THE UNIVERSITY OF TEXAS
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Protocol Page

Therapy of Myeloid Metaplasia-Myelofibrosis, Atypical Chronic Myeloid or Myelomonocytic Leukemia, C-Kit Positive Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (AML-MDS), Hypereosinophilic Syndrome, Polycythemia Vera, and Mastocytosis with Dasatinib (BMS-354825)
2004-0817

Core Protocol Information

Short Title	Dasatinib as Therapy for MPDs
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

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Supporter: Bristol-Myers Squibb Company

The University of Texas M. D. Anderson Cancer Center

Protocol 2004-0817

THERAPY OF MYELOID METAPLASIA-MYELOFIBROSIS, ATYPICAL CHRONIC MYELOID OR MYELOMONOCYTIC LEUKEMIA, C-KIT POSITIVE ACUTE MYELOID LEUKEMIA (AML) OR HIGH-RISK MYELODYSPLASTIC SYNDROME (AML-MDS), HYPEREOSINOPHILIC SYNDROME, POLYCYTHEMIA VERA, AND MASTOCYTOSIS WITH DASATINIB (BMS-354825)

1.0 OBJECTIVES

1) Primary Objectives: To determine the objective response rate in patients with myeloid metaplasia-myelofibrosis (MMM), atypical chronic myeloid or myelomonocytic leukemia (CML-CMML), acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS), hypereosinophilic syndrome (HES), polycythemia vera (PV), and mastocytosis to dasatinib.

2) Secondary Objectives: To evaluate duration of response and survival.

2.0 BACKGROUND

Despite progress in leukemia therapy, most adult patients with advanced or refractory hematopoietic malignancies still die from their disease. No generally effective therapy for agnogenic myeloid metaplasia (AMM), or the other bcr-abl negative myeloproliferative disease (MPD) has been established.[1-3] Hence, there is an urgent need to identify new agents for patients with these life-threatening diseases.

The transduction of signals from the extracellular milieu to the nucleus of a target cell (e.g., an epithelial cancer cell, a blood vessel endothelial cell or a stromal fibroblast) are receptor-mediated events. It is clear, from a large body of research, that some of the receptors that mediate critical events in signaling between tumor cells and important host tissues are receptor tyrosine kinases (RTKs). All of these molecules have an extracellular ligand binding domain, a transmembrane domain and an intracellular tyrosine kinase domain. Upon ligand binding, receptors dimerize, the tyrosine kinase is activated and the receptors become autophosphorylated.[4] The cascade triggered by RTK activation modulates cellular events such as proliferation, differentiation and morphogenesis in a positive or negative fashion. Over the past 15 years, RTKs and their downstream signaling molecules have emerged as important targets for the development of inhibitory drugs due to their role in positive growth control. Of particular interest has been the receptors platelet-derived growth factor (PDGF) receptors. PDGF receptors have been shown to have defined roles in the autocrine stimulation of tumor cells, as well as tumor cell-host cell interactions such as new blood vessel growth (or “angiogenesis”) and supporting stromal fibroblasts.[4]

PDGF is a pleiotropic factor that exists as a homo- or heterodimer of two polypeptides, the alpha- and beta-chains.[5] The PDGF ligands interact with two receptor subtypes, the PDGF receptor-α (PDGFRα) and PDGF receptor-β (PDGFRβ). PDGF receptors are normally found in connective tissue and glia but are lacking in most epithelia. However, recent studies have implicated paracrine or autocrine PDGF loops in the growth deregulation of gliomas and sarcomas as well as various human epithelial tumors. Furthermore, PDGF has been implicated in the pathogenesis of several nonmalignant proliferative diseases, including atherosclerosis, restenosis following vascular angioplasty, and fibroproliferative disorders such as obliterative bronchiolitis.[6, 7] PDGF receptors are expressed on tumor neovasculature and are up-regulated during tumor

progression.[8] Furthermore, the β-receptor appears to play a role in angiogenesis by regulating the pericytes that surround the microvessels.[9] In addition, PDGF receptor expression on tumor stromal fibroblasts may support tumor cell growth.[10, 11] Thus, PDGF may influence tumor cell growth directly or indirectly, employing both autocrine and paracrine mechanisms.[12] A large body of data supports a role for PDGF in the pathophysiology of a number of MPD.[5, 8, 10-19]

C-kit and the VEGF Flk-1 receptor (also called KDR, the human homologue, or VEGF-R2) are closely related receptor tyrosine kinases which have arisen by duplication of immunoglobulin-like domains from a common ancestor.[20] C-kit is the cellular homolog of the v-kit retroviral oncogene. The c-kit gene product is expressed in hematopoietic progenitor cells, mast cells, germ cells, and some human tumors.[21, 22] Studies with mice with inactivating mutations of c-kit or its ligand have demonstrated that the c-kit gene product is essential for maintenance of normal hematopoeisis, melanogenesis, gametogenesis, and growth and differentiation of mast cells. In addition to its normal role, deregulation of c-kit is thought to have a role in certain human tumors, including germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancers (SCLCs), melanoma, breast cancer, and neuroblastoma. In a number of tumors types, c-kit-mediated growth has been found to occur via mutation of c-kit, which results in ligand-independent activation of the receptor [23-25] C-kit is essential for the development of normal hematopoietic cells and has been proposed to play a functional role in AML. In a recent investigation of 917 adult and pediatric patients with AML, c-kit was detected on the surface of AML blasts in 63% of the samples by FACS analysis.[26] In recent publications, expression of c-kit was identified in 20 of 25 AML patients and in all of 21 cases, respectively.[27, 28] c-kit is another member of the class III family of RTKs, characterized by an extracellular ligand binding region containing 5 immunoglobulin repeats, a hydrophobic transmembrane domain, and an intracellular kinase domain split by an insert. Binding of the c-kit ligand, stem cell factor (SCF), initiates a signal transduction cascade that includes receptor autophosphorylation and subsequent phosphorylation on numerous intracellular substrates. c-kit and its ligand play a pivotal role in normal hematopoeisis, as evidenced by naturally occurring murine mutations at the Sl locus, which encodes SCF, as well as in the c-kit receptor itself. These mutations result in varying degrees of macrocytic anemia and a loss of mast cells in addition to deficiencies in gametogenesis and melanogenesis.

In addition to its role in normal hematopoeisis, c-kit is expressed in leukemic blasts in approximately 60% to 80% of patients with AML, as assessed by surface immunostaining using antibodies specific to c-kit or by expression of c-kit messenger RNA. Supporting a functional role for c-kit in AML, increased tyrosine phosphorylation of the receptor, as well as a proliferative response upon SCF stimulation, has been demonstrated in leukemic blasts in most AML cases that were c-kit+. The proliferative response to SCF has been shown to be synergistic with granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin (IL)-3, both of which are known to promote the growth of leukemic cells in vitro. We have recently reported that SU5416 and SU6668, small-molecule inhibitors

of RTKs such as Flk-1/KDR with structural and sequence similarity to c-kit, inhibit biologic functions of c-kit in MO7E cells, including ligand-induced tyrosine phosphorylation and proliferation[29] Additionally, both compounds induced apoptosis in these cells. Both SU5416 and SU6668 also inhibited SCF-induced phosphorylation of c-kit in blasts from several AML patients, one T-cell acute lymphoblastic leukemia (T-ALL) and one chronic myeloid leukemia (CML) patient, and also induced apoptosis in these cells.[29] These results suggest that c-kit inhibition may provide a useful means to treat AML.

Imatinib mesylate, a Bcr/Abl selective tyrosine kinase inhibitor, is the most active agent against CML. Preclinical studies demonstrate similar suppression of c-kit and PDGF-R kinases suggesting its potential role in a wide variety of c-kit or PDGF-R positive tumors including gastrointestinal subcutaneous tumors (GIST). AML is associated with high expression of c-kit. Other myeloproliferative disorders are associated with high expressions of PDGF and PDGF-R. They are ideal targets for therapy with new Bcr/Abl or Abl/Src inhibitors.

In this study, we propose to evaluate the efficacy of dasatinib, dual Abl/Src inhibitors in c-kit positive and PDGF-R expressing (myeloproliferative) disorders in a time-efficient approach. Some of these disorders have responded to imatinib including HES, mastocytosis, PV, and to lesser extent AML and MMM.

- Polycythemia vera (PV): This is a MPD involving excessive proliferation of the erythroid series, producing erythrocytosis, high Hb/Ht levels, vessel stasis, splenomegaly, and transformation to AML and other MPD. Response rate to PV after failure on hydrea and IFN-α to imatinib is about 50%.
- Hypereosinophilic syndrome (HES): This is an MPD of the eosinophils causing eosinophilia, skin rashes, organ infiltration, heart failure, CVAs and multi-organ failure (liver, kidney). The median survival range reported is 1-4 years. There is no effective therapy for HES. Patients with HES treated with imatinib 100mg daily had a 50% response rate. In our studies 5/9 patients with HES responded to imatinib. The efficacy of imatinib in HES has been confirmed in at least one other study.
- Responses in mastocytosis have been reported recently in 4 of 9 patients treated. In addition, patients with atypical CML or CMML with PDGF-R fusion genes have been reported to have significant activity with imatinib.

2.1 Update of May 3, 2006

As of this date, 20 patients with mastocytosis have been treated for a median of 39 days (range 6 – 147). Fifteen patients have been treated for more than one month. So far, by protocol criteria responses are: major response – 2, partial response – 6, clinical benefit – 4, for an overall response of 12/15 = 80%.

Preclinical studies suggest that high levels of dasatinib may be more effective against mastocytosis lines. Following discussion with Bristol-Myers and other investigators, it was felt that a single dose (SD) daily of

dasatinib (140 mg SD as opposed to 70 mg BID) may prove more effective. We propose to treat an additional 25 patients with mastocytosis with 140 mg SD orally daily. The statistics will be the same as for the first cohort of 25 patients. This would allow enough patients to evaluate efficacy:toxicity in order to design the FDA pivotal approval trial for mastocytosis.

2.2 Update as of July 8, 2011

Two patients with mastocytosis remain on study for over 5 years with symptom control and stability of the disease. The update reflects current monitoring practice in patients on long term therapy.

3.0 BACKGROUND DRUG INFORMATION

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 the 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 (CA180002) was conducted to determine the safety profile, tolerability, and pharmacokinetics of dasatinib in patients 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 reporters of the mechanism of action. CA180005, was designed to further evaluate the anti-tumor activity and safety of dasatinib in patients with imatinib-refractory, accelerated phase CML.

3.1 Summary of Results of Investigational Program

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

3.1.1 Preclinical Antitumor Activity

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 kinases/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 PDGFb receptor (28 nM). Dasatinib is much more potent than imatinib against several important tyrosine kinases, as outlined in Table 1 below.

Table 1 Comparative Potency of Dasatinib vs. Imatinib

Mesylate

Kinase	Fold more potent than Imatinib (based on IC_{50})
BCR-ABL	260
C-kit	8
PDGFb	60
SRC	>1000

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 217 nM 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 mM)[33] independently established by investigators at M.D. Anderson Cancer Center from the sensitive parent line by continuous exposure of K562 cells to high concentration 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 patients who failed imatinib mesylate therapy. These cells remained highly sensitive to the cell-killing effects of dasatinib.[34] Table 2 shows the IC_{50} of dasatinib compared to the IC_{50} of imatinib in these three cell lines.

Table 2 IC_{50} of Dasatinib and Imatinib mesylate in three patient 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.

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-off). 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 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.

3.1.2 Preclinical Toxicology

Additional information related to the preclinical toxicology of dasatinib is available in the Investigator 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 were no apparent sex-related differences. For rats, systemic exposure (AUC) decreased with repeated administration ~12 to 47% at dasatinib doses of ‡ 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 and 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 rat 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.

3.1.3 Preclinical Pharmacokinetics

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.

Distribution. Dasatinib is highly bound (> 91%) to proteins in mouse, rat, dog, monkey, and human sera, and its blood to plasma concentration ratio 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.

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.

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 elimination of dasatinib is by metabolism.[38]

Pharmacokinetic Drug Interactions. Caution is warranted when administering dasatinib to patients 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 mM) and a weak inhibitor of CYP1A2 and CYP2D6 (IC_{50} of > 100 mM), CYP2C9 (IC_{50} of 63 mM) and CYP2C19 (IC_{50} of 32 mM). 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 (see Section 5.3.2).

3.2 Rationale

The selective effect of imatinib against Bcr-Abl, c-kit, PDGFR, and other recently discovered kinases (e.g. FIP1 L1- PDGR R in HES) explains its efficacy, not only in Ph-positive CML and ALL, but also perhaps in other hematologic cancers including HES, mastocytosis, PV (response rates of 50%), and to a lesser extent in MMM and AML.

Dasatinib is a dual Abl/Src inhibitor. In preclinical models and in Phase I studies in CML, it appears to be far more potent than imatinib. The potency of dasatinib in some models is 260 fold more than imatinib against Bcr-Abl, 8 fold more against c-kit, 60 fold more against PDGFR, and > 1,000 fold against Scr. Thus, it is reasonable to investigate in clinical trials the potential activity of dasatinib in hematologic cancers in which these kinases might be operative. These include AML-MDS,

atypical CML and CMML, HES, PV, mastocytosis, and MMM. This is the purpose of this study.

3.2.1 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)

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, 30 tabs/bottle
BMS-354825-03	50 mg film coated tablets, 30 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 lot numbers, dosing start dates and the number of tablets for each dosage strength must be recorded on the drug accountability pages of the Case Report Form. The subject must be instructed to return all unused study medications in the provided packaging at each subsequent visit.

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 the investigational pharmacy, in accordance with the environmental conditions (temperature, light and humidity) as determined by the supplier 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 supplier
    - 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 Destruction of Investigational Product

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

Patients ≥ 18 years old who meet the following eligibility criteria:

4.1 Patients must have one of the following hematopoietic malignancies:

1) C-kit positive (10% or more bone marrow or peripheral blood mononuclear cells positive by flow) acute myeloid leukemia (AML excluding acute promyelocytic leukemia) or myelodysplastic syndrome (MDS) of the following types:
   - Refractory-relapse AML-MDS including those who fail to achieve CR after the first cycle of induction
   - Second or subsequent AML-MDS refractory-relapse
   - Newly diagnosed AML-MDS patients over 60 years of age with karyotype other than t(15:17), inv16, t(8:21), who do not want chemotherapy. Patients with MDS who do not want chemotherapy as initial treatment, or who are not eligible for the treatments of higher priority.
2) Ph negative MPD including chronic myelomonocytic leukemia (CMML)
3) Agnogenic myeloid metaplasia – myelofibrosis (MMM)
4) Hypereosinophilic syndrome (HES)
5) Polycythemia vera (PV)
6) Mastocytosis

4.2 Serum bilirubin less than 2mg%, serum creatinine less than 2mg% unless abnormality is considered due to hematologic malignancy by investigator.

4.3 ECOG Performance Status < 3.

4.4 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.

4.5 Women of pregnancy potential must practice an effective method 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) (defined as not post-menopausal for 12 months or no previous surgical sterilization) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In addition, men enrolled on this study should

understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control. Women and men 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.

4.6 Inclusion of women and minorities: As per NIH policy, women and members of minorities will be included in this protocol as they are referred in the relevant populations. There are no exclusions of women or minorities based on the study objectives.

4.7 NYHA Class < 3

4.8 Cardiac Symptoms patients meeting the following criteria are not eligible:

- 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:

1. Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)
2. 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:

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

5.0 TREATMENT PLAN

5.1 General

All patients should be registered with the Data Management Office PDMS system. Dasatinib will be supplied by Bristol-Myers Squibb Company. Patients will be assigned an identifying number once registered.

5.2 Treatment Plan

Patients will receive therapy according to the suggested guidelines below. Individual variations in the initiation of therapy, WBC count at start of therapy, individual doses are acceptable as indicated by patients condition and physicians judgment.

5.2.1 WBC reduction: hydroxyurea may be used during the first month of therapy for control of WBC or other indications. Use beyond the first month will have to be discussed with the PI and the reason clearly documented.

5.2.2 Treatment Administration

Dasatinib will be administered continually at an oral dose of 70 mg twice daily. A treatment cycle will be defined as 4 weeks (28 days), ± 7 days. Patients will be instructed to take Dasatinib in the morning (between approximately 6:00 a.m. - 10:00 a.m.) and in the evening (between approximately 6:00 p.m. - 10:00 p.m.).

Patients preferably should not take H_2 blockers. 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.

Patients should avoid taking CYP3A4 inhibitors such as: acetaminophen, aldrin, alfentanil, amiodarone, astemizole, benzphetamine, budesonide, carbamazepine, cyclophosphamide, cyclosporin, dapsone, digitoxin, diltiazem, diazepam, erythromycin, ethinylestradiol, etoposide, flutamide, hydrogxyarginine, ifosphamide, imipramine, lansoprazole, lidocaine, loratadine, losartan, lovastatin, midazolam, nifedipine, omeprazole, quinidine, paclitaxel, rapamycin, retinoic acid, steroids (e.g., cortisol), tacrolimus (FK 506), tamoxifene, teniposide, terfenadine, tetrahydrocannabinol, theophylline, toremifene, triazolam, troleandomycin, verapamil, warfarin, zatosetron, or zonisamide. If necessary, they should be taken at least 2 hours away from dasatinib dose.

If a scheduled dose is missed or dosing is interrupted for toxicity or for any other reason, these doses should be omitted. Patients will ideally be treated with dasatinib until disease progression, unacceptable toxicity, the Investigator and the patient feel that it is in the best interest of the patient to discontinue treatment, withdrawal of patient's consent, or for reasons outlined in Sections 5.2.4 and 5.6.

5.2.2.1 For patients with mastocytosis, dasatinib will be given at 140 mg single dose (SD) daily. H_1 and H_2 blockers are allowed. If worsening symptoms occur in the first week (histamine release), steroids are allowed e.g. prednisone

40-80 mg daily x 7.

5.2.3 Dose Modifications and Escalations

Patients will be monitored continuously for adverse events (toxicity) while on study therapy. Patients will be instructed to notify their physician immediately for any and all toxicity. Patients will continue to receive therapy as long as they have not had disease progression and all non-hematologic toxicities thought to be related to dasatinib are ≤ CTC Grade 1 or have returned to baseline (except alopecia and fatigue), and ANC ≥˜1000/mm ^{3}. Potassium and magnesium must continue to be within normal limits, and total serum calcium or ionized calcium must be greater than the lower limits of normal.

For any dose interruptions (as described below), initiation of additional therapy may be delayed for a maximum of 21 days to allow recovery from any toxicity.

Dose Escalations for Resistance or Progression. The dose modification levels are specified in Table 7. Patients who show evidence of progressive disease after starting treatment with dasatinib may have their dose increased to 100 mg twice daily upon agreement between the Investigator and the Medical Monitor/drug supplier. Patients who do not achieve response within 8 weeks of initiation of therapy may also escalate their dose to 100 mg twice daily starting with the 3rd cycle of therapy as long as toxicity does not cause discontinuation of therapy. Patients who achieve response on 70 mg twice daily and subsequently progress while on therapy may also escalate their dose to 100 mg twice daily. Patients who progress during 100 mg twice daily dosing will discontinue therapy. Patients with mastocytosis who do not respond may be treated at 200 mg SD daily.

Dose Modifications for Non-Hematologic Toxicity. Criteria for dose reductions and discontinuation of therapy for some specific non-hematologic toxicities are described in Table 8. Guidelines for dose reductions and discontinuation from therapy due to other non-hematologic toxicities are as follows:

- If a patient has CTC Grade 2 non-hematologic toxicity (except alopecia or fatigue) thought to be at least possibly related to dasatinib, treatment should be interrupted until the toxicity decreases to ≤ Grade 1 or to baselines levels. Therapy will then be reinitiated at the original dose. There should be no attempt to make up for doses omitted due to toxicity. If the same Grade 2 non-hematologic toxicity recurs upon retreatment with the original dose, treatment will again be interrupted until the toxicity

decreases to ≤ Grade 1 or returns to baselines levels. Therapy with dasatinib will then be reinitiated at the next dose reduction level. If the same Grade 2 non-hematologic toxicity recurs despite this dose reduction, a second dose reduction is permitted. Additional therapy following a second dose reduction vs. discontinuation of the patient from further protocol therapy will be discussed and agreed upon by the Investigator. Therapy can be permitted to continue with a Grade 2 non-hematologic toxicity if continuing treatment of the patient's cancer is thought to outweigh the risk of the toxicity and the toxicity does not progress to Grade 3. This will only be applicable after two attempts of dose reduction.

- Patients who experience CTC Grade 3 non-hematologic toxicity thought to be at least possibly related to dasatinib, will have their treatment interrupted until the toxicity decreases to ≤ Grade 1 or to baseline levels. Therapy with dasatinib will then be reinitiated at the next dose reduction level. If the same Grade 3 non-hematologic toxicity recurs despite this dose reduction, a second dose reduction is permitted. Additional therapy following a second dose reduction vs. discontinuation of the patient from further protocol therapy will be discussed and agreed upon with the Investigator. There should be no attempt to make up for doses omitted due to toxicity.

- Patients who experience a CTC Grade 4 non-hematologic toxicity thought to be at least possibly related to dasatinib will generally not receive additional protocol therapy and be removed from study. Additional therapy following a resolution in this Grade 4 toxicity to ≤ Grade 1 or to baselines levels will only be given with at least a 1 dose level reduction, if the Investigator agree that it is in the best interest of the patient to receive additional therapy with dasatinib (for example, if this or other patients have demonstrated a response to therapy).

Table 7: Dose Modification Levels

Dose Level	Dose (mg) twice daily (BID)	Single dose (SD) daily (mg)
Escalation 1	100	200
Starting Dose	70	140
Reduction 1	50	100
Reduction 2	40	80
Reduction 3	20	40

However, for an individual patient, dose reductions and discontinuations may be more conservative than indicated in the

above scheme (i.e., dose reduce or discontinue at a lower grade of non-hematologic toxicity) based on the clinical judgment of the Investigator. With the expanded NCI CTCAE Version 3, some Grade 2 toxicities may require dose reductions after the first occurrence. Also, patients experiencing some Grade 3 organ toxicities (e.g., renal, cardiac, CNS) judged to be related to study therapy should be discontinued from therapy. Patients with a QTc ≥530 msec with both the Bazett and Fridericia corrections must be discontinued from the study. Patients who have any evidence of serious bleeding or hemorrhage (e.g., cutaneous, GI, etc) must be discussed with the Investigator for possible dose adjustment or to have therapy discontinued.

- Abnormalities of LDH, alkaline phosphatase, glucose, albumin, calcium, phosphorus, uric acid, magnesium, electrolytes will be noted and corrected but will not mandate changes in dasatinib doses.

- Dose adjustments may be made at the discretion of the treating physician for patients on therapy >5 years. The lowest dose is 20mg, the highest dose is 140mg. Occasional missed doses of therapy will not be considered as protocol violations/deviations.

Table 8: Dose Modifications for Non-Hematologic Toxicity

Toxicity	Dasatinib
Grade 3 nausea/vomiting[a] (1st or 2nd event)	Decrease current dose by 1 dose level.
Grade 3 nausea/vomiting[a] (3rd event)	Off study[b]
Grade 3 diarrhea [a] (1st or 2nd event)	Decrease current dose by 1 dose level[a]
Grade 3 diarrhea [a] (3rd event)	Off study[b]
Grade 4 non-hematologic toxicities	Off study[b]
Grade 2 neuropathy (motor or sensory)	Decrease current dose by 1 dose level
≥ ˜Grade 3 neuropathy (motor or sensory)	Off study[b]
QTc > 530 msec (both Bazett and Fridericia)	Off study[b]
≥ Grade 3 cardiac troponin I	Off study
Cardiac troponin T > ULN	*** [c]
≥ Grade 2 CK or CK-MB > ULN	*** [c]
≥ Grade 2 AST, ALT	*** [c]
≥ Grade 2 bilirubin	*** [c]
Any evidence of bleeding	*** [c]

[a] Despite adequate/maximal medical intervention and/or prophylaxis.

[b] Unless Investigator agree that continued therapy at a reduced dose is in the best interest of the patient as in the case of responding patients.

[c] To be adjusted as medically indicated after discussion **with** Investigator.

Hematologic Toxicity

Neutropenia

There should be no dose modifications or treatment interruption for neutropenia during the first 14 days of therapy. If Grade 4 neutropenia (ANC < 500/mm^3) occurs after 14 days of treatment, a bone marrow aspirate and biopsy may be performed. If marrow cellularity is < 10%, study drug must be held until ANC > 1000/mm^3, at which time treatment may be resumed at full dose. If Grade 4 neutropenia persists, a repeat bone marrow aspirate and biopsy may be performed to assess the cellularity and percentage of blasts. If Grade 4 neutropenia recurs after resuming trial treatment, study drug will be held until ANC > 1000/mm^3, at which time study drug will be resumed at 1 dose level lower. If Grade 4 neutropenia occurs again, a second dose reduction should be tried. Further dose reductions versus discontinuing the patient from study drug for further episodes of grade 4 neutropenia will be decided by the Investigator. The above procedures will continue to apply if the patient receives additional treatment.

If marrow cellularity is > 10% and/or contains > 30% blasts, treatment will be continued (or restarted if it has been withheld because of marrow hypocellularity and/or granulocytopenia). If Grade 4 neutropenia persists for an additional week, a bone marrow aspirate and biopsy may be repeated and the above criteria applied. If Grade 4 neutropenia persists for an additional two weeks (i.e., a total of 4 weeks), study drug will be withheld (regardless of the bone marrow appearances) until ANC >1000/mm^3, at which time treatment will be resumed at full dose. If Grade 4 neutropenia recurs, study drug will again be withheld until ANC > 1000/mm^3 at which time study drug will be resumed at 1 dose level lower. If Grade 4 neutropenia occurs again a second dose reduction should be tried. For additional grade 4 neutropenia, further dose reductions versus discontinuing the patient from study drug will be decided by the Investigators. The above procedures will continue to apply if the patient receives additional treatment.

Patients with AML and MDS may start with low counts due to their basic disease. In them, dose interruptions/adjustments will not be considered if myelosuppression is attributed to disease.

There should be no dose modifications for thrombocytopenia without an associated bleeding complication. Patients may be supported with platelet transfusions as needed.

Febrile Neutropenia

There will be no dose modification or treatment interruption for

fever associated with neutropenia unless the neutropenia leads to dose reduction or interruption as defined above (under Neutropenia), or unless the patient has signs and symptoms of sepsis considered related to dasatinib.

Bleeding
Patients who have any evidence of bleeding or hemorrhage of any grade (e.g., skin, GI, etc.) must be discussed with the principal investigator for possible dose adjustment or to have therapy discontinued.

5.2.4 Discontinuation of Therapy

Study therapy MUST be immediately discontinued for the following reasons:

- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy

5.2.5 Treatment Compliance

Trained medical personnel will dispense dasatinib to patients. Treatment compliance will be monitored by drug accountability, as well as recording dasatinib administration using patient diaries. Drug accountability may also be reported verbally by the patient to the research team. This information will be recorded in the medical record.

5.3 Prohibited and Restricted Therapies During the Study

5.3.1 Prohibited Therapies

No other therapy for the treatment of CML, with the exception of anagrelide hydrochloride for the treatment of elevated platelet counts and hydroxyurea will be permitted while the patient is on study. 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 treating physician after discussion with the PI.

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.

Except for anagrelide and hydroxyurea, patients are prohibited from taking medications that directly inhibit platelet function (i.e., aspirin, dipyridamole, epoprostenol, eptifibatide, clopidogrel, cilostazol, abciximab, ticlopidine,) or anticoagulants (warfarin, heparin/low molecular weight heparin [e.g., danaparoid, dalteparin, tinzaparin, enoxaparin]) while on study therapy. Low-dose warfarin for prophylaxis to prevent catheter thrombosis, and heparin-flushes for IV lines is permitted.

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.

5.3.2 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.

5.4 Non-therapy Precautions and Restrictions

Based on preclinical data, dasatinib may increase the likelihood of bleeding. Hence, patients undergoing surgical procedures, including dental procedures should be instructed to inform their other doctors of this potential increase in bleeding.

5.5 The above are general guidelines to changes in therapy. However, individual variations including dose escalations or reductions as indicated by patients condition and physicians judgment, are allowed, if felt to be needed to optimize therapy. Discuss dose schedule reductions with Principal Investigator in difficult cases.

5.5 Duration of Therapy

Patients may continue on therapy indefinitely until disease progression or unacceptable toxicity.

6.0 PRETREATMENT EVALUATION

6.1 Screening Procedures

To be conducted within 28 days prior to enrollment, except where noted.

- Patient or legally authorized representative must sign the IRB approved Informed Consent Form prior to any protocol-specific procedures being performed.

- **Within 14 days prior to enrollment:** CBC, differential, platelets, serum chemistry (albumin, bilirubin, LDH, SGPT, creatinine, calcium, potassium, magnesium).

- **Within 4 weeks prior to enrollment:** Bone marrow aspirate with/without biopsy. Cytogenetics if not done within 12 months.

- Extra-medullary disease: assessment to document extent of disease. This may include CT scan of the abdomen/pelvis, CT or x-ray of the chest, ultrasound of the liver/spleen or abdomen, bone marrow scan plus additional staging as appropriate for each patient.

- Patients with AML-MDS will be screened for c-kit positivity which should be $\geq$ 10% positive.
- **Within 2 weeks:** EKG.
- **Within 1 week:** Pregnancy test.

7.0 EVALUATION DURING STUDY

7.1 CBC weekly x 4; then every 2-4 weeks on study.

7.2 Serum chemistries (see 6.1) every 2 weeks x 2 then every month on study.

7.3 Bone marrow aspirate to document CR. Repeat cytogenetics post CR if abnormal before therapy. (Patients with no bone marrow involvement on pre-treatment evaluation do not need to have any subsequent bone marrow studies.)

7.4 Laboratory Correlative Studies (optional) – to be performed on all patients whenever possible and if patient consents to additional studies. Not all samples will be collected in all patients at all points.

The laboratory correlative studies to be conducted may include:

- Blast and medullary levels of c-Kit and PDGF –R pretreatment, at CR and at failure as indicated.
- C-kit and PDGF-R levels of phosphorylation pretreatment, at CR and at failure as indicated.

7.5 One EKG between Day 4 and Day 8 of cycle 1.

7.6 After 5 years of therapy, lab tests are recommended every 6 months and are at the discretion of the treating physician.

8.0 CRITERIA FOR RESPONSE

From experience with imatinib in similar patients, responses take an average of 3 to 4 months to occur.

Patients will be evaluated for response.

All patients who receive any dasatinib will be considered evaluable for efficacy analyses. The following criteria will be utilized to judge response.

8.1 AML, MDS

Complete Remission (CR): Normalization of the peripheral blood and bone marrow with 5% or less blasts; normo- or hypercellular marrow; ANC $\geq$ 1.0 x 10^9/L, and platelet count $\geq$100 x 10^9/L.

Partial Remission: As per Complete Remission except for the presence of 6-25% marrow blasts, but reduction by ≥ 50%.

CR marrow: As per Complete Remission but platelet count < 100 x 10^9/L.

All other responses are considered failures.

8.2 MMM and CMML

Complete Response: Absence of signs or symptoms of the disease. WBC between 1 to 10 x 10^9/L with no peripheral blasts, promyelocytes, or myelocytes and with normalization of bone marrow (< 5% blasts in normocellular or hypercellular marrow) for at least 4 weeks.

Resolution of pretreatment cytopenias:

- ANC ≥ 1.0 x 10^9/L without G-CSF or GM-CSF
- Hgb ≥ 12.0 gm/dl (≥11.0 gm/dl for females) without erythropoietin or transfusion support.
- PLT ≥ 100 x 10^9/L without growth factor or transfusion support.

Resolution of pretreatment leukocytosis and/or thrombocytosis:

- WBC ≤ 10 x 10^9/L without peripheral blasts, promyelocytes, or myelocytes
- PLT ≥ 100 x 10^9/L but less than 450 x 10^9/L

Partial Response: Improvement of two or more of the following:
ANC:

- Increase by 100% and to above 10^9/L for neutropenia
- WBC between 1-10 x 10^9/L with persistence of immature cells (blasts, promyelocytes, myelocytes, metamyelocytes) for pretreatment leukocytosis.

Hemoglobin:

- Increase by 2 gm/dL if it was below 10 gm/dL
- Decrease in transfusion requirements by at least 50% (decrease in frequency and/or volume)

Platelet Count:

- below that level prior to therapy
- Persistent thrombocytosis > 450 x 10^9/L but < 50% of pretreatment

Marrow Blasts:

- Reduction of marrow blasts to 5% or less if it was above 10% in normocellular or hypercellular marrow

Organomegaly:

- Reduction in splenomegaly and/or hepatomegaly by 50% of pretreatment dimensions (measured as length below the left costal margin on palpation) confirmed by imaging in difficult cases

All other responses are considered failures.

8.3 PV

CR=normalization of Hb/Ht without need for phlebotomies and disappearance of all signs or symptoms of disease

PR=reduction of Hb by ≥ 2g/dl; reduction of splenomegaly by ≥ 50%.

8.4 HES

CR=disappearance of eosinophilia (≤ 10%) and disappearance of signs and symptoms of disease.

PR=reduction of eosinophilia by ≥ 50%; reduction of organomegaly by ≥ 50%.

8.5 Mastocytosis

Major Response: Complete resolution of at least one clinical finding [C-Finding(s)] and no progression in other C-Findings.

a. Complete remission = with disappearance of mast cell infiltrates in affected organs, decrease of serum tryptase levels to <20 ng/ml, and disappearance of SM-associated organomegaly.
b. Incomplete remission = with decrease in mast cell infiltrates in affected organs and/or substantial decrease of serum tryptase level and/or visible regression of organomegaly.
c. Pure clinical response = without decrease in mast cell infiltrates, without decrease in tryptase levels, and without regression of organomegaly.

Partial Response: Incomplete regression of one or more C-Finding(s) without complete regression and without progress in other C-Findings.

a. Good partial response: > 50% regression
b. Minor response: ≤ 50% regression

No Response: C-Finding(s) persistent or progressive.

a. Stable disease: C-Finding-parameters show constant range
b. Progressive disease: one or more C-Finding(s) show progression

9.0 CRITERIA FOR REMOVAL FROM STUDY

9.1 Patients who develop progressive disease with no response to optimization of therapy through increases of treatment doses and duration.

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

9.3 Patient request

9.4 Death

9.5 Non-compliance with the treatment schedule.

10.0 STATISTICAL CONSIDERATIONS

This is an open-label, phase II study in which patients with any of these possible hematopoietic malignancies will be treated with dasatinib.

The primary objective for the study is to determine the activity of dasatinib when given to patients in the following patient groups:

1. C-kit positive AML-MDS
2. Atypical CML or CMML
3. HES
4. PV
5. Mastocytosis
6. Myelofibrosis – myeloid metaplasia

Safety and tolerability of dasatinib in these patient groups will be assessed. An assessment of biological activity of dasatinib in these patient groups will be performed, using a variety of laboratory correlative studies, including gene and protein expression; blast, plasma, and medullary levels of significant growth factors; receptor tyrosine kinase levels and phosphorylation status; and measurements of apoptosis of hematopoietic malignant cells. cells.

10.1 Sample Size Considerations

Because dasatinib has a unique mechanism of action, a response rate as low as 10% is of interest for further investigation. A minimum-maximum total of 14-25 patients will be entered in each diagnostic group, for a total of 145 patients on the trial. This sample size will yield an 82% posterior credibility interval for P_R (probability of response) of width approximately 0.16.

If, for example, 3/25 (12%) responses are observed, the 82% posterior credibility interval will range from 2% to 18%, formally:

$$Pr\ \left[.02 < P_R < .18 \mid 3/25\ responses\ \right] = 0.82.$$

For each group, there will be one interim analysis after 14 patients have been evaluated. The trial will terminate if no responses have been observed. This is based on a Bayesian criterion to stop if:

$Pr\ [P_R > 0.1 \mid data\ ] < 0.10,\ assuming\ a\ \ beta\ (.2,\ 1.8)\ prior\ on\ P_R.$

Using these guidelines, simulation results indicate the following probabilities of early termination for several possible true rates of response:

True Response Rate	Prob. early termination
.01	.87
.05	.49
.10	.23
.20	.04
.30	.01

As a further measure to guard against exposure of patients to an agent with minimal activity, the aggregate response rate (CR+PR) will be reviewed periodically. If response rates of less than or equal to 1 in 26 patients, less than or equal to 2 in 42 patients, or less than or equal to 3 in 55 patients are observed, this would be evidence that the probability of <10% activity among this group of diseases is > 90%. Any decision regarding early termination of the study would take into account all findings in the individual disease groups. An objective response refers to the cumulative responses (e.g. CR + PR + improved) for each disease category.

The secondary objectives include analysis for the duration of response and survival. Response duration is from date of first response until relapse. Survival is from start of therapy. They will be done using the Kaplan-Meier estimators, the log-rank tests and the Cox-Cox-proportional hazards models. For correlative studies, the analysis for continuous variables will be done using thet- tests, linear regression models, etc. The analysis for categorical variables will be done using the chi-square tests and the logistic regression models.

11.0 REPORTING REQUIREMENTS

11.1 Reporting requirements will be as per institutional guidelines (Appendix C). Exceptions will include:

- Grade 3-4 myelosuppression

11.2 Adverse events related to study conditions

The SAE reporting period will begin with the signing of the informed consent.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or

those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

11.3 Handling of Serious Adverse Events (SAEs)

Drug toxicities will evaluated according to CTC version 3 (appendix B). Reporting of adverse events will be according to M. D. Anderson Guidelines for AE Reporting (Appendix C).

Serious adverse events will be delivered to Clinical Research Compliance and will be submitted to the FDA by the safety coordinator according to 21 CFR 312.32.

Investigator Communication with Drug Company
All SAEs should be faxed to Bristol-Myers Squibb at: Global Pharmacovigilance Bristol-Myers Squibb Company, fax number 609-818-3804.

11.4 Toxicities of this agent are well described. Only drug related unexpected serious adverse events will be recorded and reported.

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