TABLE OF CONTENTS

1.0 Objectives

Primary:

- To estimate the proportion of patients with previously-untreated chronic phase CML attaining major molecular response by 12 months of treatment with dasatinib.

Secondary:

- To estimate the proportion of patients with Ph-positive early chronic phase CML achieving a complete cytogenetic response after dasatinib therapy.
- To evaluate the durations of hematologic, cytogenetic and molecular response to dasatinib.
- To define the time to progression and overall survival for patients with CML in early chronic phase treated with dasatinib.
- To evaluate the toxicity profile of dasatinib in patients with CML in early chronic phase.
- To evaluate the probability of developing ABL mutations for patients with CML in early chronic phase treated with dasatinib.
- To analyze differences in response rates and in prognosis within different risk groups and patient characteristics.
- To assess correlation between trough concentration and pleural effusion.
- To assess the inhibition of platelet function and assess correlation between drug concentration and degree of platelet inhibition.
- To assess the effect of dasatinib therapy in bone metabolism as determined by changes in serum alkaline phosphatase (bone specific isoenzyme), and trabecular bone volume.
- To evaluate symptom burden in patients with CML receiving dasatinib

Exploratory Objective:

- To investigate the plasma/serum levels of specific miRNAs in CML patients receiving dasatinib as initial therapy for CML in CP.

2.0 Background

2.1 Purpose

The basic hypothesis underlying our therapeutic programs in CML is to be able to achieve meaningful and long-lasting suppression of the Philadelphia chromosome and BCR-ABL. Complete cytogenetic responses and major or complete molecular responses have been associated with improved survival in CML.

2.2 Historical Experience

The prognosis of patients with chronic myelogenous leukemia is improving.[1] Historically, the median survival of untreated patients with CML was 19 months from diagnosis. In our historical experience of 303 patients with a diagnosis of Philadelphia-positive early chronic-phase CML referred to our institution within 3 months of diagnosis with minimal or no prior therapy, the overall median survival was 39 months.[2] Patients were divided into good, intermediate and poor risk groups with different hazard rates and median survivals.[2]

Symptoms are subjective phenomena reported by patients that indicate a change in normal functioning, sensation, or appearance due to disease[44]. 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 [45]. The MD Anderson Symptom Inventory (MDASI) is a valid and reliable measure of symptom burden[46]. Recently a CML-specific version of the MDASI, the MDASI-CML, has been validated. Common symptoms of chronic myeloid leukemia (CML) and its treatment can significantly impair the daily functioning of patients [47]. Symptoms such as fatigue, nausea and vomiting, diarrhea, muscle cramps, skin changes, and headache add to the burden of CML. Patients with serious illnesses often report that they would like to “return to a normal life”[48]. 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.

2.3 Interferon Therapy in CML

At M.D. Anderson Cancer Center, 80% of patients with early chronic phase Philadelphia chromosome (Ph)-positive CML treated with interferon alpha (IFN-α) alone or in combinations, achieved a complete hematologic response (CHR); 55% had a cytogenetic response, which was major and durable in 25%.[3-5] Achieving a complete cytogenetic response was associated with estimated 10-year survival rates above 70% to 80%.[6] In randomized studies and by meta-analysis, IFN-α was associated with significant survival prolongation compared with conventional chemotherapy.[7-10] Similar associations of achieving minimal tumor burden and survival prolongation have been reported by these studies. The addition of low-dose ara-C to IFN-α may have improved outcome.[11-13]

2.4 Imatinib Mesylate (STI571; Gleevec) in CML

Imatinib is an inhibitor of the protein-tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit. CML represents an ideal disease target for imatinib, given that the Bcr-Abl kinase plays a dominant role in the deregulated myeloid cell proliferation which is the hallmark of this disease.

Imatinib shows selectivity for the Abl protein tyrosine kinase at the *in vitro*, cellular and *in vivo* level.[14] The compound specifically inhibits proliferation of Bcr-Abl expressing cells. In colony forming assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of Bcr-Abl positive colonies from CML patients.[14-16] In animal models, the compound shows potent anti-tumor activity against Bcr-Abl and v-Abl expressing cells at tolerated doses.

In phase I studies, imatinib has demonstrated activity in all CML phases post IFN-α failure and in Ph-positive ALL.[17,18]

Three large-scale pivotal trials of imatinib in CML chronic, accelerated and blastic phases have been completed.[19-22] In chronic phase CML, 454 evaluable patients who had failed IFN-α therapy were treated with imatinib 400 mg orally daily. The CHR rate was above 90%. The complete cytogenetic response rate (Ph-positive less than 35%) was 60%, including a complete response in 41%. Imatinib was well-tolerated. Side effects included nausea, vomiting, diarrhea, skin rashes, muscle cramps, bone and joint aches, and liver dysfunction. Grade 3-4 toxicities requiring discontinuation of therapy occurred in 2% or less of patients. Periorbital

and leg edema and fluid retention were frequent at imatinib doses of 600 to 1000 mg orally daily.

An open-label, multicenter, randomized phase III study (International Randomized Interferon vs. STI571 [IRIS]) has been conducted in patients with newly diagnosed Ph+ CML.[23] This study compared treatment with either single-agent Imatinib or a combination of IFN plus cytarabine (Ara-C), and allowed for crossover for lack of response, loss of response or toxicity. A total of 1106 patients have been randomized from 177 centers in 16 countries, 553 to each arm. The major cytogenetic response rate for patients treated with Imatinib was 83% (68% complete) compared to 20% with IFN and ara-C (7% complete). With the follow-up currently available, the 4-year estimated rate of free of progression was over 90% with imatinib.[24] High-dose imatinib 400 mg orally BID has improved the early incidences of complete cytogenetic and molecular remissions. Its impact on long-term prognosis remains to be determined.[25,26] This study also demonstrated the significance of achieving a molecular response. Evaluating the response at 12 months from the start of therapy, patients that had achieved a complete cytogenetic response and at least a 3-log reduction in transcript levels compared to a standardized baseline value had a 98% probability of progression-free survival at 42 months, compared to 90% those with complete cytogenetic response but less than a 3-log reduction in transcript levels. The corresponding figure for patients without a complete cytogenetic response was 75%.[24,27] Thus, in the modern era, achieving a major molecular response at 12 months of therapy has become an important goal of therapy. With standard therapy with imatinib, only 20% to 35% of patients achieve a major molecular response by 12 months and it would be advantageous to have as many patients as possible reach this goal at least by 12 months.

2.5 DASATINIB

Dasatinib is a potent inhibitor of the BCR-ABL, c-KIT, and SRC family of kinases. Pre-clinical data suggests that dasatinib is 100-300-fold more potent inhibitor of BCR-ABL kinase activity than imatinib. In addition, it inhibits the phosphorylation of BCR-ABL carrying most of the mutations clinically relevant in CML patients who have failed imatinib, and inhibits the proliferation of cells transfected with these mutated variants of BCR-ABL.[28] Dasatinib has been investigated in phase I studies on patients with CML who were resistant, refractory or intolerant to imatinib. As of September 28, 2004, 58 patients have been treated. Both twice daily and once daily administration schedules have been investigated, revealing comparable dosing interval exposures. The maximum daily dose administered was 180 mg daily (this dose was only investigated as a single dose). A dose of 70 mg twice daily or 140 mg daily has been well tolerated in all stages of the disease and surpasses the dose at which most responses were observed. Overall, hematologic and non-hematologic toxicities have been tolerable and no MTD has been reached. Sustained hematologic responses have

been achieved in over 70% of patients, and cytogenetic responses in over 40% of patients.[29,30]

2.6 Proposed Therapy with Dasatinib

In this study we propose to treat patients with early chronic phase CML with dasatinib. Due to its higher in vitro potency, we hypothesize that dasatinib may be more effective than imatinib in achieving early (i.e., at 12 months) molecular responses in patients with early chronic phase CML.

The endpoints of therapy in early chronic phase will be to achieve a PCR ratio of $\leq$ 0.05%, which is the equivalent to a 3-log reduction based on our methodology. We will also evaluate the cumulative overall incidence of complete cytogenetic response. In early chronic phase CML, BCR-ABL/ABL ratios $\leq$0.05% after 12 months of therapy occur in 20% to 35% of patients. The goal of therapy would be to improve this to at least 50%. We will treat 100 patients in a randomized phase II study, and they will be divided into two arms treated with different dose schedules (same total dose). Based on the current accrual rate of 50 patients/year with a minimum follow up of 1 year, we estimate that the study could be completed in 3 years.

2.7 Other Biologic Endpoints

In addition to the endpoints mentioned above, we would like to investigate any predictors of response. For this purpose, we will collect cells from patients to be treated in this clinical trial and they will be directly exposed to dasatinib for short-term incubation (1-2 days) and markers of cell response will be assessed using a novel direct high-throughput quantitative real-time PCR assay, without further purification. Monitored will be transcript levels of a panel of apoptotic genes, the bcr-abl transcript as well as several transcriptional targets of bcr-abl activation. We will also use a quantitative multiplex assay for detecting levels of phosphorylated bcr-abl targets in clinical samples.

2.8 Update January 2019

Ninety-four patients remain on study for a median of 9 years (range 4-13). All patients have achieved a complete cytogenetic remission and 98% achieved a major molecular remission with 77% in complete molecular remission.

There are no emerging long term toxicities and all patients are on a stable dose of dasatinib.

The study primary objective has been met as have several of the secondary objectives. The focus is now on the secondary objectives of duration of cytogenetic and molecular remission and time to progression and survival.

This amendment reflects a change to the current standard for monitoring patients on tyrosine kinase inhibitor therapy in long term cytogenetic and molecular remission.

3.0 Background Drug Information

3.1 Overview

Dasatinib, at a dose of 70 mg orally twice a day, with continuous daily dosing, has activity, as defined by hematologic response, in all phases of CML refractory to imatinib.

Dasatinib is a potent, orally active inhibitor of the BCR-ABL, c-KIT, and SRC family of kinases, which play critical roles in oncogenesis and persistence of malignant phenotypes. In preclinical studies, dasatinib has been shown to be a more potent inhibitor of BCR-ABL and c-KIT than imatinib mesylate.[31] Dasatinib is also active in patient-derived CML cells that are resistant to imatinib mesylate, and an *in vivo* xenograft model of imatinib-resistant CML. A Phase I study (CA18002) was conducted to determine the safety profile, tolerability, and pharmacokinetics of dasatinib in subjects with CML who have primary or acquired hematologic resistance to or intolerance of imatinib mesylate. This study has provided preliminary evidence of efficacy of this compound as demonstrated by hematologic and cytogenetic responses and pharmacodynamic support of the mechanism of action. CA180013 was designed to further evaluate the anti-tumor activity and safety of dasatinib in subjects with imatinib-resistant, chronic phase Ph+CML.

3.2 Summary of Results of Investigational Program

Additional background information on preclinical pharmacology, toxicology and pharmacokinetics may be found in the Investigator Brochure.[32]

3.2.1 Preclinical Antitumor Activity

3.2.1.1 In Vitro Molecular Studies

Dasatinib competes with ATP for the ATP-binding site in the kinase domain of selected protein tyrosine kinases (PTKs) and has been shown to inhibit at least five protein tyrosine kinase/kinase families: SRC family kinases (IC_{50}: SRC = 0.55 nM, LCK = 1.1 nM, YES = 0.41 nM, FYN = 0.2 nM); BCR-ABL (3 nM); c-KIT (22 nM); EPHA2 (17 nM); and the PDGFβ receptor (28 nM). Dasatinib is much more

potent than imatinib mesylate against several important tyrosine kinsases, as outlined in the table below:

Comparative Potency of Dasatinib vs Imatinib Mesylate

Kinase	Fold more potent than Imatinib (based in IC_{50})
BCR-ABL	260
c-KIT	8
PDGFβ	60
SRC	> 1000

3.2.1.2 Cellular Studies

Dasatinib inhibits the BCR-ABL kinase with an *in vitro* IC_{50} of 3 nM, a potency that was 260-fold greater than that of imatinib mesylate (IC_{50} = 790 nM). In cellular assays, Dasatinib killed or inhibited the proliferation of all BCR-ABL dependent leukemic cell lines tested to date. Dasatinib also demonstrated undiminished antitumor activity against several preclinically- and clinically-derived models of imatinib mesylate resistance. In the K562/imatinib mesylate/R model (derived from continuous exposure of K562 cells to clinically achievable concentration of imatinib mesylate), imatinib mesylate was 6-fold less effective than in the parent K562 line (IC_{50} of 1288 nM and 217nM in the resistant and parental cell lines, respectively), while dasatinib remained approximately equally active against both cell lines (IC_{50} of 0.7 nM (vs. the parent line) and 1.03 nM (vs. the resistant line)). The mechanism by which K562/imatinib mesylate/R became resistant to imatinib mesylate is not fully understood, but molecular studies demonstrated that the resistant cells show 5 to 6 fold overexpression of the FYN tyrosine kinase, a member of the SRC kinase family. Direct sequencing of the ABL portion of BCR-ABL gene failed to reveal any mutations.

A second imatinib mesylate-resistant K562 subline (designated K562-R; IC_{50} > 10 μM)[33] independently established by investigators at M.D. Anderson Cancer Center from the sensitive parent line by continuous exposure of K562 cells to high concentrations of imatinib mesylate revealed overexpression of LYN, another member of the SRC family tyrosine kinases. Evidence that SRC family kinase overexpression may play a role in

clinical resistance to imatinib mesylate was demonstrated in three CML cell lines established from subjects who failed imatinib mesylate therapy. These cells remained highly sensitive to the cell-killing effects of dasatinib.[34] The table below shows the IC_{50} of dasatinib compared to the IC_{50} of imatinib mesylate in these three cell lines.

IC_{50} of Dasatinib and Imatinib Mesylate in three subject cell lines

Cell line	IC_{50} Dasatinib	IC_{50} Imatinib Mesylate
WDT-1	5 nM	> 10000 nM
WDT-2	0.02 nM	150 nM
WDT-3	0.05 nM	500 nM

These results demonstrate that dasatinib is effective in reducing the proliferation or survival of both imatinib mesylate-sensitive and resistant cells, and its inhibitory activity is not solely dependent on BCR-ABL.

3.2.1.3 In Vivo Studies

The activity of dasatinib against CML cells *in vitro* was reproduced *in vivo* against several human CML xenograft models grown subcutaneously (SC) in scid mice. Against K562 xenografts, dasatinib was curative over a 20-fold dose range (2.5 – 50 mpk) when it was administered orally (PO), once-a-day for 10 days (QD x 10), with a 2-day break following every 5 days of treatment (5-days-on, 2-days-of). Imatinib mesylate, administered on an optimized dosing regimen (three-times-a-day, every day for 10 consecutive days) failed to elicit significant cures at its maximum tolerated dose (MTD) of 150 mg/kg/administration, although it did not produce significant growth delay.

Against the K562/imatinib mesylate/R CML model that had acquired resistance to imatinib mesylate, dasatinib produced equally impressive activity similar to that seen in the K562 model. At doses of 50, 30, or 15 mg/kg/adm, using an identical treatment schedule as described above, dasatinib was curative in 100% of the treated animals. In contrast, at its optimal dose and schedule (150 mpk TID x 10 days), imatinib mesylate was inactive.

3.2.2 Preclinical Toxicology

Additional information related to the preclinical toxicology of

dasatinib is available in the Investigator's Brochure[32] and a BMS report [35].

Principal repeat-dose drug-related toxicities were manifested in the GI, hematopoietic (bone marrow), and lymphoid systems of rats and in the GI and lymphoid systems of monkeys. GI, bone marrow, and lymphoid toxicities were considered the major causes of morbidity and death in rats.

Systemic exposure to dasatinib increased with increasing dose; there was no apparent sex-related differences. For rats, systemic exposure (AUC) decreased with repeated administration ~12 to 47% at dasatinib doses of $\geq$ 79.2 mg/m^2. For monkeys, there were no apparent differences in systemic exposure with repeated dosing.

In an *in vitro* receptor and ion-channel ligand binding assay, dasatinib had no significant inhibitory effect on any of the 42 different receptors and ion channels investigated.

Safety pharmacology of dasatinib was evaluated by *in vitro* cardiovascular assays and *in vivo* single and repeat-dose toxicity studies. Dasatinib *in vitro* activity in the HERG/IKr and Purkinje-fiber assays indicated a moderate liability for prolongation of cardiac ventricular repolarization (QT interval) in the clinic. However, there were no dasatinib -related changes observed in electrocardiograms, nervous system function, respiratory and heart rate or sounds, blood pressure, or arterial oxygen saturation in single-dose, 10-day, or 1-month oral toxicity studies in monkeys.

Because dasatinib inhibits LCK, it could potentially cause immunosuppression by virtue of its effects on T-cell proliferation and activation. At doses that are efficacious in xenografts, dasatinib had no immunosuppressive effects in a preclinical model of solid organ transplantation that assesses graft rejection as the endpoint. By contrast, dasatinib suppressed T-cell proliferation or activation in mixed-lymphocyte reaction assays at doses that are efficacious in xenografts. However, the introduction of a 2-day drug holiday ameliorated this toxicity. [36]

Dasatinib was tested for effects on *in vitro* platelet function and found to inhibit platelet aggregation induced by ADP and collagen to a greater extent than what would be expected by single pathway inhibitors such as clopidogrel or aspirin. Further effects were an inhibition of shear-induced adhesion of human platelets and a reduction in clot strength. This profile of broad-spectrum platelet

inhibition is best typified by antiplatelet agents such as the GPIIb/IIIa antagonists, integrelin ad abciximab.

Finally, modulation of SRC kinase activity could also affect osteoclast morphology and function and bone remodeling. Dasatinib was shown to have a potent inhibitory activity in vitro in the rat fetal bone resorption assay with IC_{50} of 2.0 nM, and in vivo when administered subcutaneously in the acute thyro-parathyroidectomized rat model at 10 mg/kg. This effect could potentially result in an increase in bone mineral density and a phenotype analogous to osteopetrosis.[37]

In conclusion, single or repeated oral administration of dasatinib principally affected the GI (including hepatic), hematopoietic, and lymphoid systems in rats and monkeys. Other prominent effects after single oral administration of dasatinib included renal and cardiac toxicity in rats at lethal doses, and cutaneous hemorrhage in monkeys. Dasatinib can also effect the immune system and bone turnover. These nonclinical studies identified significant target-organ toxicities of dasatinib and established 180 mg/m^2 as the single-dose rate STD_{10} and 79.2 mg/m^2 as the 1-month repeat-dose rat STD_{10}. These results suggest that the repeat-dose toxicity of dasatinib is less than additive, which is consistent with the modest decrease in systemic exposure observed in the rat after repeated dosing. In monkeys, a single dose of 180 mg/m^2 (equivalent to the rat single dose STD_{10}) and a repeat dose of 60 mg/m^2 (approximately 75% of the rat repeat-dose STD_{10}) were generally well tolerated, providing a basis for the selection of the starting dose of dasatinib in CA180002, the first-in-human Phase I dose-escalation study.

3.2.3 Preclinical Pharmacokinetics

3.2.3.1 Absorption

The extent of oral absorption of dasatinib varied among species.[38] The oral bioavailability ranged from 15.2% in monkeys to 34% in dogs, with the average oral bioavailability in mice and in rats being 16 and 27%, respectively.

3.2.3.2 Distribution

Dasatinib is highly bound (>91%) to proteins in mouse, rat, dog, monkey, and human sera, and its blood to plasma concentration ration ranges from 1.1 in rat to 1.8 in human.[38] The average steady-state volume of distribution

of dasatinib in the mouse, rat, dog, and monkey is 4.2, 6.3, 4.7, and 3.5 L/kg, respectively. These values are greater than the total body water volume of each of these species, indicating extensive extravascular distribution across species.

3.2.3.3 Metabolism

The metabolic stability of dasatinib in mouse, rat, dog, monkey and human hepatocytes predicts a moderate clearance in all five species.

Incubations with recombinant human cytochrome P450 isozymes suggest that dasatinib is primarily metabolized by the CYP3A4 enzyme. Many other enzymes, however, appear capable of metabolizing dasatinib, including CYP1A1, 2C9, 2E1, FMO3, 1B1, 2B6, 2A6, 2C8, and 4A1. It is unknown at this time what contributions these enzymes may have to the total metabolic clearance of dasatinib.

The biotransformations of dasatinib in mouse, rat, dog, monkey, and human liver microsomes and hepatocytes are qualitatively similar. The major metabolites isolated from liver microsomal and hepatocyte incubations from human non-clinical donors consist of three hydroxylated isomers, a bis-oxygenated metabolite, an N-dealkylated metabolite, a carboxylic acid metabolite, and a dehydrogenation product. Two additional metabolites, a glucuronic acid conjugate, and a sulfate conjugate, were isolated from the plasma, urine or bile of bile-duct cannulated rats treated with the compound.

3.2.3.4 Elimination

Following an intravenous dose of 10 mg/kg of dasatinib to bile-duct cannulated rats, the percent of the dose excreted in the urine and bile at the end of 9 hours was 0.8 and 9.6%, respectively, implying that the major route of administration of dasatinib is by metabolism.[38]

3.2.3.5 Pharmacokinetic Drug Interactions

Caution is warranted when administering dasatinib to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic

index.[38] Systemic exposures to these medications could be increased while receiving dasatinib. In *in vitro* studies, dasatinib is a strong inhibitor of the human CYP3A4 (IC_{50} of 1.9 μM) and a weak inhibitor of CYP1A2 and CYP2D6 (IC_{50} of > 100 μM), CYP2C9 (IC_{50} of 63 μM) and CYP2C19 (IC_{50} of 32 μM). Until information regarding exposure-toxicity and exposure-response relationships are available with dasatinib, concomitant CYP3A4 inhibitors and inducers should be avoided, if possible, since they could alter the systemic exposure to dasatinib. Incubations with recombinant human cytochrome P450 isozymes suggest that dasatinib is primarily metabolized by the CYP3A4 enzyme.

3.2.4 Phase I Experience: CA180002

Also refer to recent publications[39,40,41,42] and the most current revision of the Investigator Brochure.[32]

The phase I dose escalation study was conducted in two major hematologic malignancy referral centers in the U.S. This study allowed inter- and intra-subject dose escalation. Pharmacokinetics (PK) were evaluated during the first month of treatment. The first patient was enrolled in November 2003. As of April 2005, 84 subjects have been enrolled: 40 in chronic phase CML, 10 in accelerated phase CML, 24 in myeloid blast phase CML, 5 in lymphoid blast phase CML and 5 in Ph+ ALL.

Chronic phase CML subjects were initially treated with a QD 5 days on/2 days off schedule and later the protocol was amended to include BID 5 days on/2 days off and BID continuous daily dosing (CDD) schedules. A total of 40 subjects have enrolled in doses ranging from 15 - 180 mg QD and 25 - 70 mg BID on the 5 days on/2 days off schedule and 70 - 90 mg BID on the CDD schedule. All 44 subjects with advanced phase disease were enrolled in dose cohort ranging 35 - 120 mg BID CDD.

Chronic Phase CML

Of the 40 chronic phase CML subjects, 53% were male and 47% were female. The median age was 61 years. The median duration of CML was 8 years (range 1-17). Eighty percent were clinically resistant to imatinib and 20% were intolerant. Intolerance included hepatotoxicity, rash or avascular necrosis that required discontinuation of imatinib. Most subjects had received > 600 mg/day of imatinib (65%). Only 38% previously had a major cytogenetic response to imatinib. Seventy-four percent were found

to have a mutation in the BCR-ABL protein that has been reported in the literature to confer resistance to imatinib. The median duration of follow-up on study for chronic phase CML subjects was 14 months. Of the 40 subjects in chronic phase 36 remain on study as of April 2005.

Safety

Hematologic adverse events are shown below. Myelosuppression and thrombocytopenia were common but reversible and easily managed with drug interruption.

Table 1: Hematologic Adverse Events			
	ANC	**Hemoglobin**	**Platelets**
Grade 3	23%	25%	18%
Grade 4	15%	8%	10%

Non-hematologic events included mild elevations in transaminases and creatinine that were asymptomatic, diarrhea, paresthesias and headache. One case of grade 3 pleural effusion was noted on the BID dosing schedule and was managed with thoracentesis and diuretics. The subject continues on study treatment. There were 2 episodes of grade 3 GI hemorrhage. There were no episodes of QTc prolongation over 500 msec and no reported cardiac symptoms related to prolonged QT intervals.

Table 2: Non-hematologic Adverse Events		
Adverse event	Grade 1–2 n (%)	Grade 3–4 n (%)
Elevated ALT	11 (28)	0 (0)
Elevated creatinine	9 (23)	1 (3)
Diarrhea	7 (18)	0 (0)
Paresthesia	4 (10)	0 (0)
Headache	4 (10)	0 (0)
Nausea	2 (5)	0 (0)
Peripheral edema	2 (5)	0 (0)
Pleural effusion	1 (3)	1 (3)
GI hemorrhage	0 (0)	2 (5)

Efficacy
Out of the 40 subjects, 39 had been followed for at least 3 months for the first bone marrow and cytogenetic evaluation on the protocol. The hematologic and cytogenetic response rates are shown below.

Table 3: Chronic Phase CML: Treatment Response		
	Number of patients (N=39)	
	Resistant (N=31)	Intolerant (N=8)
CHR – n (%)	26 (84)	8 (100)
CyR – n (%)		
Complete (CCyR)	9 (29)	4 (50)
Partial (PCyR)	2 (6)	1 (13)
Overall	16 (52)*	7 (88)

*Includes 2 patients with no previous cytogenetic response to imatinib

CHR = complete hematologic response; CyR = cytogenetic response

CCyR = 0% Ph+; PCyR = 1–35% Ph+; minor CyR = 35–65% Ph+

Overall CyR = CCyR + PCyR + minor CyR + minimal CyR

Complete hematologic responses were seen in 87% of the evaluable subjects. The overall cytogenetic response rate was 59%. Cytogenetic and hematologic responses were also examined in patients sub grouped according to mutational status, resistance versus intolerance and BID versus QD dosing. No differences in response were observed between the different dose regimens. However, hematologic and cytogenetic responses were higher in imatinib intolerant compared to imatinib resistant subjects.

Advanced Phase CML and Ph+ ALL
There were 10 accelerated phase CML, 29 blast phase CML and 5 Ph+ ALL subjects enrolled in CA180-002 as of April 2005. There were 59% male and 41% female. The median age for accelerated phase CML subjects was 64 and for blast phase CML/Ph+ ALL subjects it was 53. Median duration of CML for accelerated phase CML was 3 years and for blast phase CML/Ph+ ALL it was 3 years. Clinical resistance to imatinib was reported in 84% of subjects and

mutations in BCR-ABL that have been reported to confer resistance to imatinib were noted in 55% of subjects at study entry. Previous complete hematologic response with imatinib was noted in 70% patients entered. Twenty-five percent of subjects had grade 3-4 neutropenia before beginning dasatinib. The median duration of follow-up on study for advanced subjects was 5 months. Of the 44 subjects in advanced phase CML/ALL, 17 subjects remain on trial as of April 2005.

Safety

Grade 3-4 hematologic toxicity was common but could be managed with dose interruption and reduction.

Table 4: Advanced Phase CML/Ph+ ALL: Grade 3-4 Hematologic Adverse Events

	ANC	Hemoglobin	Platelets
Accelerated phase (N=10)	70%	80%	80%
Blast phase CML/ALL (N=34)	91%	74%	76%

Grade 3-4 non-hematologic adverse events included pleural effusions, pericardial effusions, diarrhea and rectal hemorrhage. Two subjects had grade 3-4 tumor lysis syndrome.

Table 5: Advance Phase CML/Ph+ ALL: Grade 3-4 Non-Hematologic Adverse Events

	Accelerated Phase CML	Blast Phase CML/Ph+ ALL
Pleural effusion	0%	12%
Pericardial effusion	0%	6%
Tumor lysis syndrome	0%	6%
Diarrhea	0%	3%
Rectal hemorrhage	0%	3%
Dyspnea	0%	3%
Pneumonia	10%	0%
Sinusitis	10%	0%
Elevated total bilirubin	0%	6%
Elevated creatinine	0%	3%

There were no QTc prolongation greater than 500 msec and no cardiac symptoms related to prolonged QT.

Efficacy

A major hematologic response was noted in 80% of accelerated phase and 69% of blast phase/ALL subjects. Overall cytogenetic response was 40% in accelerated phase and 56% in blast phase/ALL subjects.

Table 6: Advanced Phase CML/Ph+ ALL: Responses		
	Accelerated Phase CML	**Blast Phase CML/Ph+ ALL**
Major Hematologic Response	80%	69%
CHR	50%	28%
NEL	30%	41%
Overall CyR	40%	56%
CCyR	30%	19%
PCyR	10%	16%

Major HR is defined as bone marrow blasts <5%, and has two subgroups: CHR and NEL

CHR = complete hematologic response (<5% blasts in bone marrow and return of peripheral blood to normal parameters)

NEL = no evidence of leukemia (same as CHR, but without hematopoietic recovery of the peripheral blood parameters)

Dose schedule

Recently, a randomized trial comparing 4 different schedules of administration of dasatinib in patients with resistance or intolerance to imatinib has been completed and the results are being submitted for publication. Patients were randomized to receive 1 of 4 different dose schedules: 50 mg twice daily, 100 mg once daily, 70 mg twice daily (the standard dose at the time), or 140 mg once daily[43]. The results are summarized in the following table:

Table 7. Dasatinib dose optimization in patients with CML in CP after imatinib failure:

Parameter	Percentage				p value
	100mg QD N=166	50mg BID N=166	140mg QD N=163	70mg BID N=167	
MCyR	64	58	62	58	NS
CCyR	46	46	47	50	NS
Progression	10	13	14	18	0.032
Anemia	10	18	19	17	0.105
Neutropenia	34	46	43	43	0.123
Thrombocytopenia	22	34	40	38	0.003
Pleural effusion	10	16	20	18	NS
Interruption	58	66	69	71	0.047
Reduction	33	45	54	57	<0.001

Based on these results, the standard dose for patients with CML in CP after imatinib failure was changed by the FDA to 100mg once daily. In view of this we plan to close the 50mg twice daily dose arm and continue accrual only with the 100mg once daily arm.

3.3 INVESTIGATIONAL PRODUCT

Investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded.

3.3.1 Investigational Product Identification

The following investigational product, Dasatinib, will be supplied by Bristol-Myers Squibb Pharmaceutical Research Institute in two different strengths:

Dasatinib 20 mg film coated tablets, biconvex, round, white to off-white in appearance with “20” debossed on one side and “527” on the other side.
Dasatinib 50 mg film coated tablets, biconvex, oval, and white to off-white in appearance with “50” debossed on one side and “528” on the other side.

3.3.2 Packaging and Labeling

Dasatinib will be labeled in open-label fashion per site requirements.

BMS-354825 will be labeled in open-label fashion.

Study Drug	Packaging
BMS-354825-03	20 mg film coated tablets, 60 tabs/bottle
BMS-354825-03	50 mg film coated tablets, 60 tabs/bottle

3.3.3 Handling and Dispensing of Investigational Product

It is recommended that investigational product should only be handled by

the subject. While the risk for dermal exposure is considered minimal, it is recommended that only the study subject handle the study medication. In particular, pregnant women or women who are breastfeeding should **not** handle the study drug. Also children who are not study participants should not handle the drug. If caregivers must handle or come in contact with the drug, it is advised that protective gloves be worn.

Bristol-Myers Squibb will be responsible for assuring that the quality of Dasatinib is adequate for the duration of the trial.

Investigational product should be stored in a secure area, at 59°F to 77°F (15°C to 25°C).

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of each strength tablet to the subject to satisfy dosing requirements for the study. The containers provided to the subject should be labeled with proper instructions for use. Subjects should be instructed to return all unused drug to the site in the same container. Re-supplies can be obtained by completing the SRC re-supply request form and fax to 203-677-6489 or submit the electronic copy to srcsupply@bms.com. These re-supply requests need to be submitted at-least 2 weeks before the expected delivery date.

Drug re-supply will be provided at the Investigator's request at least two weeks before needed.

The subject must be instructed to return all unused study medications in the provided packaging at each subsequent visit. Returned drugs from patients will be destroyed at MD Anderson Cancer Center.

The Investigator must be satisfied the subject returned or accounted for all unused medication before additional medication is dispensed. If the number of tablets used is substantially different from the number of tablets dispensed, the subject must be counseled on how study therapy should be taken. If such deviations persist, the Investigator may consider discontinuing the subject for non-compliance.

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The Investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light and humidity) as determined by the Sponsor and defined in the Investigator

Brochure or SmPC/reference label.

3.3.4 Investigational Product Records at Investigational Sites

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Amount transferred to another area/site for dispensing or storage.
    - Label ID number or batch number and use date or expiry date
    - Dates and initials of person responsible for each investigational product inventory entry/movement
    - Amount dispensed to and returned by each subject, including unique subject identifiers
    - Non-study disposition (e.g., lost, wasted, broken)
    - Amount returned to Sponsor
    - Amount destroyed at study site, if applicable
    - Retain samples sent to third party for bioavailability/bioequivalence, if applicable

Investigational product dispensing record/inventory logs and copies of signed packing lists must be maintained at the investigational site. Batch numbers for dasatinib must be recorded in the drug accountability records.

3.3.5 Return and Destruction of Investigational Product

3.3.5.1 Return of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to BMS unless BMS specifically states (in writing) at that time the investigational product can be destroyed by MD Anderson Cancer Center.

All investigational products returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping

container. Returned supplies should be in the original containers. Empty containers should not be returned to BMS. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational products should be arranged by the responsible Investigator at the site.

3.3.5.2 Destruction of Investigational Product

If investigational product is to be destroyed on site, it is Investigators responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by BMS, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after appropriate instruction by BMS.

4.0 Patient Eligibility

4.1 Diagnosis of Ph-positive or Bcr-Abl positive CML in early chronic phase CML (i.e., time from diagnosis $\leq$ 12 months). Except for hydroxyurea, patients must have received no or minimal prior therapy, defined as <1 month (30 days) of prior IFN-α (with or without ara-C) and/or an FDA approved TKI.

4.1.1 Clonal evolution defined as the presence of additional chromosomal abnormalities other than the Ph chromosome has been historically been included as a criterion for accelerated phase. However, patients with clonal evolution as the only criterion of accelerated phase have a significantly better prognosis, and when present at diagnosis may not impact the prognosis at all. Thus, patients with clonal evolution and no other criteria for accelerated phase will be eligible for this study.

4.2 Age $\geq$16 years (Age > 18 years to participate in optional symptom burden assessment)

4.3 ECOG performance of 0-2.

4.4 Adequate end organ function, defined as the following: total bilirubin <1.5x ULN, SGPT <2.5x ULN, creatinine <1.5x ULN.

4.5 Patients must sign an informed consent indicating they are aware of the investigational nature of this study, in keeping with the policies of the hospital.

4.6 Reliable telephone access to receive calls from an interactive voice response system (IVR) (only applicable to patients who will participate in

optional symptom burden assessment).

4.7 Exclusions:

a. NYHA cardiac class 3-4 heart disease

b. Cardiac Symptoms: Patients meeting the following criteria are not eligible unless cleared by Cardiology:

- Uncontrolled angina within 3 months
- Diagnosed or suspected congenital long QT syndrome
- Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes).
- Prolonged QTc interval on pre-entry electrocardiogram (> 450 msec) on both the Fridericia and Bazett's correction.
- Uncontrolled hypertension.
- History of significant bleeding disorder unrelated to cancer, including:

  Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)

  Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies)
- Patients currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes including:

1. quinidine, procainamide, disopyramide
2. amiodarone, sotalol, ibutilide, dofetilide
3. erythromycins, clarithromycin
4. chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

c. Patients with active, uncontrolled psychiatric disorders including: psychosis, major depression, and bipolar disorders.

d. Women of pregnancy potential must practice 2 effective methods of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Postmenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Women must continue birth control for the

duration of the trial and at least 3 months after the last dose of study drug.

Pregnant or breast-feeding women are excluded.

All WOCBP MUST have a negative pregnancy test prior to first receiving investigational product. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study.

4.8 Patients in late chronic phase (i.e., time from diagnosis to treatment >12 months), accelerated or blast phase are excluded.

The definitions of CML phases are as follows:

a. Early chronic phase: time from diagnosis to therapy $\leq$ 12 months

   Late chronic phase: time from diagnosis to therapy > 12 months

b. Blastic phase: presence of 30% blasts or more in the peripheral blood or bone marrow.

c. Accelerated phase CML: presence of any of the following features:

   - Peripheral or marrow blasts 15% or more
   - Peripheral or marrow basophils 20% or more
   - Thrombocytopenia < 100 x 10^9/L unrelated to therapy
   - Documented extramedullary blastic disease outside liver or spleen

d. Clonal evolution defined as the presence of additional chromosomal abnormalities other than the Ph chromosome has been historically been included as a criterion for accelerated phase. However, patients with clonal evolution as the only criterion of accelerated phase have a significantly better prognosis, and when present at diagnosis may not impact the prognosis at all. Thus, patients with clonal evolution and no other criteria for accelerated phase will be eligible for this study.

5.0 Treatment Plan

5.1 General

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

5.2 Treatment Plan

Patients will receive dasatinib therapy according to the suggested

guidelines below. Individual minor variations in the initiation of therapy, WBC count at start of therapy, are acceptable as indicated by patient condition and physician judgment.

5.2.1 CML debulking: patients may receive hydroxyurea for debulking before and during the first 6 weeks of therapy. Patients who cannot take hydroxyurea may receive other agents such as 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG).

5.2.2 Therapy: Patients will receive dasatinib at a dose of 100 mg orally, once daily.

5.2.3 Dose adjustments: Dose adjustments will be allowed at the discretion of the treating physician.

Dose modifications will be made according to the Dasatinib package insert.

5.3 Dose modifications of Dasatinib

General guidelines include the following:

a) Non-Hematologic Toxicity

Recommended management of non-hematologic toxicity sis allowed per the discretion of the treating physician.

b) Hematologic Toxicity

Recommended management of hematologic toxicity is allowed per the discretion of the treating physician.

c) Modifications of dose schedules are allowed per the discretion of the treating physician.

5.3.1 Patients currently enrolled receiving BID schedule may be converted to a once daily schedule if it is considered in the best interest of the patient. Dose adjustments can be done according to the once daily schedule thereafter.

5.3.2 Dose Escalations

Dose escalations are allowed at the discretion of the treating physician for loss of or failure to achieve major molecular remission. Maximum dose is 100mg daily.

5.4 Occasional missed doses will not be considered a deviation. Missed dosed of ≥ 2 weeks will be considered a protocol deviation.

5.5 Duration of Therapy

Total duration of therapy will be 15 to 18 years. Subsequent changes of duration of treatment will depend on the earlier analyses of data. Consider holding therapy if BCR-ABL is undetectable continuously over 2 years.

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 for the treatment of elevated platelet counts (> 700,000/mm^3), and hydroxyurea for WBC greater than 50,000/mm^3, will be permitted while the patient is on study. The exception will be the use of agents for management of minimal residual disease on clinical trial such as Azacitidine (as per protocol 2011-0254) or Ruxolitinib (protocol 2012-0697) provided patients are experiencing no unacceptable toxicity with dasatinib and meet all eligibility criteria for these trials. These include adequate response to dasatinib, a minimum of 18 months on therapy with dasatinib, adequate organ function as defined in those studies, and a stable dose of dasatinib. Hydroxyurea use should be limited to approximately 4 weeks duration whenever possible. Use of anagrelide and hydroxyurea, as well as colony-stimulating factors (e.g., G-CSF, GM-CSF, etc) and erythropoietin, is permitted at the discretion of the investigator.

Medications associated with QT prolongation that are prohibited on this study include:

- quinidine, procainamide, disopyramide
- amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants. It is recommended that antiplatelet agents or anticoagulants are avoided in setting of Grade 3 or 4 thrombocytopenia.

Ideally, subjects enrolled in this study should not be taking and not 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, the Investigator must check that the subject's prior on-therapy ECG has not shown a QTcF $\geq$ 480 msec or an increase in QTc $\geq$ 60 msec over the baseline value. Additional ECG(s) will be done one week later or more at the Investigator's discretion to ensure the subject's safety.

5.6.2 Restricted Therapies

Caution is warranted when administering dasatinib to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. Systemic exposures to these medications could be increased while receiving dasatinib. In *in vitro* studies, dasatinib is a strong inhibitor of the human CYP3A4 enzyme and a weak inhibitor of CYP1A2, CYP2D6 and CYP2C19. dasatinib shows time-dependent inhibition of CYP3A4; however, there appears to be a low probability for drug-drug interactions due to metabolism-dependent CYP3A4 inactivation. Results from an *in vitro* hPXR trans-activation study suggest that dasatinib has little potential to induce CYP3A4 through the activation of hPXR.

Until information regarding exposure-toxicity and exposure-response relationships is available with dasatinib, concomitant CYP3A4 inhibitors and inducers should be avoided, if possible, since they could alter the systemic exposure to dasatinib. Incubations with recombinant human CYP450 isozymes suggest that dasatinib is primarily metabolized by the CYP3A4 enzyme. Many other enzymes appear capable of metabolizing dasatinib, including CYP1A1, 2C9, 2E1, FMO3, 1B1, 2B6, 2A6, 2C8, and 4A1; however, it is unknown at this time what contributions these enzymes may have to the total metabolic clearance of dasatinib.

In vitro solubility data indicate that dasatinib may have decreased solubility and absorption at pH > 4. Until further data are available, subjects should try to avoid taking proton pump inhibitors and H_2 antagonists. Short-acting antacid agents may be taken, but it is recommended that these not be taken from 4 hours before to 4 hours after dosing of dasatinib.

6.0 Pretreatment Evaluation

6.1 A complete history and physical examination including performance status.

6.2 CBC, platelet count and differential (differential not required if WBC < 0.5 x 10^9/L), total bilirubin, SGPT (or SGOT), HBV screening, and creatinine within 1 week.

6.3 Bone marrow aspirate for morphology and cytogenetics or FISH (if not done within 3 months).

6.4 EKG within 2 weeks

6.5 Pregnancy test (blood or urine) for female patients of childbearing potential within 7 days before initiation of study drug dosing

6.6 Peripheral blood and bone marrow for correlative studies (optional*). Not all optional samples may be collected.

6.7 Peripheral blood or bone marrow for quantitative PCR (QPCR)

6.8 Platelet aggregation study and PK (optional*)

6.9 miRNA analysis (optional): one single blood sample (5cc) will be collected only by EDTA or citrate (Dr. Calin's lab at MD Anderson Cancer Center).

6.10 Serum alkaline phosphatase (bone-specific isoenzyme) (optional*).

6.11 Bone marrow biopsy for trabecular bone volume (optional*). Will not be done if a repeat bone marrow is required for this purpose only.

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

* Missed collection of any of the optional procedures will not be considered a protocol deviation or violation.

7.0 Evaluation During Study

7.1 Physical exam and evaluation of toxicity (clinic visit or telephone interview) every 3 months (±1 month) for the first year then recommended every 6 to 12 months at the discretion of the treating physician.

7.2 CBC, platelet, differential every 1-2 weeks for 4 weeks, every 4-6 weeks until 1 year from the start of therapy, then every 3-4 months until 2 years, then at the discretion of the treating physician.

7.3 Bone marrow aspirate with cytogenetics or FISH every 3-4 months in year 1, then at the discretion of the treating physician.

7.4 Total bilirubin, SGPT or SGOT, and creatinine every 2-4 weeks for 1 month then every 4-6 weeks until 1 year from the start of therapy, then every 3-4 months until 2 years, then at the discretion of the treating physician.

7.5 EKGs to be done approximately every 3 months until month 12 from the start of therapy then at the discretion of the treating physician.

7.6 Adherence to the prescribed therapy will be verified by diary or verbally by patient interview (Appendix D)

7.7 Peripheral blood or bone marrow for quantitative PCR (QPCR) every 3-4 months for 1 year then every 6-12 months until 2 years on therapy then every year (+/- 3 months).

8.0 Criteria for Response

8.1 Complete Hematologic Remission (CHR) - normalization for at least 4 weeks of the bone marrow (less than 5% blasts) and peripheral blood with WBC < 10 x 10^9/L and no peripheral blasts, promyelocytes or myelocytes. This is in addition to disappearance of all signs and symptoms of the disease.

Partial Hematologic Response (PHR) = CHR except for persistence of immature cells (myelocytes, metamyelocytes), or splenomegaly < 50% of

pretreatment, or thrombocytosis >450x10^9/L but <50% of pretreatment.

8.2 Complete hematologic remission will further be classified according to suppression of the Philadelphia chromosome (Ph) by cytogenetics (FISH if cytogenetic analysis not informative, e.g., insufficient metaphases)

a) No cytogenetic response - Ph positive 100% of pretreatment value

b) Minor cytogenetic response - Ph positive 35-90% of pretreatment value

c) Partial cytogenetic response - Ph positive 1-34% of pretreatment value

d) Complete cytogenetic response - Ph positive 0%

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

8.3 Molecular response

a) Major (MMR): BCR-ABL/ABL ratio $\leq$ 0.05%

b) Complete: Undetectable BCR-ABL, confirmed by nested PCR

9.0 Criteria for Removal from the Study

9.1 Patients who develop accelerated disease features (except clonal evolution if it is the only criterion for accelerated phase) or blastic phase with no response to optimization of therapy as defined under 5.2 and 5.3.

9.2 Failure to achieve CHR after 3 months of therapy.

9.3 Unacceptable severe (grade 3-4) toxicity despite dose optimization

9.4 Patient request

9.5 Physician's decision when judged to be in the best interest of the patient

9.6 Other – recurrent and irremediable lack of adherence to treatment plan, recurrent and consistent protocol violations, etc.

10.0 Statistical Considerations

The new trial is a phase II study of BMS354825 to assess Time to first Molecular Response prior to 12 months (MMR) in patients with early phase chronic CML. Two endpoints will be monitored, the probability of MMR by 12 months, and the 12 month toxicity rate. The goal of this study is to determine if the compound has activity with respect to the MMR while maintaining an acceptable toxicity rate. MMR will be measured every 3 months (a total of 4 assessments within one year of therapy. Because of the discrete nature of the measurements, continuous time models would be inappropriate. As such we use an ordinal sequential model with discrete time hazards to define the likelihood.

$Y_{r,k}$ be an ordinal outcome associated with the kth treatment arm which can take on values 1,…, J and represents (for a given patient) either the visit at which MMR was first observed or the last follow-up visit (which ever is less). Let d_r be a censoring indicator

where d_r=0 means that the patient was not censored and d_r =0 indicates the patient was censored. Note that (ignoring censoring for the moment) the discrete time hazard for the jth interval is equal to

$$p_{r,j} = \Pr(Y_r = j \mid Y_r \geq j) = \frac{\Pr(Y_r = j)}{\Pr(Y_r \geq j)}$$

Moreover note that

$$1 - p_{r,j} = \frac{\Pr(Y_r \geq j) - \Pr(Y_r = j)}{\Pr(Y_r \geq j)} = \frac{\Pr(Y_r \geq j+1)}{\Pr(Y_r \geq j)}$$

The above identity allows us to exploit a recursive relationship between the hazard function during period *j* and the probability of response beyond period *j* via

$$(1 - p_{r,j}) \Pr(Y_r \geq j) = \Pr(Y_r \geq j+1)$$

Since Pr($Y_r \geq 1$)=1 we have that

$$\Pr(Y_r \geq 2) = 1 - p_{r,2}$$

$$\Pr(Y_r \geq 3) = (1 - p_{r,2}) \Pr(Y_r \geq 2)$$

$$\vdots$$

$$\Pr(Y_r \geq j) = (1 - p_{r,j-1}) \Pr(Y_r \geq j-1)$$

This allows us to express the contribution to the likelihood of an event that occurs in the jth interval as

$$\Pr(Y_r = j, d_r = 0) = p_{r,j} \prod_{h=1}^{j-1} (1 - p_{r,h})$$

The contribution to the likelihood for a censored observation (i.e., the discrete time survival function) having maximum followup in the jth interval is

$$\Pr(Y_r = j, d_r = 1) = \prod_{h=1}^{j-1} (1 - p_{r,h})$$

The likelihood for toxicity events can be constructed in a similar manner.

For the kth arm, we assume (a priori) that each $p_{r,j}$ (for *j*=1,…, 4) follows a beta(0.03,0.97) distribution and each $p_{t,j}$ (for *j*=1,…, 4) follows a beta(.5,.5) distribution. For purposes of trial monitoring we assume independence between toxicity and response.

Let the 12 month MMR response rate in the kth arm be $\pi_r = 1 - \prod_{h=1}^{4}(1 - p_{r,h})$ and denote the 12 month toxicity rate as $\pi_t = 1 - \prod_{h=1}^{4}(1 - p_{t,h})$.

While the trial is ongoing, the *k*th arm will be declared **unacceptable for completion** if

$$\Pr(\pi_r < 0.50 \mid data) > .975 \quad \text{or}$$

$$\Pr(\pi_t > 0.10 \mid data) > .90 \quad \text{or}$$

A maximum of n=75 patients will be treated per arm. The stopping rules for response will be applied 52 weeks after the first patient accrues to the study (and every 13 weeks thereafter) while the toxicity rules will be applied 13 weeks after the first patient accrues to the study (and every 13 weeks thereafter). An arm that is not declared unacceptable for completion will be completed. At the end of the trial we will calculate, for any completed arms

$$\Pr(\pi_{r,k} < 0.50 \mid data) > .975$$

The following Table shows the scenarios studied using the above design. In this simulation we assume that, on average between 2 or 3 patients accrue to the study every month. *Also recall that 33% of the patients have already accrued to the study. Thus, the simulation results presented below combine fixed observed data with future as yet unobserved data. Each virtual t*rial was simulated (1000 simulations per scenario), and the tables summarize the design's average behavior given the already accrued data.

Scenario	Toxicity Rate*	MMR*	Prob of Stopping Before 75 patients accrue to study	Expected Sample Size Enrolling to Study
Scenario 1	0.25	0.80	0.206	73.29
Scenario 2	0.05	0.30	0.454	70.11
Scenario 3	0.05	0.80	0.003	74.90
Scenario 4	0.25	0.30	0.555	69.50
*Rates for future patients (already accrued patients have already been observed)				

10.1 Updated Statistical Design

To date, 33 patients have been treated with the 50mg BID dose schedule, now discontinued, and 56 patients have been treated with the 100mg QD

dose schedule, for a total of 89. Under the current design, which has target total sample size 100, 11 additional patients would be treated using the 100mg QD schedule, giving a subtotal of 56+11 = 67. Under the proposed design with target total sample size 150, 61 additional patients would be treated using the 100mg QD schedule, giving a subtotal of 56+61 = 117. Assuming a non-informative beta(0.5, 0.5) prior on Pr(MMR12) = probability of major molecular response at 12 months, the trial's primary endpoint, and assuming that the currently observed rate of 76% for MMR12 persists, under the current design if 51/67 (76%) MMR12's were observed in the 100mg QD dose schedule patients then a posterior 95% credible for Pr(MMR12) would be [0.650 – 0.851] which has a width of 0.205. Under the proposed design with 50 more patients, if 89/117 (76%) MMR12's were observed in the 100mg QD dose schedule patients then a posterior 95% credible for Pr(MMR12) would be [0.678 – 0.831] which has a width of 0.153. Consequently, in terms of reliability of estimation, 50 additional patients would provide a 25% reduction in the width of a posterior 95% credible interval for Pr(MMR12). Similarly, substantial improvements in statistical reliability would be obtained for estimates all other parameters of interest, including the probability of complete cytogenetic response, distribution of response duration, Kaplan-Meier estimates of progression-free and overall survival time distributions, and toxicity rates.

10.2 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. Logistic regression will be used to assess the impact of patient, disease, and treatment characteristics on symptom severity and interference. Correlations of symptom severity and therapy adherence (from research nurse records) will be determined.

11.0 Reporting Requirements

11.1 Serious adverse events and unanticipated events will be reported as per institutional policy and as noted below.

Information on adverse events and concomitant medications will recorded in the medical record.

11.3 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death

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

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator 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:

For reporting purposes, BMS also considers the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events.

Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.

All serious AEs whether related or unrelated to investigational product, must be immediately reported to BMS (or designee) by confirmed facsimile transmission. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should simultaneously be faxed to Bristol-Myers Squibb at:
Global Pharmacovigilance
Bristol-Myers Squibb Company
Fax Number: 609-818-3804

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

11.4 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events).

11.5 Reporting of AE Information Following Study Completion

Collection of safety information following the end of investigational product administration is important in assisting in the identification of possible delayed toxicities or withdrawal effects. In BMS trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE that may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

12.0 References

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