%), with two deaths secondary to cerebrovascular accident.

Venous Thromboembolic Events

In clinical trials, venous thromboembolic events have been reported, including deaths. In a controlled clinical study with axitinib for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving axitinib and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving axitinib (including pulmonary embolism, deep vein thrombosis, retinal vein occlusion and retinal vein thrombosis) and 2/355 patients (1%) receiving sorafenib. Fatal pulmonary embolism was reported in 1/359 patients (<1%) receiving axitinib and none of the patients receiving sorafenib. In clinical trials with axitinib, venous thromboembolic events were reported in 22/715 patients (3%), with two deaths secondary to pulmonary embolism.

Hemorrhage

In a controlled clinical study with axitinib for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving axitinib and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 (1%) patients receiving axitinib (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 (3%) patients receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving axitinib (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

Cardiac Failure

In a controlled clinical study with axitinib for the treatment of patients with RCC, cardiac failure was reported in 6/359 patients (2%) receiving axitinib and 3/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving axitinib and 1/355 patients (<1%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (1%) receiving axitinib and 1/355 patients (<1%) receiving sorafenib. Monitor for signs or symptoms of cardiac failure throughout treatment with axitinib. Management of cardiac failure may require permanent discontinuation of axitinib.

Gastrointestinal Perforation and Fistula Formation

In a controlled clinical study with axitinib for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving axitinib and none of the patients receiving sorafenib. In clinical trials with axitinib, gastrointestinal perforation was reported in 5/715 patients (1%), including one death. In addition to cases of gastrointestinal perforation, fistulas were reported in 4/715 patients (1%).

Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment with axitinib.

Thyroid Dysfunction

In a controlled clinical study with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving axitinib and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving axitinib and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving axitinib and 25/232 patients (11%) receiving sorafenib.

Monitor thyroid function before initiation of, and periodically throughout, treatment with axitinib. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.

Wound Healing Complications

No formal studies of the effect of axitinib on wound healing have been conducted.

Stop treatment with axitinib at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible Posterior Leukoencephalopathy Syndrome

In a controlled clinical study with axitinib for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359

patients (<1%) receiving axitinib and none of the patients receiving sorafenib. There were two additional reports of RPLS in other clinical trials with axitinib.

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. Discontinue axitinib in patients developing RPLS. The safety of reinitiating axitinib therapy in patients previously experiencing RPLS is not known.

Proteinuria

In a controlled clinical study with axitinib for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%) receiving axitinib and 26/355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving axitinib and 6/355 patients (2%) receiving sorafenib.

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment.

Elevation of Liver Enzymes

In a controlled clinical study with axitinib for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the axitinib arm and 2% of patients on the sorafenib arm.

Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with axitinib.

Hepatic Impairment

The systemic exposure to axitinib was higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B). Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Pregnancy

Axitinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women using axitinib. In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose.

3.1.10 Adverse Events (using NCI CTCAE version 3.0)

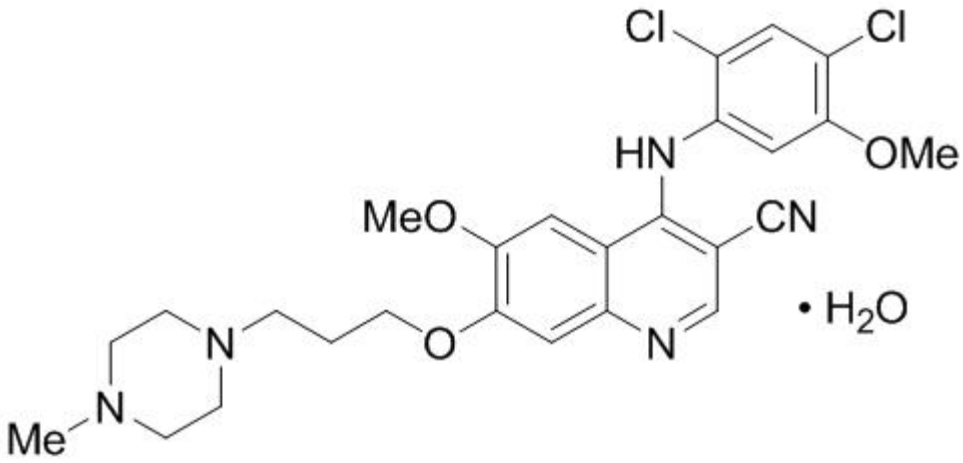
Adverse Reaction	Axitinib (N=359)		Sorafenib (N=355)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
Diarrhea	55	11	53	7
Hypertension	40	16	29	11
Fatigue	39	11	32	5
Decreased appetite	34	5	29	4
Nausea	32	3	22	1
Dysphonia	31	0	14	0
Palmar-plantar erythrodysesthesia syndrome	27	5	51	16
Weight decreased	25	2	21	1
Vomiting	24	3	17	1
Asthenia	21	5	14	3
Constipation	20	1	20	1
Hypothyroidism	19	<1	8	0
Cough	15	1	17	1
Mucosal inflammation	15	1	12	1
Arthralgia	15	2	11	1
Stomatitis	15	1	12	<1
Dyspnea	15	3	12	3
Abdominal pain	14	2	11	1
Headache	14	1	11	0
Pain in extremity	13	1	14	1
Rash	13	<1	32	4
Proteinuria	11	3	7	2
Dysgeusia	11	0	8	0
Dry skin	10	0	11	0
Dyspepsia	10	0	2	0
Pruritus	7	0	12	0
Alopecia	4	0	32	0
Erythema	2	0	10	<1

Laboratory Abnormality	Axitinib N	Axitinib All Grades %	Axitinib Grade 3/4 %	Sorafenib N	Sorafenib All Grades %	Sorafenib Grade 3/4 %
Hematology						
Hemoglobin decreased	320	35	<1	316	52	4
Lymphocytes (absolute) decreased	317	33	3	309	36	4
Platelets decreased	312	15	<1	310	14	0
White blood cells decreased	320	11	0	315	16	<1
Chemistry						
Creatinine increased	336	55	0	318	41	<1
Bicarbonate decreased	314	44	<1	291	43	0
Hypocalcemia	336	39	1	319	59	2
ALP increased	336	30	1	319	34	1
Hyperglycemia	336	28	2	319	23	2
Lipase increased	338	27	5	319	46	15
Amylase increased	338	25	2	319	33	2
ALT increased	331	22	<1	313	22	2
AST increased	331	20	<1	311	25	1
Hypernatremia	338	17	1	319	13	1
Hypoalbuminemia	337	15	<1	319	18	1
Hyperkalemia	333	15	3	314	10	3
Hypoglycemia	336	11	<1	319	8	<1
Hyponatremia	338	13	4	319	11	2
Hypophosphatemia	336	13	2	318	49	16

3.2 Bosutinib (BOSULIF®)

3.2.1 Product Description

Bosutinib is a kinase inhibitor indicated for the treatment of adult patients with CP, AP or BP Ph^+ CML with resistance or intolerance to prior therapy.. The chemical name for bosutinib monohydrate is 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate (1:1). Its chemical formula is C26H29Cl2N5O3·H2O (monohydrate); its molecular weight is 548.46 (monohydrate), equivalent to 530.46 (anhydrous). Bosutinib monohydrate has the following chemical structure:



Bosutinib monohydrate is a white to yellowish-tan powder. Bosutinib monohydrate has a pH dependent solubility across the physiological pH range. At or below pH 5, bosutinib monohydrate behaves as a highly soluble compound. Above pH 5, the solubility of bosutinib monohydrate reduces rapidly.

Bosutinib tablets are supplied for oral administration in two strengths: a 100 mg yellow, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "100" on the other; and a 500 mg red, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "500" on the other.

Each 100 mg bosutinib tablet contains 103.40 mg of bosutinib monohydrate, equivalent to 100 mg of bosutinib; each 500 mg bosutinib tablet contains 516.98 mg of bosutinib monohydrate, equivalent to 500 mg of bosutinib. The following inactive ingredients are included in the tablets: microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow (for 100 mg tablet) and iron oxide red (for 500 mg tablet).

3.2.2 Storage and handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

3.2.3 How supplied

Bosutinib tablets are supplied for oral administration in two strengths: a 100 mg yellow, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "100" on the other; and a 500 mg red, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "500" on the other.

3.2.4 Route of administration and pharmacokinetics

Oral.

Absorption

Following administration of a single dose of bosutinib 500 mg with food in patients with cancer, the median time-to-peak concentration (Tmax) was 4–6 hours. Bosutinib exhibits

dose proportional increases in AUC and Cmax, over the dose range of 200 to 800 mg. After 15 daily doses of bosutinib (500 mg) with food in patients with CML, the mean (SD) Cmax value was 200 (12) ng/mL, and the mean (SD) AUC was 3650 (425) ng·h/mL. When given with a high fat meal, the Cmax and AUC of bosutinib increased 1.8- and 1.7-fold, respectively.

Distribution

Bosutinib is highly bound to human plasma proteins *in vitro* (94%) and *ex vivo* in healthy subjects (96%), and binding was not concentration-dependent. Bosutinib is a P-gp substrate and inhibitor in vitro. No studies have been conducted with other transporters.

Metabolism

Bosutinib is primarily metabolized by CYP3A4 to oxydechlorinated (M2) and N-desmethylated (M5) bosutinib (major metabolites) and bosutinib N-oxide (M6) - minor metabolite. All the metabolites are inactive.

Elimination

In patients with CML given single oral doses of bosutinib 500 mg with food, the mean terminal phase elimination half-life (t1/2) was 22.5 (1.7) hours, and the mean (SD) clearance (Cl/F) was 189 (48) L/h. The vast majority is eliminated in the feces, and a very small amount in the urine.

Hepatic Impairment

In a dedicated hepatic impairment trial, a single dose of bosutinib 200 mg was administered with food to 18 volunteers with hepatic impairment (Child-Pugh classes A, B, and C) and 9 matched healthy volunteers. Cmax of bosutinib increased 2.4-fold, 2-fold, and 1.5-fold, respectively, in Child-Pugh classes A, B, and C, and bosutinib AUC increased 2.3-fold, 2-fold, and 1.9-fold, respectively.

Renal Impairment

In a dedicated renal impairment trial, a single dose of bosutinib 200 mg was administered with food to 26 subjects with mild (CLcr: 51 to 80 mL/min), moderate (CLcr: 30 to 50 mL/min) or severe renal impairment (CLcr less than 30 mL/min) and to 8 subjects with normal renal function. Creatinine Clearance for category classification was calculated by the Cockcroft-Gault formula. Subjects with moderate and severe renal impairment had a 35% and 60% increase in AUC compared to subjects with normal renal function, respectively. Bosutinib exposure was not changed in subjects with mild renal impairment. The bosutinib dose should be reduced in patients with severe (CLcr less than 30 mL/min) or moderate (CLcr between 30 to 50 mL/min) renal impairment.

3.2.5 Availability

Bosutinib tablets for this study will be provided by Pfizer.

3.2.6 Agent Destruction and Return

Unused/expired drug will be disposed of onsite according to institutional guidelines.

3.2.7 Contraindications

Hypersensitivity to bosutinib. In clinical trials, anaphylactic shock occurred in less than 0.2% of treated patients.

3.2.8 Drug Interactions

Drugs That May Increase Bosutinib Plasma Concentrations

CYP3A or P-glycoprotein (P-gp) 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. In a dedicated cross-over drug-interaction trial in healthy volunteers (N=24), concomitant ketoconazole (strong CYP3A inhibitor) increased bosutinib Cmax 5.2-fold and AUC 8.6-fold compared to bosutinib alone.

Drugs That May Decrease Bosutinib Plasma Concentrations

CYP3A Inducers: Avoid the concomitant use of strong or moderate CYP3A inducers with bosutinib as a large reduction in exposure is expected. In a dedicated cross-over drug-interaction trial in healthy volunteers (N=24), concomitant rifampin (strong CYP3A inducer) decreased bosutinib Cmax by 86% and AUC by 94% compared to bosutinib alone.

Proton Pump Inhibitors: In a dedicated cross-over drug-interaction trial in healthy volunteers (N=24), concomitant lansoprazole (PPI) decreased bosutinib Cmax by 46% and AUC by 26% compared to bosutinib alone.

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.

Drugs That May Have Their Plasma Concentrations Altered By Bosutinib

Substrates of P-glycoprotein: An *in vitro* study suggests that bosutinib may have the potential to increase the plasma concentrations of drugs that are P-gp substrates, such as digoxin.

3.2.9 Warnings and Precautions

Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, and abdominal pain occur with bosutinib treatment. Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and fluid replacement. In the single-arm Phase 1/2 clinical trial, the median time to onset for diarrhea (all grades) was 2 days and the median duration per event was 1 day. Among the

patients who experienced diarrhea, the median number of episodes of diarrhea per patient during treatment with bosutinib was 3 (range 1–221).

Myelosuppression

Thrombocytopenia, anemia and neutropenia occur with BOSULIF treatment. Perform complete blood counts weekly for the first month of therapy and then monthly thereafter, or as clinically indicated.

Hepatic Toxicity

One case consistent with drug induced liver injury (defined as concurrent elevations in ALT or AST greater than or equal to 3×ULN with total bilirubin greater than 2×ULN and alkaline phosphatase less than 2×ULN) occurred in a trial of bosutinib in combination with letrozole. The patient recovered fully following discontinuation of bosutinib. This case represented 1 out of 1209 patients in bosutinib clinical trials.

In the 546 patients from the safety population, the incidence of ALT elevation was 17% and AST elevation was 14%. Twenty percent of the patients experienced an increase in either ALT or AST. Most cases of transaminase elevations occurred early in treatment; of patients who experienced transaminase elevations of any grade, more than 80% experienced their first event within the first 3 months. The median time to onset of increased ALT and AST was 30 and 33 days, respectively, and the median duration for each was 21 days.

Perform hepatic enzyme tests monthly for the first three months of bosutinib treatment and as clinically indicated. In patients with transaminase elevations, monitor liver enzymes more frequently.

Fluid Retention

Fluid retention occurs with bosutinib and may manifest as pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema.

In the single-arm Phase 1/2 clinical trial in 546 patients with CML treated with prior therapy, severe fluid retention was reported in 14 patients (3%). Specifically, 9 patients had a Grade 3 or 4 pleural effusion, 3 patients experienced both Grade 3 or Grade 4 pleural and pericardial effusions, 1 patient experienced Grade 3 peripheral and pulmonary edema, and 1 patient had a Grade 3 edema.

Renal Toxicity

An on-treatment decline in estimated glomerular filtration rate (eGFR) has occurred in patients treated with bosutinib. Table 2 identifies the shift from baseline to lowest observed estimated glomerular filtration rate (eGFR) during bosutinib therapy for patients

in the global Ph^+ Leukemia studies. The median duration of therapy with bosutinib was approximately 17 months (range, 0.03 to 95) for patients in these studies.

Embryofetal Toxicity

There are no adequate and well controlled studies of bosutinib in pregnant women. Bosutinib can cause fetal harm when administered to a pregnant woman. Bosutinib caused embryofetal toxicities in rabbits at maternal exposures that were greater than the clinical exposure at the recommended bosutinib dose of 500 mg/day.

3.2.10 Adverse Events

	Chronic Phase CML N=406		**Advanced Phase CML N=140**	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Diarrhea	84	9	76	5
Nausea	46	1	47	2
Abdominal Pain	40	1	29	5
Thrombocytopenia	40	26	42	37
Vomiting	37	3	42	4
Rash	34	8	35	4
Fatigue	26	1	20	4
Anemia	23	9	37	26
Pyrexia	22	<1	36	3
Increased alanine aminotransferase	20	7	10	5
Headache	20	1	18	4
Cough	20	0	21	0
Increased aspartate aminotransferase	16	4	11	3
Neutropenia	16	11	19	18
Edema	14	<1	14	1
Arthralgia	14	<1	13	0
Decreased appetite	13	1	14	0
Respiratory tract infection	12	<1	10	0
Nasopharyngitis	12	0	5	0
Back pain	12	1	7	1
Asthenia	11	1	10	1
Pruritus	11	1	8	0
Dizziness	10	0	13	1
Dyspnea	10	1	19	6

Chronic Phase CML	Advanced Phase CML	All CP and AdvP CML
	N=406	N=140	N=546
	n (%)	n (%)	n (%)
Hematology Parameters			
Platelet Count (Low) less than 50×109/L	102 (25)	80 (57)	182 (33)
Absolute Neutrophil Count less than 1×109/L	74 (18)	52 (37)	126 (23)
Hemoglobin (Low) less than 80 g/L	53 (13)	49 (35)	102 (19)
Biochemistry Parameters			
SGPT/ALT greater than 5.0×ULN	39 (10)	8 (6)	47 (9)
SGOT/AST greater than 5.0×ULN	17 (4)	4 (3)	21 (4)
Lipase greater than 2×ULN	33 (8)	4 (3)	37 (7)
Phosphorus (Low) less than 0.6 mmol/L	30 (7)	10 (7)	40 (7)
Total Bilirubin greater than 3.0×ULN	3 (1)	2 (1)	5 (1)

4.0 Patient Eligibility

4.1 Inclusions:

4.1.1 Diagnosis of Ph^+ (by cytogenetics or FISH) or BCR-ABL^+ (by PCR) CML in CP (cohort 1), AP (cohort 2) or BP (cohort 2).

4.1.2 Patients should have failed (demonstrated resistance, intolerance or treatment discontinuation for any other reason of) at least 3 FDA-approved TKIs if in CP (cohort 1), or at least 1 FDA-approved TKI if in AP (cohort 2). Resistance will be defined as meeting the criteria for failure or warning by the European LeukemiaNet (ELN, Appendix)[1]. No prior therapy is necessary for patients in BP (cohort 2). Patients in CP who have failed <3 TKIs, but are ineligible to receive other FDA-approved TKIs, may also be enrolled in cohort 1. At least 10 CP patients with the T315I mutation affecting the kinase domain of Bcr-Abl will be enrolled in cohort 1, as well as in the phase II portion of cohort 2.

4.1.3 Age ≥18 years.

4.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

4.1.5 Adequate end organ function, defined as the following: total bilirubin ≤1.5 x ULN (unless due to Gilbert syndrome, in which case it should be ≤3.0 x ULN), ALT and AST ≤2.5 x ULN, serum creatinine ≤1.5 x ULN.

4.1.6 Patients must sign the IRB-approved informed consent document for this trial.

4.1.7 Reliable telephone access so as to be able to receive calls from an IVR system (only applicable to patients participating in the optional symptom burden assessment portion).

4.1.8 Women of childbearing potential (WOCBP) must practice 2 effective methods of birth control during the course of the study. Male patients who are partners of WOCBP should also practice an effective method of contraception. Effective methods of birth control

include diaphragm or condoms with spermicidal foam or jelly, birth control pills (BCPs), injections or patches, intra-uterine devices (IUDs) and surgical sterilization.

- Postmenopausal women must be amenorrheic for ≥12 months to be considered of non-childbearing potential.
- Women and men must continue birth control for the duration of the trial and ≥3 months after the last dose of study drug.
- All WOCBP MUST have a negative pregnancy test prior to first receiving study medication(s).

4.1.9 Patients should have discontinued therapy with imatinib, dasatinib, nilotinib, ponatinib, omacetaxine or other anti-leukemia therapy (except hydroxyurea) ≥48 hours prior to start of study therapy and recovered from any toxicity due to these therapies to grade ≤1. Hydroxyurea may be received up to the time of enrollment and for the first 6 weeks of study treatment if necessary.

4.2 Exclusions:

4.2.1 Prior therapy with axitinib. Prior therapy with bosutinib is allowed, except in the following circumstances:

4.2.1.1 the subject is currently on bosutinib
4.2.1.2 bosutinib is the subject's most recent TKI for CML
4.2.1.3 the subject has a history of intolerance to bosutinib.

4.2.2 Active gastrointestinal conditions that are expected to impair absorption of orally administered medications.

4.2.3 Patients who currently have or have a history of the following within 6 months preceding study entry are not eligible:

- Unstable angina (UA), myocardial infarction (MI), transient ischemic attack (TIA), stroke, deep vein thrombosis (DVT), acute peripheral or pulmonary arterial thromboembolism (PE).
- Clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, or *torsades de pointes*).
- New York Heart Association class III or IV heart failure.

4.2.4 Patients with active, uncontrolled psychiatric disorders including: psychosis, major depressive, and bipolar disorders.

4.2.5 Patients with uncontrolled hypertension (defined as sustained systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg).

4.2.6 Pregnant or breast-feeding women are excluded.

4.2.7 Inability to understand a written informed consent document.

4.2.8 Patients receiving anticoagulants that are unable to be discontinued.

4.2.9 Patients with active, uncontrolled infection.

4.2.10 Patients with a history of hypersensitivity to bosutinib or axitinib.

4.2.11 Patients on proton pump inhibitors, potent CYP3A or P-glycoprotein substrates, inhibitors or inducers – minimum 7 day period washout required unless discontinuation or substitution is not in the best interests of the patient as determined by the investigator. In instances where use of these agents is felt to be required for optimal management, inclusion of such patients should be discussed with the PI and the rationale documented. These patients, if enrolled on study, may require dose modifications for both axitinib and bosutinib (see further below in section 5.6).

The list of drugs that interact with cytochrome P450 enzymes can be found online at:
http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx

5.0 Treatment Plan

5.1 General

All patients should be registered with the Data Management Office PDMS/CORE system.

5.2 Treatment Plan

Patients will be enrolled in one of two cohorts. Patients in CP will be enrolled in cohort 1, and will receive axitinib and bosutinib in alternating, 3-month cycles. Those with BCR-ABL T315I or with a history of treatment with bosutinib will begin therapy with axitinib, whereas those without this KD mutation and no history of having received bosutinib will begin therapy with bosutinib. Patients in AP or BP will be enrolled in cohort 2. These patients will receive the 2 agents in combination in monthly cycles. As data are not available on the tolerability of axitinib and bosutinib in combination, cohort 2 patients will initially be dosed according to a "3+3" dose escalation schema (phase I portion) until a RPTD is identified. Once the RPTD is defined, all subsequent patients in cohort 2 will be treated at this dose (phase II portion).

5.2.1 **CML Debulking:** patients may receive hydroxyurea for debulking before and during the first 6 weeks of therapy.

5.2.2 **Therapy:** Patients in cohort 1 will receive axitinib and bosutinib at the FDA-approved doses of 5 mg bid and 500 mg/d, respectively, in alternating 3-month cycles. Patients in

cohort 2 will receive axitinib and bosutinib in combination according to the dose levels described below (phase I portion) continuously in monthly cycles. Once the RPTDs are determined, subsequent patients in cohort 2 (phase II portion) will be treated at these doses. If no MTD is defined up to the target doses (see below) of the two agents in combination, then the latter will constitute the RPTDs and the phase II portion of the study will begin at this dose. If the MTDs of the two agents in combination are exceeded at dose level 0, dose levels -1, -2 and -3 will be explored. Dose levels 3, 4 and 5 are provided only for the purposes of dose escalation, at the discretion of the principal or co-principal investigator, during the phase II portion of the study for cohort 2 patients in order to optimize anti-leukemic efficacy as long as there is no grade ≥3 toxicity (see section 5.3 (d), Dose escalations). Doses of axitinib and bosutinib may also be escalated at the discretion of the principal or co-principal investigator for optimization of anti-leukemic efficacy in appropriate cohort 1 patients as defined in section 5.3 (d).

Dose Level	**Axitinib (mg) orally twice daily**	**Bosutinib (mg) orally once daily**
-3	1	300
-2	2	300
-1	3	300
0 (starting dose)	3	400
1	5	400
2 (target dose)	5	500
3	7	500
4	7	600
5	10	600

5.2.3 Dose escalation schema and definition of dose limiting toxicity (DLT)

Definition of DLT (cohort 2, phase I portion) (in cohort 1 and phase 2 portion of cohort 2, this DLT definition will be used for purpose of toxicity monitoring per statistical section): DLT will be defined by adverse events occurring during the first cycle of therapy that are clinically significant and are not related to CML, concomitant medications or comorbidities.

Adverse events will be reported on a scale of 1-4 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Non-hematologic DLT is defined as any grade ≥3 toxicity that is clinically significant and not related to CML, concomitant medications or comorbidities, 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 electrolyte abnormalities will only be considered DLT if not corrected by optimal replacement therapy.
- Grade 3 ALT or AST abnormalities that resolve within 7 days.

Hematologic DLT is defined as follows:

- Grade ≥3 neutropenia and/or thrombocytopenia with a hypocellular bone marrow with <5% bone marrow blasts lasting for ≥6 weeks. Hypocellular bone marrow with <5% blasts needs to be confirmed with another bone marrow aspiration and/or biopsy within 7 -14 days (1-2 weeks) to be counted as DLT. Once one bone marrow study is obtained that meets this criterion, study drugs should be stopped and a repeat bone marrow aspiration and/or biopsy done within 7-14 days. If this bone marrow is confirmed hypocellular and with <5% blasts, a DLT is defined. The confirmation bone marrow aspiration and/or biopsy might occur after the 6 week timepoint. (In case of a normocellular bone marrow with <5% blasts, ≥8 weeks of grade ≥3 neutropenia and/or thrombocytopenia will be considered DLT). Anemia will not be considered for the definition of DLT.
- Cohort 1 (CP) (to be used for purpose of toxicity monitoring per statistical section): neutropenia and/or thrombocytopenia grade 4 lasting more than 7 days.

Definition of maximally tolerated dose (MTD): The MTD will be defined as the highest dose level at which ≤1 of 6 patients experience a first cycle (i.e., the first month) DLT. If no MTD is identified at dose level 2 (i.e., the target dose) , this dose will be explored further in the phase II portion of the study and no further dose escalation for the purpose of defining an MTD will be pursued.

Patients in cohort 2 will be enrolled on the phase I portion to the above dose levels (see 5.2.2) according to the following "3+3" schema. DLT is defined above. DLTs will be defined only during the first cycle (i.e., the first month) of therapy. Subjects will not be enrolled onto a higher dose level until all subjects in the current cohort have completed the first cycle of treatment.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level.

	If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.3 Dose Modifications:

Dose adjustments for toxicity for one or both drugs will be made, based on attribution, by dropping the daily dose to the next lower level (see below). For patients receiving combination therapy, the dose of only one drug may be adjusted when the adverse event is considered to be related to one of the study drugs. For example, GI toxicities (e.g., diarrhea), myelosuppression, hepatotoxicity, fluid retention and nephrotoxicity are more likely a result of bosutinib, while hypertension, vascular events, bleeding, CHF, GI perforation/fistula formation, thyroid dysfunction, wound healing complications, reversible posterior leucoencephalopathy and proteinuria are more likely to be a result of axitinib. In instances where it is considered appropriate to stop or delay therapy with one agent, administration of the other agent may continue as planned. *Doses may be re-escalated upon resolution of the toxicity to grade ≤1, but not above the starting dose for a given patient* except as specifically noted under "dose escalations".

Dose modifications for bosutinib and axitinib

Bosutinib dose	Axitinib dose
500 mg/d	**5 mg bid**
400 mg/d	**3 mg bid**
300 mg/d	**2 mg bid**
200 mg/d	**1 mg bid**

Dose reductions will be based on the nearest available strength of the pill. Dose escalations/reductions different from those described in this table (e.g., dose reductions by more than one dose level at a time) should be discussed with the PI or co-PI.

a) Non-Hematologic Toxicity

- **Grade 2:** Patients with persistent grade 2 toxicity that is considered clinically significant and unresponsive to appropriate therapy may have treatment held until the toxicity has resolved to grade ≤1. Study drug(s) may then be resumed at the same dose the patient was receiving at the time treatment was interrupted. If the grade 2 toxicity recurs, study drug(s) may be held until the toxicity has resolved

to grade ≤1. Treatment may then be resumed with a one dose level reduction.

- Patients with sustained grade 2 hypertension (systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg) unresponsive to optimal therapy may have treatment with axitinib held until hypertension resolved to grade ≤1. Axitinib may then be resumed at the same dose the patient was receiving at the time treatment was interrupted. If sustained grade 2 toxicity recurs, axitinib may be held until the toxicity has resolved to grade ≤1. Treatment may then be resumed with a 1 dose level reduction.

- **Grade 3-4**: If a patient experiences Grade 3-4 toxicity that is considered clinically significant and related to study drug(s), therapy must be withheld until the toxicity has resolved to Grade ≤ 1. Study drug(s) may then be resumed with a one dose level reduction. In the case of elevated liver transaminases not related to leukemia, concomitant medications or comorbidities, discontinue bosutinib if recovery takes longer than 4 weeks or if grade 4.

- Patients who develop confirmed myocardial infarction, stroke, TIA, peripheral arterial occlusive disease, pulmonary thromboembolism, reversible posterior leucoencephalopathy, GI perforation or fistula formation or become pregnant on study should have axitinib stopped and **should be removed** from the study.

- If transaminase elevations greater than or equal to 3×ULN occur concurrently with bilirubin elevations greater than 2×ULN and alkaline phosphatase less than 2×ULN, discontinue bosutinib and **remove** the patient from the study.

b) Hematologic Toxicity – cohort 1

If granulocytes are <1 x 10^9/L or platelets are <50 x 10^9/L, hold therapy until granulocytes ≥1 x 10^9/L and platelets ≥ 50 x 10^9/l, then resume therapy.

If recovery takes 2 weeks or more, resume study drug(s) 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 study drug(s) at the same dose the patient was receiving at the time treatment was interrupted. If myelosuppression recurs, resume study drug(s) 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.

Hematologic toxicity – cohort 2

Patients with neutropenia or thrombocytopenia as a consequence of the disease prior to the start of therapy do not require treatment interruptions for myelosuppression. Dose-reductions and treatment interruptions in these patients should be considered on a case by case basis and discussed with the PI or co-PI. No dose-reductions or

treatment interruptions for myelosuppression are planned during the first month of therapy for patients with CML-BP, or for thrombocytopenia for patients with CML-AP who are classified into CML-AP because of thrombocytopenia. The following guidelines can be used for these patients:

Patients with a MaHR and pre-cycle counts of ANC >1 x 10^9/L and platelets >50 x 10^9/L who have sustained low counts of ANC <0.5 x 10^9/L or platelets <25 x 10^9/L for ≥2 consecutive
weeks in the current cycle, with <5% blasts in the bone marrow, may receive a subsequent course at a one dose level reduction. A reduction of two dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.

If WBC >10 x 10^9/L and/or absolute blast count >2 x 10^9/L, may continue treatment regardless of neutrophil and platelet count and give transfusions and other support as needed.

If WBC is 5 to 10 x 10^9/L or absolute blast count 0.5 to 2 x 10^9/L and platelet count ≥20 x 10^9/L, may continue treatment at same doses unless drop in platelet count represents a decrease of ≥50%, in which case may decrease dose(s) by one level. If platelets <20 x 10^9/L and <50% drop from baseline, also may decrease dose(s) by one dose level.

If WBC is <5 x 10^9/L and absolute blast count <0.5 x 10^9/L and platelet count ≤20 x 10^9/L, may interrupt therapy until platelets ≥50 x 10^9/L. Then re-start therapy with a dose reduction of one dose-level. If WBC increases to >10 x 10^9/L or blasts to ≥5 x 10^9/L before platelets recover, may re-start therapy with a one dose level reduction.

c) Modifications of dose schedules other than the above will be allowed within the following guidelines:

- Further dose reductions can be made to keep toxicity grade ≤2. However, the lowest acceptable dose of axitinib is 1 mg bid and the lowest acceptable dose of bosutinib is 200 mg daily.

- Dose adjustments by more than 1 dose level at a time (e.g., from 5 mg bid to 2 mg bid for axitinib or from 500 mg/d to 300 mg/d for bosutinib) can be considered when judged to be in the best interests of the patient (e.g., neutropenia with sepsis, bleeding requiring platelet transfusions) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co PI and documented in the medical record.

- A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made by 1 dose level increments only, and not more frequently

than every month.

- The maximum allowable daily dose of axitinib is 10 mg bid, and that of bosutinib is 600 mg/d, to be possibly used in patients resistant to lower levels, as discussed above.

d) Dose escalations

Cohort 1 patients who tolerate axitinib for at least 1 month with no grade ≥3 adverse reactions attributable to axitinib (with the same exceptions as noted at the beginning of this section under definition of DLT), are normotensive, and are not receiving anti-hypertensive medications may have their doses escalated if required to optimize efficacy from 5 mg bid to 7 mg bid, and then from 7 mg bid to 10 mg bid at the discretion of the principal investigator or co-principal investigator.

Cohort 1 patients on 500 mg of bosutinib daily who do not reach CHR by 2 months or CCyR by 3 months and do not have grade ≥3 adverse reactions attributable to bosutinib (with the same exceptions as noted at the beginning of this section under definition of DLT) may have their dose escalated to 600 mg daily at the discretion of the principal investigator or co-principal investigator.

As the above dose escalations are within the range approved by the FDA and included in the prescribing information for each drug, and as cohort 1 patients will receive the drugs as single agents, no formal "3+3" dose escalation is necessary to determine safety.

For cohort 2 patients: If no significant anti-leukemic effect is observed after the first cycle of therapy and in the absence of grade ≥3 clinically significant non-hematologic toxicity that is related to the study drug(s), with the same exceptions as noted at the beginning of this section under definition of DLT, patients may be dose-escalated to the next dose level, provided the latter has already been deemed safe according to the phase I dose escalation rules. Dose levels 3, 4 and 5 are provided only for the purposes of dose escalation during the phase II portion of the study. As there is no precedent for using these two agents in combination, any dose escalation beyond the target doses of the study drugs (5 mg bid of axitinib and 500 mg/d of bosutinib) will be conducted only in the context of a rigorous "3+3" schema to assess safety and tolerability, following the same dose escalation rules as in the phase I portion. For the phase II portion of the study, if patients need to be escalated to dose levels 3, 4 or 5, if at any time ≥33% of patients experience DLT at a given dose level during the first cycle they receive at that dose, the dose level would be considered to have exceeded MTD and should not be used any further.

5.4 Missed Doses

Occasional missed doses will not be considered a deviation. Missed doses for ≥2 weeks with no proper justification will be considered a protocol deviation. Missed doses will not be made up.

5.5 Duration of Therapy

Study treatments will continue as long as patients continue to derive clinical benefit without unacceptable toxicity, and the study drugs are available from Pfizer. CP patients (cohort 1) who do not reach a CHR (unless there is evidence of improvement in cytogenetic or molecular response) by 3 months (1 cycle) will come off study due to lack of efficacy. Similarly, AP/BP patients (cohort 2) who exhibit no significant anti-leukemic effect (e.g., failure to decrease the WBC count by ≥50% if initial WBC >10 x 10^9/L, or failure to decrease peripheral blood blasts by ≥50% if initial WBC ≤10 x 10^9/L) after 6 cycles of therapy (unless there is evidence of improvement in cytogenetic or molecular response) will be taken off study.

5.5.1 Consider holding therapy if BCR-ABL is undetectable continuously for ≥2 years and patient is aware of the potential risks of treatment discontinuation.

5.5.2 A minimum of 2 full cycles will be required for a patient to be considered as having received an adequate trial of the study drugs to evaluate for efficacy unless they discontinue therapy because of progressive disease. Patients who fail to complete 2 full cycles of therapy will be replaced to reach the planned patient accrual. All patients receiving at least one dose of axitinib will be considered evaluable for toxicity. Patients achieving a PR or with SD may continue on therapy until definite evidence of disease progression.

5.6 Prohibited and Restricted Therapies During the Study

5.6.1 Prohibited Therapies

No other therapy for the treatment of CML, with the exception of anagrelide hydrochloride and/or hydroxyurea, will be permitted while the patient is on study. Hydroxyurea use should be limited to the first 6 weeks of therapy. Use of anagrelide, WBC colony-stimulating factors (e.g., G-CSF, GM-CSF, etc.), and TPO-mimetics (romiplostim, eltrombopag) and erythropoietin, is permitted at the discretion of the investigator.

Medications that prolong the QT interval should be avoided, but are not prohibited. If such medications are necessary, and used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

The list of drugs that can be associated with *torsades de pointes* or prolonged QT interval can be found online at:
http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm.

The concomitant use of proton pump inhibitors with bosutinib should be avoided whenever possible. Instead, the use of short-acting antacids or H2 blockers is recommended. Antacid or H2 blocker dosing should be separated from bosutinib dosing by ≥2 hours. There is no restriction for use of PPIs in cohort 1 while patients are on axitinib therapy.

5.6.2 Restricted Therapies

Ideally, subjects enrolled in this study should not be taking or begin taking medications known to prolong the QT interval. However, should the investigator believe that beginning therapy with a potentially QT prolonging medication (other than the ones explicitly prohibited) is vital to an individual subject's care, additional ECG(s) will be done as clinically indicated.

Similarly, subjects enrolled in this study should avoid, whenever possible, medications that are strong or moderate CYP3A inhibitors or inducers. However, should the investigator believe that beginning therapy with a strong or moderate CYP3A inhibitor is vital to an individual subject's care, the dose of axitinib is recommended to be reduced by one dose level. Such cases must be discussed with the PI or the co-PI.

6.0 Pretreatment Evaluation

6.1 A complete history and physical examination including blood pressure, performance status and concomitant medications within 2 weeks prior to start of study treatment.

6.2 CBC and differential (differential not required if WBC $<0.5 \times 10^9$/L), coagulation tests (PT, PTT, INR), serum sodium, potassium, bicarbonate, calcium, chloride, glucose, phosphate, total protein, serum albumin, total bilirubin, SGPT (ALT), SGOT (AST), alkaline phosphatase, amylase, lipase, LDH, BUN, creatinine and urinalysis within 1 week prior to start of study treatment.

6.3 Bone marrow aspirate for morphology and cytogenetics or FISH within 3 months of study enrollment for CP patients (cohort 1), 2 weeks for AP/BP patients (cohort 2).

6.4 EKG within 2 weeks and echocardiogram within 1 month prior to start of study treatment.

6.5 Pregnancy test (blood or urine) for female patients of childbearing potential within 7 days (1 week) prior to initiation of study treatment.

6.6 Peripheral blood or bone marrow for quantitative PCR (QPCR) for BCR-ABL and ABL sequencing within 1 month of study enrollment for CP patients (cohort 1), 2 weeks for AP/BP patients (cohort 2).

6.7 MDASI-CML and single item quality of life (QOL) rating completed by patient (optional*).

* Missed collection of an optional procedure will not be considered a protocol deviation or violation.

7.0 Evaluation During Study

7.1 For CP patients (cohort 1): Physical exam (including heart rate, respiratory rate, blood pressure and urinalysis with quantification of urinary protein) and evaluation of performance status, adverse events and concomitant medications (clinic visit or telephone interview) every 3 months (±1 month) for the first year, then every 6-12 months (±1 month). If the evaluation for toxicity is done by telephone, a report of the physical exam from the home physician is acceptable provided there is a physical exam at MDACC at least every 6 months (± 1 month) for the first year and every 12 months (± 1 month) thereafter. For AP/BP patients (cohort 2): every month (±1 week) for the first 3 months, then every 3 months (±1 month) until the end of the first year, then every 6 months (±1 month).

7.2 For CP patients (cohort 1): CBC and differential every 1-2 weeks for 1 month, then every 4-6 weeks until 1 year from the start of therapy, then every 3 months until 2 years (±1 month), then every 4 to 6 months thereafter (±1 month). For AP/BP patients (cohort 2): weekly for the first 3 months, then every 2-4 weeks for the next 3 months, then every 3 months until 2 years (±1 month), then every 4 to 6 months thereafter (±1 month). Differential not required if WBC $\leq 0.5 \times 10^9$/L.

7.3 For CP patients (cohort 1): Bone marrow aspirate with cytogenetics or FISH every 3 months in year 1 (±1 month), then every 4-6 months until 3 years, then as clinically indicated. For AP/BP patients (cohort 2): after 1 month (±1 week), then after 3 months (±2 weeks), then every 3 months (±1 month) until the end of the first year, then every 6 months (±1 month) until the end of the second year, then as clinically indicated.

7.4 For CP patients (cohort 1): Total bilirubin, total protein, serum albumin, SGPT (ALT) or SGOT (AST), alkaline phosphatase, amylase, lipase and serum sodium, potassium, bicarbonate, chloride, calcium, phosphate, glucose, LDH, BUN and creatinine every 2-4 weeks for 1 month, then every 4-6 weeks until 1 year from the start of therapy, then every 3 months until 2 years (±1 month), then every 4 to 6 months thereafter (±1 month). For AP/BP patients (cohort 2): every 1-2 weeks for the first 3 months, then every 4-6 weeks until 1 year from the start of therapy, then every 3 months until 2 years (±1 month), then every 4 to 6 months thereafter (±1 month).

7.5 Coagulation tests (PT, PTT, INR) to be conducted approximately every month for the first 3 months, then approximately every 3 months.

7.6 EKGs to be done approximately every 3 months until 1 year from the start of therapy.

7.7 Echocardiogram after approximately 3 months and 1 year from the start of therapy.

7.8 Peripheral blood or bone marrow for quantitative PCR (QPCR) every 3 months (± 1 month).

7.9 Abl sequencing after 3 months of therapy and at the end of study.

7.10 MDASI–CML weekly during the first 3 months of treatment, then every other week for the remainder of the study. MDASI-CML will be collected on paper, on the computer, or by the IVR system. Patients will be instructed during the first visit on the use of the Interactive Voice Response (IVR) system (optional*).

7.11 Single item QOL at each clinic visit during study (optional*).

* Every effort will be made to collect data on optional procedures at all time points for all patients; however, missing collection at one or more of these time points in occasional consenting patients will not be considered a protocol deviation/violation.

7.12 Standard tests such as CBC, blood chemistries, EKGs and echocardiograms may be done at outside facilities. Under exceptional circumstances other tests might be done at outside facilities after discussion with PI.

7.13 Patients that come off therapy will continue follow-up for toxicity (clinic visit or telephone interview) for 30 days (+/- 5 days) after end of therapy. At the end-of-study visit, patients will have a physical exam, including recording of vital signs, weight and assessment of performance status, a CBC, urinalysis and serum chemistries, PT/PTT/INR, adverse event evaluation, a bone marrow aspiration with cytogenetics or FISH, Q-PCR for BCR-ABL, Abl sequencing and all optional tests they may have consented for (MDASI-CML and/or other QOL assessments).

7.14 All study participants will be given study drug diaries to keep a log of each dose of study drug(s) taken, the time the dose was taken, and any missed doses along with the reason for missing the dose, as well as doses that may be vomited up.

Study calendar for cohort 1 patients (CML-CP) – 1 cycle = 3 months

	Pre-Study	M 3	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 33	M 36	Off Study (30±5 days after last dose)
Axitinib (A)/Bosutinib (B)		A	B	A	B	A	B	A	B	A	B	A	B	
Bosutinib (B)/Axitinib (A)		B	A	B	A	B	A	B	A	B	A	B	A	
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											X	
[c]Physical exam	X	X[d]	X[d]	X[d]	X[d]	Every 6-12 months (±1 month)								X
[c]Vital signs	X	X[d]	X[d]	X[d]	X[d]									X
Height	X													
[c]Weight	X	X[d]	X[d]	X[d]	X[d]	Every 4-6 months (±1 month)								X
[c]Performance status	X	X[d]	X[d]	X[d]	X[d]									X
CBC w/diff (diff not required if WBC <0.5 x 10^9/l)	X	q1-2 weeks for 1 month, then q4-6 weeks				X[d]	X[d]	X[d]	X[d]	q4-6 months (±1 month)				X
Serum chemistry[a]	X	q2-4 weeks for 1 month, then q4-6 weeks				X[d]	X[d]	X[d]	X[d]	q4-6 months (±1 month)				X
[c]Urinalysis	X	X[d]	X[d]	X[d]	X[d]	Every 4-6 months (±1 month)								X
PT, PTT, INR	X	X[f]	X[f]	X[f]	X[f]	Every 3 months (±1 month)								X
EKG	X	X	X	X	X									
Echocardiogram	X	X			X									
Bone marrow aspiration	X	X[d]	X[d]	X[d]	X[d]	Every 4-6 months until 3 years, then as clinically indicated								X
Q-PCR for BCR-ABL	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X
Adverse event evaluation		X----------											X	X
B-HCG	X[b]													
ABL sequencing	X	X												X
MDASI-CML and/or other QOL assessments[c]	X	MDASI-CML weekly during the first 3 months, then every other week; single-item QOL assessment at each clinic visit during study (both optional)												X

Axitinib (A): Dose as assigned; *orally twice daily.* Patients with the T315I mutation or with a history of prior bosutinib treatment will start with axitinib.
Bosutinib (B): Dose as assigned*; orally once daily.* Patients without the T315I mutation and no history of prior bosutinib treatment will start with bosutinib.
[a]Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase.
[b]Serum or urine pregnancy test (women of childbearing potential) within 7 days (1 week) prior to initiation of study treatment.
[c]Optional.
[d]±1 month.
[e]If the evaluation for toxicity is done by telephone, a report of the physical exam from the home physician is acceptable provided there is a physical exam at MDACC at least every 6 months (±1 month) for the first year and every 12 months (±1 month) thereafter.
[f]Every month (±1 week) for the first 3 months, then every 3 months (±1 month).
Patients who receive cycle 1 of study treatment at home will receive a phone call from the designated MDACC research nurse on day 14 (±5 days) of cycle 1 for assessment of toxicity.

Please see text (section 7) for details. Standard tests may be done at outside facilities.

Study calendar for cohort 2 patients (CML-AP/BP) – 1 cycle = 1 month

	Pre-Study	M 3	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 27	W 30	M 33	M 36	Off Study (30±5 days after last dose)
Axitinib (A)		A	A	A	A	A	A	A	A	A	A	A	A	
Bosutinib (B)		B	B	B	B	B	B	B	B	B	B	B	B	
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	q1 month (±1 week) for the first 3 months, then q3months (±1 month)					X^e		X^e		X^e		X^e	X
Vital signs	X													X
Weight	X						X^e		X^e		X^e		X^e	X
Performance status	X													X
Height	X													
CBC w/diff (diff not required if WBC <0.5 x 10^9/L)	X	Weekly for the first 3 months, then q2-4weeks		X^e	X^e	X^e	X^e	X^e	X^e	q4-6 months (±1 month)				X
Serum chemistry[a]	X	q1-2weeks for the first 3 months, then q4-6 weeks				X^e	X^e	X^e	X^e	q4-6 months (±1 month)				X
Urinalysis	X	q1month (±1 week) for the first 3 months, then q3months (±1 month)					X^e		X^e		X^e		X^e	X
PT, PTT, INR	X	q1month (±1 week) for the first 3 months, then q3months (±1 month)												X
EKG	X	X	X	X	X									
Echocardiogram	X	X			X									
Bone marrow aspiration[d]	X	X^f	X^e	X^e	X^e		X^e		X^e	As clinically indicated				X
Q-PCR for BCR-ABL	X	X^e	X^e	X^e	X^e	X^e	X^e	X^e	X^e	X^e	X^e	X^e	X^e	X
Adverse event evaluation		X----------X												X
B-HCG	X^b													
ABL sequencing	X	X												X
MDASI-CML and/or other QOL assessments[c]	X	MDASI-CML weekly during the first 3 months, then every other week; single-item QOL assessment at each clinic visit during study (both optional)												X

Axitinib (A): Dose as assigned; *orally twice daily.*
Bosutinib (B): Dose as assigned*; orally once daily.*
[a]Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase.
[b]Serum or urine pregnancy test (women of childbearing potential) within 7 days (1 week) prior to initiation of study treatment.
[c]Optional.
[d]Cohort 2 patients also need a bone marrow aspiration after 1 month (±1 week) of study treatment initiation.
[e]±1 month.
[f]±2 weeks.
Patients who receive cycle 1 of study treatment at home will receive a phone call from the designated MDACC research nurse on day 14 (±5 days) of cycle 1 for assessment of toxicity.

Please see text (section 7) for details. Standard tests may be done at outside facilities.

Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to participate in the patient's care.
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. All decisions regarding dose adjustments and treatment interruptions or re-initiation of treatment, grading and attribution of adverse events and assessment of efficacy will be done by MDACC investigators. The home physician will not make any decisions regarding dose adjustments and/or treatment interruptions or resumption of treatment, grading and/or attribution of adverse events, or assessment of efficacy. These will all be done by the MDACC investigators.
6. Only routine, standard-of-care laboratory assessments will be done by the home physician. All protocol-specific tests will be done at MDACC.
7. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
8. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies, and documentation of any hospitalizations.
9. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
10. Cohort 1 (CP) patients will return to MDACC every 3-6 months during the first year and every 4-6 months thereafter for evaluation. Cohort 2 (AP/BP) patients will return to MDACC for evaluation every cycle (1 month) for the first 3 months, then every 2-4 cycles for the first year, and every 6 (±1) cycles thereafter.
11. Patients who receive cycle 1 of study treatment at home will receive a phone call from the designated MDACC research nurse on day 14 (±5 days) of cycle 1 for assessment of toxicity.

8.0 Criteria for Response

8.1 Complete Hematologic Remission (CHR) – non-palpable spleen and normalization of the bone marrow (≤5% blasts) and peripheral blood with WBC <10 x 10^9/L and ANC ≥1 x 10^9/L, <5% basophils, no peripheral myeloblasts or promyelocytes, <5% myelocytes plus metamyelocytes, and platelet count 100-450 x 10^9/L. This is in addition to disappearance of all signs and symptoms of the disease.

8.2 Morphologic Leukemia-free state (MLFS) – All CHR criteria met except for ≥1 of the

following:
a. 20 x 10^9/L ≤ Platelets <100 x 10^9/L
b. 0.5 x 10^9/L ≤ ANC <1 x 10^9/L

8.3 **Partial Hematologic Response (PHR) -** CHR except for persistence of immature cells (myelocytes, metamyelocytes), or splenomegaly < 50% of pretreatment, or thrombocytosis >450 x 10^9/L but <50% of pretreatment.

8.4 **Minor Hematologic Response (MiHR)** - <15% bone marrow and peripheral blood blasts, <30% blasts + promyelocytes in bone marrow and peripheral blood, <20% peripheral blood basophils and no extra-medullary disease apart from hepatosplenomegaly.

8.5 **Major Hematologic Response (MaHR)** – Either CHR or MLFS qualifies as a MaHR. Thus, the sum of the CHR rate and the rate of MLFS is the MaHR rate.

8.6 A **confirmed** HR is obtained when all HR criteria are fulfilled at least 28 days after they are first met.

8.7 **Cytogenetic response** is classified according to suppression of the Philadelphia chromosome (Ph) by conventional karyotyping (FISH if cytogenetic analysis not informative, e.g., insufficient metaphases)

8.7.1 No cytogenetic response - Ph positive >95% of pretreatment value

8.7.2 Minimal cytogenetic response – Ph positive 66-95%

8.7.3 Minor cytogenetic response - Ph positive 36-95% of pretreatment value

8.7.4 Partial cytogenetic response - Ph positive 1-35% of pretreatment value

8.7.5 Complete cytogenetic response - Ph positive 0%

* Major cytogenetic response = complete + partial (Ph positive <35%)

8.8 Molecular Response

8.8.1 Major (MMR): BCR-ABL/ABL ratio ≤0.1% (IS). Currently, results from the MDACC laboratory can be converted to the IS by multiplying the BCR-ABL/ABL ratio by 0.35.

8.8.2 MR4: BCR-ABL/ABL ratio ≤0.01% (IS).

8.8.3 MR4.5: BCR-ABL/ABL ratio ≤0.0035% (IS)

8.8.4 CMR: Undetectable BCR-ABL.

9.0 Criteria for Removal from the Study

9.1 Patients with clinically significant progressive disease (excludes patients in CP who develop clonal evolution but no other criterion for progression to AP).

9.2 Poor compliance with study treatments or protocol-mandated study procedures.

9.3 Unacceptable severe (grade 3-4) toxicity despite dose optimization and optimal management of toxicity in the absence of significant anti-leukemic effect.

9.4 Patient request.

9.5 Lack of appreciable benefit in the presence of better therapeutic options in the opinion of the investigator.

10.0 Statistical Considerations

10.1 Sample Size and Estimation of Efficacy.

This is a 2-cohort study of axitinib and bosutinib in CML patients. Cohort 1 will enroll CP patients who will receive alternating axitinib and bosutinib. Cohort 2 will enroll patients in AP or BP who will receive the two drugs in combination. In cohort 2, it will be initially in a phase I dose-finding portion and then in the phase II portion once the RPTDs are determined.

A maximum of 52 patients will be enrolled in this study.

Cohort 1:
Cohort 1 will enroll CP patients who will receive alternating axitinib and bosutinib in 3 month rotation. A total of 20 patients will be enrolled, including at least 10 with the T315I mutation. The primary objective is to evaluate major cytogenetic response during the first 12 months of therapy. The target response rate is 20%. There is one prior study using bosutinib as third line treatment[34]. In that study, the rate of MCyR was reported as 32%[34]. The following considerations went into effect when choosing this rate as a signal to consider further studies of this combination in this setting:

1. The prior study[34] included 115 patients treated with two prior TKIs and only 3 patients who had received 3 prior TKIs. In our proposed study, patients are required to have received <u>at least</u> 3 prior TKIs, unless ineligible to receive other FDA-approved TKIs.
2. The MCyR rate of 32% in the prior study[34] represents a cumulative response reported after a median follow-up of 28.5 months. Our 20% goal is set at 12 months of therapy, reflecting both the more refractory nature of our patient population, and the shorter time requirement for response.

3. The design of the proposed study requires that at least 10 of the 20 patients in cohort 1 have the T315I mutation. Bosutinib alone has no *in vitro* or *in vivo* activity against this mutation.

The Bayesian approach of Thall, Simon, Estey[61] will be implemented for the futility monitoring. The following futility stopping rule will be applied in cohort size of 5, starting from the 10th patient: prob{p(RR)> 0.2) < 0.08, where p(RR) denotes the response rate. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 8% chance that the OR is more than 20%. Assuming that the prior distribution of p(RR) is beta (0.4, 1.6), the stopping boundaries corresponding to this futility monitoring rule are shown below in Table 10.1. The operating characteristics (OCs) for this futility stopping rule are summarized in Table 10.2. Futility summaries in cohorts of five for cohort 1 will be submitted to the medical monitor at the IND office.

Table 10.1. Futility stopping boundaries for cohort 1, in cohort size of 5.

Number of patients	Stop the trial if there are this many or fewer patients achieving RR
10	0
15	1

Table 10.2. Operating characteristics for the monitoring of response rate in cohort 1.

True RR Rate	Early Stopping Probability	Average number of patients treated
0.1	0.58	15.4
0.2	0.2	18.5
0.25	0.1	19.2
0.3	0.05	19.6
0.4	0.01	19.9
0.5	0.001	20.0

Cohort 2:

Cohort 2 will enroll patients in AP or BP who will receive the two drugs in combination, initially in a phase I dose-finding portion and then in the phase II portion once the RPTDs are determined.

Phase I

First, phase I study is performed to assess the safety of different dosing regimens. Three combination dose levels (dose level 0, 1, 2) are defined. A 3+3 design will be used to for

dose escalation. Detailed dose escalation rules are described in the following section. A maximum of 18 patients will enroll in the phase I study.

Dose Escalation Procedures

The dose of treatment agent will be escalated in successive cohorts of patients.

Patients will be entered sequentially to each dose level. 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.

A cohort summary will be submitted to the medical monitor at the IND office before moving to the next dose level for the phase I portion of Cohort 2.

Phase II

A total of 20 patients will be enrolled in phase II of cohort 2, including at least 10 with the T315I mutation. The 6 patient in the phase I of MTD will be included in phase II part. The primary objective is to evaluate hematologic response during the first 3 cycles (1 month per cycle) of therapy. The target response rate is 30%. The Bayesian approach of Thall, Simon, Estey[61] will be implemented for the futility monitoring. The following futility stopping rule will be applied in cohort size of 5, starting from the 10th patient: prob{p(RR)> 0.3) < 0.08, where p(RR) denotes the response rate. That is, the trial will be stopped early due to futility, if during the study we determine that there is less than 8% chance that the OR is more than 30%. Assuming that the prior distribution of p(RR) is beta (0.6, 1.4), the stopping boundaries corresponding to this futility monitoring rule are shown below in Table 10.3. The operating characteristics (OCs) for this futility stopping rule are summarized in Table 10.4. Futility summaries in cohorts of five for cohort 2 will be submitted to the medical monitor at the IND office.

Table 10.3. Futility stopping boundaries for cohort 2, in cohort size of 5.

Number of patients	Stop the trial if there are this many or fewer patients achieving RR
10	1
15	2

Table 10.4. Operating characteristics for the monitoring of response rate in cohort 2.

True RR Rate	Early Stopping Probability	Average number of patients treated
0.1	0.74	12.1
0.2	0.47	15.7
0.3	0.19	18.3
0.4	0.06	19.5
0.5	0.01	19.9

10.2 Safety Monitoring.

The Bayesian approach of Thall, Simon, Estey[61] will be implemented for toxicity monitoring for patients enrolled in cohorts 1 and 2 separately, where toxicity is defined as any event meeting the definition of DLT as per section 5.2.3. The toxicity, denoted as TOX will be monitored by the Bayesian stopping boundaries calculated based on beta-binomial distributions. We assume as a priori, p(TOX) ~ beta (0.6, 1.4). The study will be stopped for toxicity if Pr(p(TOX)> 0.30 | data) >0.85. That is, we will stop the trial for new patient enrollment if at any time during the study we determine that there is more than 85% chance that the toxicity rate is more than 30%. The toxicity monitoring rule will be applied starting from the 5th patient, and then in cohort size of 5. The toxicity will be considered continuously throughout the study treatment duration. Stopping boundaries corresponding to this toxicity monitoring rule are shown in Table 10.5 below. The operating characteristics for toxicity monitoring are summarized in Table 10.6. Toxicity summaries will be submitted to the Medical Monitor at the IND office after 5, 10, and 15 participants for cohorts 1 and 2.

Table 10.5. Toxicity stopping boundaries in cohort size of 5 for patients enrolled in cohorts 1 or 2.

Number of patients	Stop the trial if there are this many or more patients having toxicity
5	3
10	5
15	7

Table 10.6. Operating characteristics for toxicity monitoring.

True Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.1	0.01	19.9
0.2	0.08	19.0
0.3	0.26	16.8
0.4	0.53	13.5
0.5	0.78	10.1

10.3 Data Analyses.

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The response rate will be estimated along with the 95% credible interval. For the time-to event variables, like duration of response, overall survival will be estimated by Kaplan-Meier estimates. 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 drug 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. Concomitant medications will be documented on the case report forms at baseline only. All other concomitant medications will be documented in the medical record.

10.4 Statistical Considerations for MDASI and QoL

Continuous variables (e.g., age, hematology values) will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. The t-tests and chi-square tests (or Fisher's exact tests when sample sizes for some categories are smaller than 5) will be used to evaluate the statistical significance levels of observed differences.

11.0 Reporting Requirements

These guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course of protocol defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably or definitely related to the study drugs(s).
    b. All serious adverse events regardless of attribution to the study drug(s).
    c. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g., marrow hypocellularity on day 42 or later (6 weeks) from

start of therapy without evidence of leukemia (<5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.

5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemic-specific adverse event recording and reporting guidelines.

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

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 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).

- **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:

These reports will also be submitted to Pfizer safety (fax number 1-866-997-8322).

Reporting of External SAEs

- The MDACC institutional policy for reporting of external SAEs will be followed.

12.0 Confidentiality Plan

All data will be entered in PDMS/CORE.

13.0 References

References

1. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884.

2. Cortes J and Kantarjian H. How I treat newly diagnosed chronic phase CML. Blood. 2012;120(7):1390-1397.

3. Falchi L, Kantarjian HM, Wang X, et al. Significance of deeper molecular responses in patients with chronic myeloid leukemia in early chronic phase treated with tyrosine kinase inhibitors. Am J Hematol. 2013;88(12):1024-1029.

4. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med. 1999;341(3):164-172.

5. Sawyers CL. Chronic myeloid leukemia. N Engl J Med. 1999;340(17):1330-1340.

6. Quintas-Cardama A and Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. Blood. 2009;113(8):1619-1630.

7. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. Blood. 2008;112(13):4808-4817.

8. Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. The Lancet Haematology. 2015;2:e186-e193.

9. Hehlmann R. How I treat CML blast crisis. Blood. 2012;120(4):737-747.

10. Schiffer CA. BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia. N Engl J Med. 2007;357(3):258-265.

11. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med. 2002;346(9):645-652.

12. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia. 2009;23(6):1054-1061.

13. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood. 2002;99(6):1928-1937.

14. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood. 2002;99(10):3530-3539.

15. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood. 2002;100(6):1965-1971.

16. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004;305(5682):399-401.

17. Shah NP, Guilhot F, Cortes JE, et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood. 2014;123(15):2317-2324.

18. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-2270.

19. Cortes JE, Saglio G, Baccarani M, et al. Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056). Blood. 2014;124(21):152-152.

20. Apperley JF, Cortes JE, Kim DW, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. J Clin Oncol. 2009;27(21):3472-3479.

21. Cortes J, Kim DW, Raffoux E, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. Leukemia. 2008;22(12):2176-2183.

22. Saglio G, Hochhaus A, Goh YT, et al. Dasatinib in imatinib-resistant or imatinib-intolerant chronic myeloid leukemia in blast phase after 2 years of follow-up in a phase 3 study: efficacy and tolerability of 140 milligrams once daily and 70 milligrams twice daily. Cancer. 2010;116(16):3852-3861.

23. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell. 2005;7(2):129-141.

24. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. Leukemia. 2013;27(1):107-112.

25. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251-2259.

26. Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011;12(9):841-851.

27. Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia. 2012;26(10):2197-2203.

28. Larson RA, Kim D, Issaragrisil S, et al. Efficacy and Safety of Nilotinib (NIL) vs Imatinib (IM) in Patients (pts) With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Long-Term Follow-Up (f/u) of ENESTnd. Blood. 2014;124(21):4541-4541.

29. le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. Leukemia. 2012;26(6):1189-1194.

30. Giles FJ, Kantarjian HM, le Coutre PD, et al. Nilotinib is effective in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blastic phase. Leukemia. 2012;26(5):959-962.

31. Golas JM, Arndt K, Etienne C, et al. SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, is a potent antiproliferative agent against chronic myelogenous leukemia cells in culture and causes regression of K562 xenografts in nude mice. Cancer Res. 2003;63(2):375-381.

32. Gambacorti-Passerini C, Brummendorf TH, Kim DW, et al. Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: Minimum 24-month follow-up. Am J Hematol. 2014;89(7):732-742.

33. Gambacorti-Passerini C, Khoury HJ, Kantarjian HM, et al. Bosutinib As Third-Line Therapy in Patients (Pts) with Chronic Phase Chronic Myeloid Leukemia (CP CML) Following Failure with Imatinib Plus Dasatinib and/or Nilotinib: 48-Month Update of a Phase 1/2 Study. Blood. 2014;124(21):4559-4559.

34. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012;119(15):3403-3412.

35. Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol. 2012;30(28):3486-3492.

36. Brummendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. Br J Haematol. 2015;168(1):69-81.

37. Kantarjian HM, Cortes JE, Kim DW, et al. Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. Blood. 2014;123(9):1309-1318.

38. Gambacorti-Passerini C, Cortes JE, Lipton JH, et al. Safety of bosutinib versus imatinib in the phase 3 BELA trial in newly diagnosed chronic phase chronic myeloid leukemia. Am J Hematol. 2014;89(10):947-953.

39. Shah NP, Nicoll JM, Nagar B, et al. Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell. 2002;2(2):117-125.

40. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. Clin Cancer Res. 2006;12(24):7374-7379.

41. Branford S, Rudzki Z, Walsh S, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood. 2003;102(1):276-283.

42. Soverini S, Martinelli G, Rosti G, et al. ABL mutations in late chronic phase chronic myeloid leukemia patients with up-front cytogenetic resistance to imatinib are associated with a greater likelihood of progression to blast crisis and shorter survival: a study by the GIMEMA Working Party on Chronic Myeloid Leukemia. J Clin Oncol. 2005;23(18):4100-4109.

43. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science. 2001;293(5531):876-880.

44. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-471.

45. O'Hare T, Eide CA, Deininger MW. Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood. 2007;110(7):2242-2249.

46. Roche-Lestienne C, Lai JL, Darre S, Facon T, Preudhomme C. A mutation conferring resistance to imatinib at the time of diagnosis of chronic myelogenous leukemia. N Engl J Med. 2003;348(22):2265-2266.

47. Bradeen HA, Eide CA, O'Hare T, et al. Comparison of imatinib mesylate, dasatinib (BMS-354825), and nilotinib (AMN107) in an N-ethyl-N-nitrosourea (ENU)-based mutagenesis screen: high efficacy of drug combinations. Blood. 2006;108(7):2332-2338.

48. Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? Blood. 2009;114(27):5426-5435.

49. Cortes J, Jabbour E, Kantarjian H, et al. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. Blood. 2007;110(12):4005-4011.

50. Hughes T, Saglio G, Branford S, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J Clin Oncol. 2009;27(25):4204-4210.

51. Muller MC, Cortes JE, Kim DW, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood. 2009;114(24):4944-4953.

52. Shah NP, Rousselot P, Schiffer CA, et al. Seven-Year (yr) Follow-up of Patients (pts) with Imatinib-Resistant or -Intolerant Chronic-Phase Chronic Myeloid Leukemia (CML-CP) Receiving Dasatinib in Study CA180-034, Final Study Results. Blood. 2014;124(21):520-520.

53. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009;16(5):401-412.

54. Zabriskie MS, Eide CA, Tantravahi SK, et al. BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia. Cancer Cell. 2014;26(3):428-442.

55. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369(19):1783-1796.

56. Cortes JE, Kim D, Pinilla-Ibarz J, et al. Long-Term Follow-up of Ponatinib Efficacy and Safety in the Phase 2 PACE Trial. Blood. 2014;124(21):3135-3135.

57. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. Blood. 2012;120(13):2573-2580.

58. Cortes J, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. Am J Hematol. 2013;88(5):350-354.

59. Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: Results with 24 months of follow-up. Cancer. 2015.

60. Jabbour E and Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. Am J Hematol. 2014;89(5):547-556.

61. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931-1939.

62. Pemovska T, Johnson E, Kontro M, et al. Axitinib effectively inhibits BCR-ABL1(T315I) with a distinct binding conformation. Nature. 2015;519(7541):102-105.

63. O'Hare T, Walters DK, Stoffregen EP, et al. Combined Abl inhibitor therapy for minimizing drug resistance in chronic myeloid leukemia: Src/Abl inhibitors are compatible with imatinib. Clin Cancer Res. 2005;11(19 Pt 1):6987-6993.

64. Shah NP, Kasap C, Weier C, et al. Transient potent BCR-ABL inhibition is sufficient to commit chronic myeloid leukemia cells irreversibly to apoptosis. Cancer Cell. 2008;14(6):485-493.

65. O'Hare T, Eide CA, Agarwal A, et al. Threshold levels of ABL tyrosine kinase inhibitors retained in chronic myeloid leukemia cells determine their commitment to apoptosis. Cancer Res. 2013;73(11):3356-3370.

66. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-1646.

67. Williams LA, Garcia Gonzalez AG, Ault P, et al. Measuring the symptom burden associated with the treatment of chronic myeloid leukemia. Blood. 2013;122(5):641-647.