2011-204: Phase I/II Study of Dasatinib in Recipients of Allogeneic Stem Cell Transplantation for Hematologic Malignancies.

BMS Protocol Number: CA-180-384

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Version: Amendment 2.0 30-September-2015

Original 27-October-2011
Revised 14-December-2011
15-February-2012
26-April-2012
15-May-2012
30-September-2015

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1. OBJECTIVES

PRIMARY:

To establish the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of dasatinib in the recipient of allogeneic stem cell transplantation (ASCT) for hematologic malignancies.

SECONDARY

1. To estimate the non-DLTs associated with administration of dasatinib in ASCT recipients

2. To estimate the incidence of large granular lymphocytosis (LGL) and its clinical course in recipients of ASCT

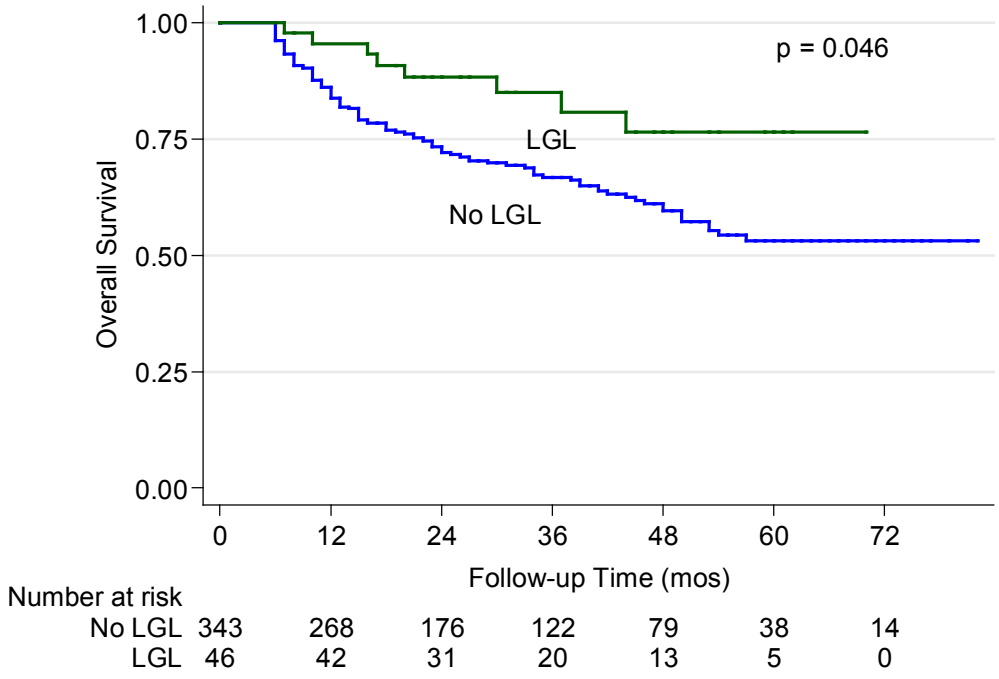
3. To perform correlative in vitro studies to see if the large granular lymphocytes show enhanced cytotoxicity to leukemia/ lymphoma cell lines

2. BACKGROUND

Immune reconstitution after ASCT follows the developmental ontogeny of the immune system. Regardless of the sources of the stem cell, natural killer (NK) cells usually recover within the first month after stem cell transplant[1-4]. The pattern of T-cell immune recovery is similar in both autologous and allogeneic transplantation at least in the pediatric populations. Prompt recovery of NK cells might decrease the risk of viral infections as well as enhance the graft-versus-malignancy effect [5]. In 1995, Dolstra et al reported the expansion of CD8+/CD57+ cells in 46% of the recipients of T-depleted stem cell transplant[6]. Importantly, recipients with an expanded population of CD8+/CD57+ T cells showed a lower incidence of leukemic relapse than those without LGL. The 3-year probability of relapse was 19% versus 64% (P = 0.03), respectively. Subsequently, Mohty et al reported the first case of large granular lymphocyte expansion in a patient who received non-myeloablative conditioning regimen[7]. Further studies by the same investigators reported 6 cases of LGL expansion that occurred among 201 consecutive patients. The LGL expansion was seen more frequently following fludarabine and anti-T lymphocyte globulin-based preparative regimens (4 cases/49), than after a conventional myeloablative regimen (2 cases/152). Expansion of LGL was seen between 3 and 15 months following ASCT. These patients had mild to severe cytopenia and other autoimmune manifestations including polyarthritis and hypergammaglobulinemia were also observed.

We reported our own experience with LGL in recipients of ASCT in 2009 [8]. This retrospective study was done on all adult patients who underwent ASCT at the Karmanos Cancer Institute (KCI) between January 1, 2004 and June 30, 2009. In patients with persistent lymphocytosis (≥ 3000 cells/mm3) post ASCT, expansion of LGL phenotype was identified by flow cytometry (CD2, CD3, CD5, CD7, CD8 and CD57 positive) and clonality was confirmed by T cell receptor beta and/or gamma gene rearrangement (TCR-GR) using southern blot analysis and polymerase chain reaction (PCR). We identified LGL in 24 patients with persistent lymphocytosis using flow cytometry. The median age of patients with LGL expansion was 50 years (range 24-68 years); with a median time to detection of 275 days post HSCT (range 69-1454 days) and median duration of follow-up was 811 days (range 85-1701 days). All 24 patients achieved full donor chimerism post transplantation by short tandem repeat (STR) analysis. Fourteen of 24 patients with T-LGL expansion had positive TCR-GR; in 2 patients

TCR-GR was not done and in the remainder was negative. Twenty of 24 patients had cytomegalovirus (CMV) viremia confirmed by PCR before the onset of T-LGL; the remainder had no CMV viremia. In all patients with LGL there was no subsequent recurrence of CMV viremia or infection. All 24 patients had documented graft versus host disease (GvHD). In the group with LGL only 2 patients relapsed with primary disease and only one patient died (due to a cardiac event). The cumulative incidence of LGL was estimated at 4.4%.
We have now extended our series to 46 patients, with estimated incidence of LGL of 8% (95% CI, 6%-10%) (Unpublished): 17 of 250 patients who received allogeneic grafts from family-related donors (6.8%; 95% CI, 4%-11%), and 29 of 359 patients who received allogeneic grafts from unrelated donor (8%; 95% CI, 5%-11%) (P = 0.44, Fisher's exact test) developed LGL. Using a landmark analysis at 6 months, patients who developed LGL expansion had a significantly better survival than those who did not develop LGL expansion (p=0.046).



Recently, several investigators reported that one of the immunomodulatory effects of dasatinib in patients treated for CML may include an expansion of LGL[9-11]. A study by Kreutzman et al observed that 10 of 20 patients with CML treated with dasatinib developed a clonal expansion of lymphocytes with T/NK cell phenotypes. A similar group of patients treated with imatinib did not show the same clonal expansion. In addition this clonal expansion of T/NK cells was associated with favorable treatment response and survival compared to patients without clonal expansion.
At Karmanos, we observed 4 cases of LGL among 15 patients treated with dasatinib (26.6%); 2 of these patients were treated for blast crisis with dasatinib alone and remain in molecular remission[12, 13]. Subsequently, Schiffer et al analyzed the data on 1897 patients who were treated in phase II and phase III studies of dasatinib after 2 years of treatment [14]. Lymphocytosis was observed in a large proportion of dasatinib-treated patients in chronic (31%), accelerated (39%), and myeloid blast (34%) phase, also the incidence of lymphocytosis was similar in patients in chronic phase receiving total doses of 100 or 140 mg

of dasatinib. The same authors then evaluated the occurrence of lymphocytosis in patients participating in a phase III randomized study comparing 12-month therapy with dasatinib vs. imatinib [15]. Patients who received dasatinib developed lymphocytosis more frequently (24% vs. 5%) and earlier (3 months vs. 4.7 months) than patients who received imatinib. Furthermore, in dasatinib treated patients, lymphocytosis was associated with a higher complete cytogenetic response (CCyR) rate (84% with vs. 75% without). In both studies, the incidence of pleural effusions was higher in patients who developed lymphocytosis. Unfortunately flow cytometry data is not available form these large muticenter studies to confirm that the lymphocytosis in these patients was indeed LGL. These observations suggested that lymphocytosis associated with dasatinib therapy might confer immunomodulatory and antitumor activity. Further elucidation of the biology of TKI-induced lymphocytosis is needed.

Combining the observations of spontaneous LGL expansion in allogeneic transplant setting with the dasatinib associated LGL expansion, we hypothesize that dasatinib therapy in recipients of allogeneic transplantation might favor the expansion of LGL, which may confer antitumor effects. In this proposal, we want to explore the tolerance and dose-limiting toxicity of dasatinib in recipients of allogeneic transplantation and to estimate the frequency of development of expansion of LGL at the optimal dose

3. ELIGIBILITY CRITERIA

3.1. Inclusion Criteria

1. Recipients of first ASCT from related or unrelated donor for the treatment of hematologic malignancies (Acute myeloid leukemia, Chronic Myeloid leukemia, Acute Lymphoblastic leukemia, Chronic Lymphocytic Leukemia, Myelodysplastic syndrome Hodgkins and Non Hodgkin Lymphoma) who are 1-antigen or 1-allele mismatched or fully matched at HLA-A, -B, -C and –DR as defined by high resolution typing.
2. Patients must be ≥18 years of age.
3. Patients must be between 100 - 200 days after allogeneic stem cell transplantation.
4. Dasatinib use prior to ASCT is allowed
5. Performance Status ≥60%
6. Presence of LGL clone prior to enrollment will not be an exclusion criterion if the LGL clone is < 25% of T cell population
7. Adequate Organ Function
    a. Total bilirubin < 2.0 times the institutional Upper Limit of Normal (ULN)
    b. Hepatic enzymes (AST, ALT) ≤ 2.5 times the institutional ULN
    c. Serum Creatinine < 1.5 time the institutional ULN
    d. Hemoglobin ≥8 g/dL, absolute neutrophil count ≥1,500 cells per µL and platelets ≥ 75,000 per µL.
8. Patient should be able to provide signed Written Informed Consent
    a. Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

b. Written consent will include a HIPAA form according to institutional guidelines

9. Patient should be able to take oral medication (dasatinib must be swallowed whole)

3.2. Exclusion Criteria

1. Recipient of mismatched (allele or antigen level) graft in more than one loci of HLA-A, -B, -C or –DR loci will not be eligible, i.e. recipients of 2-antigen or 2-allelele mismatched graft
2. Patients on investigational therapy for GVHD
3. Patients with uncontrolled acute or chronic GVHD or refractory disease not responding to conventional therapy
4. Patients who have evidence of disease progression before day 100 after ASCT
5. Sex and Reproductive Status
    a. WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 4 weeks after the last dose of study drug.
    b. Women who are pregnant or breastfeeding.
    c. Women with a positive pregnancy test.
    d. Sexually active fertile men not using effective birth control if their partners are WOCBP
6. Medical history and concurrent diseases
    a. No malignancy [other than for which patient underwent transplant] which required radiotherapy or systemic treatment within the past 5 years.
    b. Concurrent medical condition which may increase the risk of toxicity, including:
        I. Pleural or pericardial effusion of any grade at the time of screening for study
        II. Cardiac Symptoms; any of the following should be considered for exclusion:
            - Uncontrolled angina, congestive heart failure or MI within (6 months)
            - Diagnosed congenital long QT syndrome
            - Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes)
    c. 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)
        - Ongoing or recent (≤ 3 months) significant gastrointestinal bleeding
7. Any previous history of ≥ grade 3 toxicity to Dasatinib
8. Prohibited treatments and or therapies

a. Category I drugs that are generally accepted to have a risk of causing Torsades de Pointes including: (Patients must discontinue drug 7 days prior to starting dasatinib)
   - quinidine, procainamide, disopyramide
   - amiodarone, sotalol, ibutilide, dofetilide
   - erythromycin, clarithromycin
   - chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
   - cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

b. Patient agrees to discontinue St. Johns Wort while receiving dasatinib therapy (discontinue St. Johns Wort at least 5 days before starting dasatinib)

c. Patient agrees that IV bisphosphonates will be withheld for the first 8 weeks of dasatinib therapy due to risk of hypocalcemia

9. Other exclusion criteria
   a. Prisoners or subjects who are involuntarily incarcerated.
   b. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (egg, infectious disease) illness.

4. DRUG INFORMATION

4.1 Product Description

SPRYCEL® [16] (dasatinib, Bristol-Myers Squibb [BMS]-354825) is a potent, broad spectrum inhibitor of 5 critical oncogenic tyrosine kinases/kinase families (BCR-ABL, SRC, c-KIT, PDGF receptor β [PDGFRβ], and ephrin [EPH] receptor kinases), each of which is linked to multiple forms of human malignancies, and was discovered and developed by BMS. SPRYCEL® is approved in the United States (US), Europe (EU), and several other countries for the treatment of adults in all phases of chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib, and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to prior therapy[17].
The recommended starting dosage for subjects with chronic phase CML is 100 mg administered orally once daily (QD). The recommended starting dosage for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally once daily. In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended starting dosage.

4.2 Pharmacokinetics

Dasatinib is rapidly absorbed following oral administration in subjects with leukemia.[18] Across all treatment regimens, disease status, and study days; mean C_{max} values were attained at median T_{max} values that ranged from 0.45 to 3.18 hours postdose. The overall median T_{max} value was approximately 1 hour. There was no influence of treatment regimens, disease status, or study days on the half-life (T-HALF) of dasatinib.

The overall mean T-HALF value was approximately 3 to 5 hours. Dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. There were no clinically meaningful relationships between steady state CLo and body weight or body surface area. Statistical linear regression analyses were performed on log (AUC) versus log (DOSE) to assess dose proportionality. The AUC of dasatinib is approximately dose proportional in the dose range of 15 to 240 mg/day, suggesting that the drug exhibited linear kinetics over the entire dose range. However, the 90% CIs are wide, indicating that the variability in AUC is high. There was no marked effect of disease state, age, gender, and race on the PK parameters CLo, Vz/F, and T-HALF, suggesting that dose adjustment in these subpopulations may not be necessary.[19] The geometric mean accumulation index (AI) ranged from 1.01 to 1.61 between days 5/8 and 26/29 and no consistent dose-related trends were observed in the accumulation of dasatinib after repeated administration.
Data from a study of 54 healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following consumption of a high-fat meal resulted in a 14% increase in the mean AUC of dasatinib.[20] The observed food effects were not clinically relevant.
Dasatinib is extensively metabolized in humans. Unchanged dasatinib represented 29% of circulating radioactivity in plasma after a 100 mg dose of [^{14}C]-labeled dasatinib was administered to 8 healthy subjects in study CA180019.[21] Elimination is predominantly in the feces, mostly as metabolites. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 85% of the dose was recovered in the feces within 10 days, and approximately 4% of the administered radioactivity was recovered in the urine.
The cytochrome p450 enzyme CYP3A4 plays a major role in the metabolism of dasatinib in the humans. Dasatinib has little potential to induce CYP3A4 and, at concentrations ≤ 25 μM (1 μM = 488 ng/mL), dasatinib did not induce CYP1A2, CYP2B6, CYP2C9, and CYP3A4 in primary cultures of human hepatocytes.[22] Based on these data and plasma concentrations observed in vivo, dasatinib is unlikely to decrease the exposure of co-administered drugs that are metabolized by CYP1A2, CYP2B6, CYP2C9, or CYP3A4. In human liver microsomes, dasatinib did not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP2E1 at concentrations up to 50 μM.[22] It inhibited CYP2A6 (IC50 = 35 μM), CYP2C8 (IC50 = 12 μM), CYP2C9 (IC50 = 50 μM), and CYP3A4 (IC50 values of 18 and 10 μM for midazolam and testosterone substrates, respectively).[22]

4.3 Drug Interactions

4.3.1 Drugs That May Increase Dasatinib Plasma Concentrations
CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. In a study of 18 patients with solid tumors, 20-mg SPRYCEL once daily co administered with 200 mg of ketoconazole twice daily increased the dasatinib Cmax and AUC by four- and five-fold, respectively. Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. In patients receiving treatment with SPRYCEL, close monitoring for toxicity and a SPRYCEL dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

4.3.2 Drugs That May Decrease Dasatinib Plasma Concentrations
CYP3A4 Inducers: When a single morning dose of SPRYCEL was administered following 8 days of continuous evening administration of 600 mg of rifampin, a potent CYP3A4 inducer, the mean Cmax and AUC of dasatinib were decreased by 81% and 82%, respectively. Alternative agents with less enzyme induction

potential should be considered. If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered.

4.3.3 Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. In a study of 24 healthy subjects, administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single 50-mg dose of SPRYCEL was associated with no relevant change in dasatinib AUC; however, the dasatinib Cmax increased 26%. When 30 mL of aluminum hydroxide/magnesium hydroxide was administered to the same subjects concomitantly with a 50-mg dose of SPRYCEL, a 55% reduction in dasatinib AUC and a 58% reduction in Cmax were observed. Simultaneous administration of SPRYCEL with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of SPRYCEL.

4.3.4 H2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H2 antagonists or proton pump inhibitors (egg, famotidine and omeprazole) is likely to reduce dasatinib exposure. In a study of 24 healthy subjects, administration of a single 50-mg dose of SPRYCEL 10 hours following famotidine reduced the AUC and Cmax of dasatinib by 61% and 63%, respectively. In a study of 14 healthy subjects, administration of a single 100-mg dose of SPRYCEL 22 hours following a 40-mg omeprazole dose at steady state reduced the AUC and Cmax of dasatinib by 43% and 42%, respectively. The concomitant use of H2 antagonists or proton pump inhibitors with SPRYCEL is not recommended. The use of antacids (at least 2 hours prior to or 2 hours after the dose of SPRYCEL) should be considered in place of H2 antagonists or proton pump inhibitors in patients receiving SPRYCEL therapy.

4.3.5 Drugs That May Have Their Plasma Concentration Altered By Dasatinib CYP3A4 Substrates: Single-dose data from a study of 54 healthy subjects indicate that the mean Cmax and AUC of simvastatin, a CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin was administered in combination with a single 100-mg dose of SPRYCEL. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL.

4.3.6 Drugs That May Prolong QT Interval: Dasatinib may prolong QT interval and caution is need when used with other drugs that prolonged QT interval e.g. amiodarone, disopyramide, quinidine and procainamide; or conditions that prolonged QT interval such as hypokalemia and hypomagnesemia.

4.3.7 Medications that Inhibit Platelet Function and Anticoagulants: Src-family kinase inhibition potentially reduces platelet aggregation. Caution should thus be exercised if subjects are required to take medications that inhibit platelet function or anticoagulants. Such medications include:

a. aspirin or aspirin-containing combinations, clopidogrel, dipyridamole
b. tirofiban, di pyridamole, epoprostenol, ept ifibatide, c ilostazol, abc iximab, ticlopidine, cilostazol

c. warfarin, heparin/low molecular weight heparin [eg, danaparoid, dalteparin, tinzaparin, enoxaparin]

d. exceptions ar e low-dose warfarin for p rophylaxis t o prevent c atheter thrombosis and heparin for flushes of intravenous lines.

4.3.8 Commonly Used Drugs in Allogeneic Transplantation and Interaction

Immunosuppressants

Cyclosporine	Increase cyclosporine exposure Increase dasatinib exposure
Tacrolimus	Increase tacrolimus exposure Increase dasatinib exposure
Sirolimus	Increase sirolimus exposure
Mycophenolate mofetil	No interaction
Methotrexate	No interaction

SSRI

Fluoxetine	Increase QT by additive effect
Paroxetine	No interaction
Citalopram	Increase citalopram exposure
Sertraline	Increase sertraline exposure

Benzodiazepines/Psychotropic and other CNS drugs

Lorazepam	No interaction
Clonazepam	Increase clonazepam exposure
Alprazolam	Increase alprazolam exposure
Zolpidem	Increase zolpidem exposure
Bupropion	No interaction
Gabapentin	No interaction
Sumatryptan	No interaction

Opioids

Tramadol	Increase tramadol exposure
Methadone	Increase QT interval Increase methadone exposure Increase dasatinib exposure
Oxycodone	Increase oxycodone exposure
Morphine	No interaction
Hydromorphone	No interaction

Anti-infectives

Penicillins	No interaction
Cephalosporins	No interaction
Azithromycin	No interaction
Doxycycline	No interaction
Erythromycin	Increase dasatinib exposure
Norfloxacin	Increase QT interval
Ciprofloxacin	Increase QT interval Increase dasatinib exposure

Levofloxacin	Increase QT interval Increase dasatinib exposure
Co-trimoxazole	No interaction
Itraconazole	Increase dasatinib exposure
Fluconazole	Increase QT interval Increase dasatinib exposure
Voriconazole	Increase QT interval Increase dasatinib exposure
Rifampin	Increase dasatinib exposure
Acyclovir	No interaction
Valciclovir	No interaction
Valganciclovir	No interaction
Ganciclovir	No interaction
Lamivudine	No interaction

For Drugs not included in the table above please refer to article by Haouala et al[23]

4.4 Common Adverse Drug Reactions (ADRs):

The data presented in Table below reflect exposure to dasatinib in 2182 patients with leukemia in clinical studies (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The median duration of therapy was 11 months (range 0.03–26 months).
The majority of dasatinib-treated patients (1,864 [85%]) experienced at least 1 drug-related adverse reaction at some time. Drug was discontinued for adverse reactions in 14% (296/2182) of subjects. Drug related AEs leading to discontinuation in any 1 category occurred in ≤1% of the subjects with the exception of pleural effusion (85/2182; 4%). In subjects with chronic phase CML, drug-related pleural effusion accounted for discontinuation in 52 of the 1150 subjects. Only 1 subject in the 100 mg QD group had discontinuation due to drug-related pleural effusion compared with 35 subjects in the 70 mg BID group. In subjects with advanced phase CML or Ph+ ALL, drug-related pleural effusion accounted for discontinuation in 33 of the 1032 subjects. Six subjects in the 140 mg QD group had discontinuation due to drug-related pleural effusion compared with 27 subjects in the 70 mg BID group.
Overall, 59% (1287/2182) of subjects across all disease phases reported SAEs (any grade). Drug-related SAEs were reported in 53% (681/2182) of subjects. In subjects with chronic phase CML, notable common drug-related AEs included dyspnea, pleural effusion, congestive heart failure, febrile neutropenia, and thrombocytopenia. In most cases, a lower proportion of subjects in the 100 mg QD group reported drug-related SAEs than subjects in the 70 mg BID or other dose groups. In subjects with advanced phase CML or Ph+ ALL, notable common drug-related AEs included dyspnea, pleural effusion, diarrhea, and hematological toxicities. In most cases, there was little difference in these SAEs between the 140 mg QD and 70 mg BID groups. Rates of severe drug-related pleural effusion were lower in the 140 mg QD group (3%) vs. the 70 mg BID (6%).
The most frequently reported ADRs are shown in Table below.

Very Common and Common ADRs Reported in Subjects in Clinical Studies

	All Subjects (N = 2182) Percent (%) of Subjects	
	All Grades	**Grades 3/4**
Nervous system disorders *Very common*: headache	25	1
Common: neuropathy (including peripheral neuropathy)	7	<1
dizziness	5	<1
dysgeusia	2	0
somnolence	2	<1
Respiratory, thoracic and mediastinal disorders *Very common*: pleural effusion	27	7
dyspnea	24	5
cough	10	<1
Common: pulmonary edema	2	<1
lung infiltration	2	<1
pneumonitis	2	<1
pulmonary hypertension	1	<1
Gastrointestinal disorders *Very common*: diarrhea	33	4
nausea	23	1
vomiting	13	1
abdominal pain	11	<1
Common: gastrointestinal bleeding	8	4
mucosal inflammation (including mucositis/stomatitis)	7	<1
dyspepsia	6	0
abdominal distension	5	0
constipation	5	<1
gastritis	2	<1
colitis (including neutropenic colitis),	2	<1
oral soft tissue disorder	2	0
Skin and subcutaneous tissue disorders *Very common*: skin rash[a]	23	<1
Common: pruritus	7	<1
acne	5	<1
alopecia	5	0

Very Common and Common ADRs Reported in Subjects in Clinical Studies

	All Subjects (N = 2182) Percent (%) of Subjects	
	All Grades	**Grades 3/4**
dry skin	3	0
hyperhidrosis	2	0
urticaria	1	<1
dermatitis (including eczema)	1	0
Musculoskeletal and connective tissue disorders *Very common*: musculoskeletal pain	15	1
Common: arthralgia	9	<1
myalgia	8	<1
muscle inflammation	3	<1
muscular weakness	1	<1
musculoskeletal stiffness	1	0
Metabolism and nutrition disorders *Common*: anorexia	9	<1
appetite disturbances	2	<1
hyperuricaemia	1	<1
Infections and infestations *Very Common*: infection (including bacterial, viral, fungal, nonspecific)	11	3
Common: pneumonia (including bacterial, viral, fungal)	5	3
upper respiratory tract infection/inflammation	5	<1
herpes viral infection	1	<1
enterocolitis infection	1	<1
sepsis (including fatal outcome)	1	<1
Cardiac Disorders *Common*: pericardial effusion	5	1
arrhythmia (including tachycardia)	3	<1
congestive heart failure/cardiac dysfunction[b]	3	2
palpitations	2	0
Vascular disorders *Very common:* hemorrhage[c]	16	2
Common: flushing	4	0
hypertension	2	<1
Blood and lymphatic system disorders *Common:* febrile neutropenia,	5	5

Very Common and Common ADRs Reported in Subjects in Clinical Studies

	All Subjects (N = 2182) Percent (%) of Subjects	
	All Grades	Grades 3/4
pancytopenia	1	<1
General disorders and administration site conditions *Very common*: fatigue	23	2
superficial edema[d]	22	1
pyrexia	14	1
Common: asthenia	9	<1
pain	8	<1
chest pain	6	<1
generalized edema	4	<1
chills	3	<1
Psychiatric disorders *Common:* insomnia	2	0
depression	2	<1
Eye disorders *Common:* visual disorder (including visual disturbance, vision blurred, and visual acuity reduced)	2	<1
dry eye	1	<1
Ear and labyrinth disorders *Common:* tinnitus	1	0
Investigations *Common*: weight increased	5	<1
weight decreased	5	<1
Injury, poisoning, and procedural complications *Common:* contusion	2	<1

Note: Frequencies are defined as: very common (≥ 1/10) and common (1/100 to < 1/10)
Source: Dasatinib Investigator Brochure[24]

[a] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, fungal rash, generalized erythema, genital rash, heat rash, miliaria, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, and urticaria vesiculosa.

[b] Includes ventricular dysfunction, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

[c] Excludes gastrointestinal bleeding and CNS bleeding; these adverse drug reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.

[d] Includes aur icular s welling, c onjunctival edema, e ye edem a, eye s welling, e yelid edema, face edema, gravitational edema, lip edema, localized edema, mascular edema, edema genital, edema mouth, edema peripheral, orbital edema, penile edema, periorbital edema, pitting edema, scrotal edema, swelling face, and tongue edema.

4.5 Laboratory Abnormalities with Dasatinib

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML. Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.
In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption and/or reduction; permanent discontinuation of treatment occurred in 1% of patients. Grade 3 or 4 elevations of transaminase or bilirubin and Grade 3 or 4 hypocalcemia and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminase or bilirubin were usually managed with dose reduction or interruption.
Patients developing Grade 3 or 4 hypocalcemia during the course of dasatinib therapy often had recovery with oral calcium supplementation. In the Phase 2 randomized study, the frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was 63%, 56%, and 19%, respectively, in the dasatinib group and 39%, 14%, and 8%, respectively, in the imatinib group. The frequency of Grade 3 or 4 hypocalcemia was 4% in the dasatinib group and 0% in the imatinib group. Laboratory abnormalities reported in the Phase 3 dose-optimization study in patients with chronic phase CML are shown in the table below.

CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies

	Chronic Phase[a] (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase and Ph+ ALL (n=250)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	47	69	80	78
Thrombocytopenia	41	72	82	78
Anemia	19	55	75	46
Biochemistry Parameters				
Hypophosphatemia	10	12	19	20
Hypocalcemia	2	7	16	11
Elevated SGPT (ALT)	1	3	6	7

CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies

	Chronic Phase[a] (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase and Ph+ ALL (n=250)
	Percent (%) of Patients			
Elevated SGOT (AST)	1	1	4	5
Elevated Bilirubin	1	1	4	5
Elevated Creatinine	1	2	3	1

[a] The chronic phase data include patients prescribed any dose of dasatinib.

CTC grades: neutropenia (Grade 3 ≥0.5–1.0 × 109/L, Grade 4 < 0.5 × 109/L); thrombocytopenia (Grade 3 ≥10–50 × 109/L, Grade 4 < 10 × 109/L); anemia (hemoglobin ≥65–80 g/L, Grade 4 < 65 g/L); elevated creatinine (Grade 3 > 3–6 × upper limit of normal range (ULN), Grade 4 > 6 × ULN); elevated bilirubin (Grade 3 > 3–10 × ULN, Grade 4 > 10 x ULN); elevated SGOT or SGPT (Grade 3 > 5-20 x ULN, Grade 4 > 20 x ULN); hypocalcemia (Grade 3 < 7.0-6.0 mg/dL, Grade 4 < 6.0 mg/dL); hypophosphatemia (Grade 3 < 2.0-1.0 mg/dL, Grade 4 < 1.0 mg/dL).

4.6 Warnings and Precautions

4.6.1 Myelosuppression: Treatment with dasatinib is associated with severe (NCI CTCAE Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or dose reduction.1 In a Phase 3 dose-optimization study in patients with chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily.

4.6.2 Bleeding Related Events: Severe CNS hemorrhages, including fatalities, occurred in ≤ 1% of patients receiving dasatinib. Severe gastrointestinal hemorrhage occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution.) Patients were excluded from participation in dasatinib clinical studies if they took medications that inhibit platelet function or anticoagulants. In some trials, the use of anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with dasatinib if the platelet count was 50,000 to 75,000. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants

4.6.3 Fluid Retention: Dasatinib is associated with fluid retention. In all clinical studies, severe fluid retention was reported in 10% of patients, including pleural and pericardial effusion reported in 7% and 1% of patients, respectively. Severe ascites

and generalized edema were each reported in < 1% of patients. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution)
In the Phase 3 dose-optimization study in patients with chronic phase CML, fluid retention events were reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily
.

4.6.4 QT Prolongation A comprehensive evaluation of data from Phase 2 studies (N = 865) examined the possible effect of dasatinib on ECG parameters, particularly the QTc interval. The mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4 to 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 7 msec. On-study, a total of 5 subjects (< 1%) reported a QTcF > 500 msec; 1 of these 5 subjects reported a QTcF > 500 msec on both Day 1 and Day 8. No events of torsade de pointes were reported. Nine of the 1150 subjects with chronic phase CML had QTc prolongation reported as an adverse event. Of these 9 subjects, 7 were considered related to drug. None of the 9 subjects who reported QTc prolongation were from the 100 mg QD group compared with 8 subjects from the 70 mg BID group. Ten of the 1032 subjects with advanced disease had QTc prolongation reported as an adverse event. Of these 10 subjects, 7 were considered drug-related. All 10 of the subjects who reported QTc prolongation were from the 70 mg BID group. Overall, of the 2182 subjects treated with dasatinib, 21 (1%) subjects across the studies reported a QTcF > 500 msec.

5. Drug Supply

5.1 Packaging and Labeling

Dasatinib is supplied as 5 mg, 20 mg, and 50 mg film coated tablets containing dasatinib with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating contains hydroxypropyl methylcellulose, titanium dioxide, and polyethylene glycol (triacetin in the 5 mg film coated tablet). Tablets for clinical studies are supplied in high-density polyethylene bottles containing a desiccant and cotton. The bottles are heat-induction sealed with child resistant caps.

Each bottle is labeled in an open label manner. Labels contain, at a minimum, the following information: product name, tablet strength, batch number, directions for use, storage conditions, and appropriate caution statements.

Strength	Description
5 mg	white, round, film coated tablet
20 mg	white to off-white, biconvex, round, film coated tablet with either "20" or "BMS" debossed on one side and "527" on the other side

Strength	Description
50 mg	white to off-white, biconvex, oval, film coated tablet with either “50” or “BMS” debossed on one side and “528” on the other side

5.2 Storage

Bottles containing dasatinib tablets should be stored at 15° - 25°C.
Dasatinib will be stored in a secure area in the pharmacy supervised by investigational drug pharmacist who is responsible for dispensing investigational drug to study subjects.

5.3 Handling and Dispensing

Procedures for proper handling of anticancer drugs will be followed according to the institutional policies and procedures.
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. The lot numbers, dosing start dates and the number of tablets for each dosage strength must be recorded on the drug accountability pages of record for the site. The subject must be instructed to return all unused dasatinib in the provided packaging at each subsequent visit.

5.4 Drug Ordering

Initial Orders of dasatinib should be requested by completing the Dasatinib (Sprycel®) Drug Supply Form for Investigator Sponsored Studies and submitting the request form electronically via e-mail at least 5-7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday. The drug supply form will be sent to srcsupply@bms.com.
Initial drug supply will be provided for a 12-week treatment period per subject. Re-supply requests will be sent to the same email address. Please check “Re-supply” on the drug supply form. Re-supply requests should be submitted at least 5-7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

5.5 Drug Accountability

Investigational drug pharmacist will ensure that a current record of disposition of investigational product is maintained where the investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

a. amount received and placed in storage area
b. amount currently in storage area
c. label identification number or batch number and use date or expiry date
d. dates and initials of person responsible for each inventory entry/movement
e. amount dispensed to and returned by each subject, including unique subject identifiers

f. amount transferred to another area/site for dispensing or storage
g. non-study disposition (eg, lost, wasted, broken)
h. amount destroyed at study site, if applicable, and
i. retain samples sent to third party for bioavailability/bioequivalence, if applicable.
j. Dasatinib dispensing record/inventory logs and copies of signed packing lists must be maintained at the investigational site.
k. Batch numbers for dasatinib must be recorded in the drug accountability records.

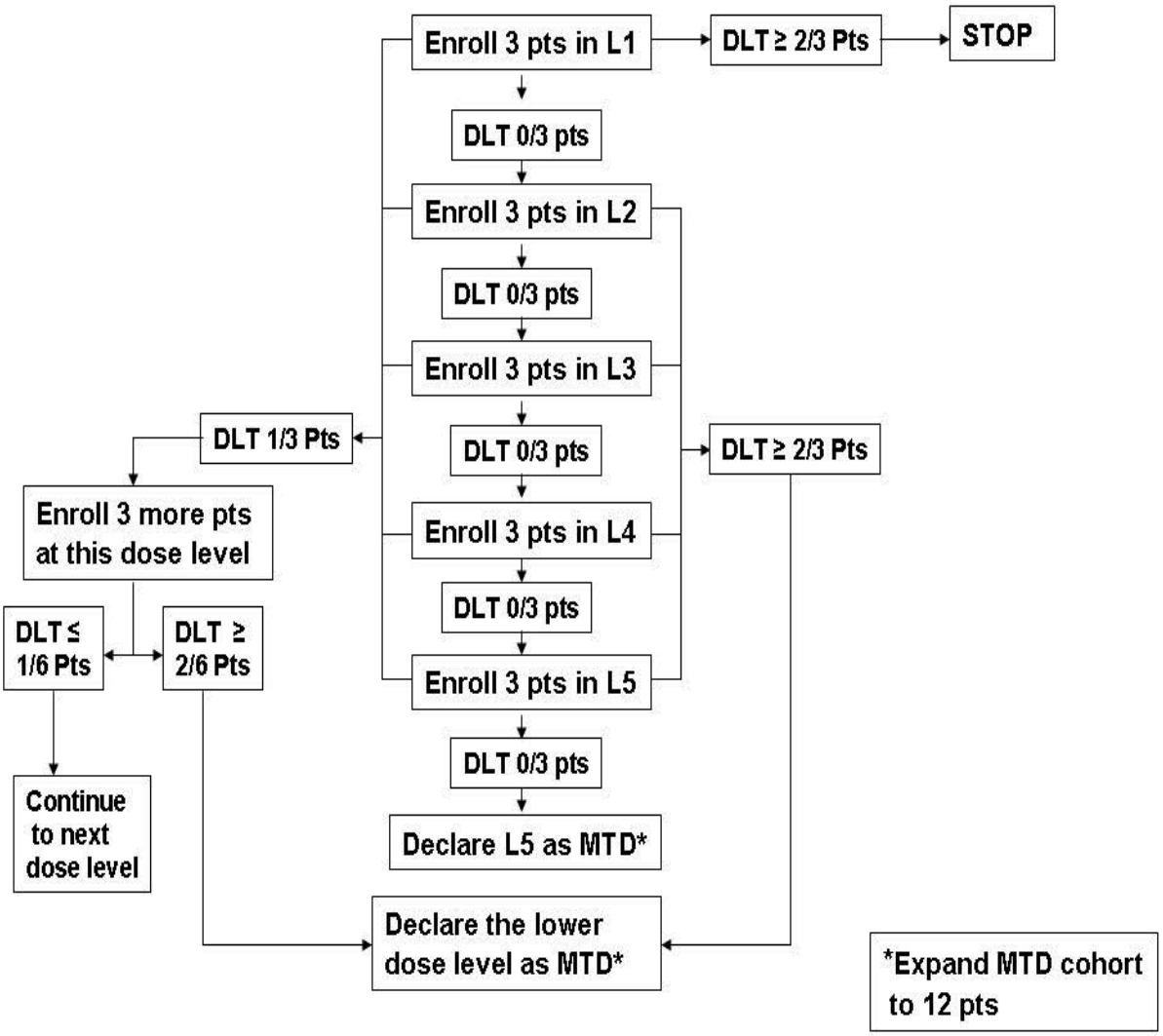
If dasatinib is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal will be maintained.

6. Treatment Schema

This is a phase 1 dose escalation study, using a standard 3+3 design. Dasatinib is administered orally once daily in the outpatient setting. Patients who are day 100-180 post transplant will be eligible. The treatment will be started as close to day 100 as possible. The range of days is provided to ensure that patients have recovered from toxicities associated with ASCT and are not deemed ineligible if they were recovering from any toxicity associated with ASCT at day 100.The starting dose of dasatinib is 20 mg daily. The increment of dose escalation is 20 mg per dose level. Thus, there will be 5 dose levels (20 mg, 40 mg, 60 mg, 80 mg and 100 mg, respectively) with 3 patients in each cohort. Patients will continue on dasatinib for 6 months.

Dose Level	Dasatinib Dose
L1	20 mg PO q 24 hrs
L2	40 mg PO q 24 hrs
L3	60 mg PO q 24 hrs
L4	80 mg PO q 24 hrs
L5	100 mg PO q 24 hrs

The dosing time may be adjusted as required. If doses are missed for toxicity, they should not be replaced. If a dose is not taken due to an error, it may be taken up to 12 hours later. If vomiting occurs within 30 minutes of intake, that dose may be repeated. Adverse events not related to dasatinib will be managed per standard of care for and use of growth factors is allowed at the discretion of treating physician.



7. Registration and Definitions

7.1 Protocol Registration

The Investigators will consider the patient for the study. All patient information will be forwarded to the Data Management office (313-576-9277)) for determination of eligibility. Upon informed consent and eligibility confirmation, the patient will be registered to the study.

7.2 Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the NCI Common Toxicity Criteria for Adverse Events CTCAE version 4[25]. The following treatment-related adverse events are considered dose-limiting toxicities (DLT) if related to dasatinib therapy and occur within 2 months of starting treatment:

a. Grade 4 neutropenia
b. Grade 4 thrombocytopenia
c. Grade 3 nausea and vomiting if it occurs despite maximal (5HT3 antagonist and corticosteroid) antiemetic therapy, and if hydration is required for >24 hours.
d. Grade 3 diarrhea despite patient compliance with anti-diarrheal therapy.
e. Grade 3 bleeding/hemorrhage (Requiring Transfusion)
f. Grade 4 hypertension
g. Grade 3 pericardial effusion (effusion with physiologic consequence)
h. Grade 2 pleural effusion (symptomatic and requires therapeutic intervention).

7.3 Large Granular Lymphocytosis- Definition

Lymphocytosis will be defined as absolute lymphocyte count of ≥ 2000 cells/mm^3 post ASCT with LGL phenotype identified by flow cytometry (CD3, CD8, CD16 and CD57) which constitutes ≥ 25% of T cell population or when LGL phenotype identified by flow cytometry (CD3, CD8, CD16 and CD57) constitutes ≥ 25% of T cell population without absolute lymphocyte count of ≥ 2000 cells/mm^3 .

7.4 Dose Escalation – Rules and Definitions

Patients who experienced DLT will discontinue treatment until toxicity improves at least by one grade. Treatment can be resumed with dose reduction by one level. There will be no intra-individual dose escalation. Dose escalation for the subsequent cohort will follow the guideline listed below:

a. As toxicity for other causes is very high in transplant patients, only DLTs that occur during the first 2 month of treatment will be used to guide dose escalation.
b. Patients who are not evaluable for DLT will be replaced.
c. If one patient experiences a DLT, an additional 3 patients will be entered at the same dose level to a maximum of 6 patients. If an additional DLT is encountered there will be no further dose escalation. Three patients will then be enrolled onto the next lower level. If there is no further toxicity noted, then this will be the MTD. If 6 patients were previously entered into the lower dose level, there would be no further patient entered to the lower dose level and the lower dose level will be declared MTD.
d. MTD is the highest dose at which no more than one of DLT is observed (among the first 6 patients treated and evaluable for toxicity for the purpose of cohort dose escalation decisions).

7.5 Stopping Rules

The stopping rule for dose escalation is determined by MTD as well as the occurrence of the desirable biological effect, i.e. lymphocytosis.

a. If MTD has not been reached but lymphocytosis was attained in the entire cohort of three patients, dose escalation will be terminated. Then, additional patients will be entered to a total of 12 patients to complete the phase II portion of this study.
b. If lymphocytosis was not observed in all 3 patients in the cohort, then dose escalation will continue until the MTD is reached.
c. Once the MTD had been reached, the phase II portion of the study will

commence with additional patient to be enrolled at the MTD dose to a total of 12 patients.

d. If MTD was not reached after completion of all 5 levels of the dose-escalation schema, then additional patients will be enrolled at the highest level to a total of 12 patients.

Drug will be discontinued after 6 months in all patients. For patients who develop LGL, blood counts will be followed as standard of care.

7.6 Discontinuation of Participants from Treatment

Participants MUST discontinue study treatment and withdraw from the study if any of the following occurs:

1. Withdrawal of informed consent (subject's decision to withdraw for any reason)
2. Progressive disease or recurrence of underlying malignancy at any time
3. Excessive toxicity despite dose reduction
4. Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
5. Pregnancy
   - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.
   - The investigator must immediately notify BMS if a study subject becomes pregnant.
6. Termination of the study by BMS.
7. Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

7.7 Statistical Considerations

7.7.1 Estimation of Probability of LGL Lymphocytosis: Estimation of the probability of LGL among 12 patients treated on MTD is as follows:

LGL Lymphocytosis Observed in a Cohort of Size 12		
N	Proportion	95% C.I.
3	0.25	0.09, 0.53
4	0.33	0.14, 0.61
5	0.42	0.19, 0.68
6	0.50	0.25, 0.75
7	0.58	0.32, 0.81
8	0.67	0.39, 0.86
9	0.75	0.47, 0.91
10	0.83	0.55, 0.95
11	0.92	0.65, 0.99
12	1.00	0.75, 1.00

With the information derived from this cohort of 12 patients, we will determine whether treatment with dasatinib is associated with the development of LGL lymphocytosis. According to our estimate based on the spontaneous LGL lymphocytosis in 46 out of 636 allograft recipients, if at least 3 of 12 patients in this study develop lymphocytosis then it is likely that dasatinib is associated with incidence of LGL lymphocytosis (upper 95% confidence limit greater than 0.50). This finding would provide the basis to proceed with larger clinical trials.

We estimate there would be a maximum of 30 patients enrolled in this entire study. In 2011, 114 allogeneic SCT and 158 autologous transplants were performed at KCC. With large number of patients available, we should be able to recruit 15-20 patients on the trial / yr with accrual duration being 2 years. The total study duration will be at the most 2-3 years

8. Study Monitoring

8.1 Pre-Enrollment Clinical and Laboratory Requirements (Within 1 week prior to enrollment on the protocol)

1. Baseline symptoms and signs of residual regimen-related toxicity or GVHD.
2. Pregnancy test in woman of child-bearing potential (WOCBP): urine or serum to be done within 72 hours of initiation of dasatinib.
3. Laboratory studies: CBC with differential, Electrolytes, BUN, creatinine, ALT, AST, T bilirubin, magnesium, phosphorus, PTT, PT, INR, peripheral blood flow cytometry to determine and enumerate mononuclear cells expressing CD3, CD8, CD16 and CD57
4. EKG

8.2 Clinical Monitoring

Patient will be seen every 2 weeks for first 2 months after starting dasatinib and once a month, thereafter or as clinically indicated. They will be evaluated for the development of GVHD at each visit and grading will be done according to the standard of care using consensus criteria for acute GVHD and NIH criteria for chronic GVHD. Development of GVHD is not included in the evaluation of dose-limiting toxicity of dasatinib, although it may be an important biologic phenomenon associated with the dasatinib administration because of the inhibitory effects of dasatinib on T-cell activation. The administration of dasatinib should not influence the decision on management of GVHD, e.g. initiation of steroids or secondary therapy for GVHD. The final visit should be conducted 30 days (+/- 7 days) after the last dose of study drug.

8.3 Laboratory Monitoring

1. CBC with differential weekly for the first month after starting dasatinib
2. CBC with differential, Electrolytes, BUN, creatinine, ALT, AST, T bilirubin, magnesium, phosphorus and will be obtained at each visit.
3. EKG once a month for first 2 months and then as clinically indicated.
4. Therapeutic drug monitoring such as immunosuppressives, antibiotics and IgG will be obtained as clinically indicated.
5. Tumor imaging studies, bone marrow aspiration and associated studies will be done according to standard of care.
6. Flow cytometry of peripheral blood will be obtained every 4 weeks till confirmation of LGL. Peripheral blood mononuclear cells will be examined for the

expressions of the following antigens: CD3, CD8, CD16 and CD57.

7. T-cell receptor gene rearrangement in patients who develop LGL expansion.

8.4 Sample Collection for Correlative studies: Peripheral blood mononuclear cells (PBMC) and serum will be collected from peripheral blood of participants (approximately 20 ml in 3 green top tubes and 1 red top tube) if they consent to collection and use of their cells. The PBMC will be separated by Ficoll Hypaque separation. They will be washed and stored in liquid nitrogen. Samples will be collected prior to initiation of dasatinib and at any time after development of LGL. These cells will be used in the future to provide preliminary data about the mechanism by which dasatinib may cause LGL. And also to test cytotoxicity of these cells against leukemia/ lymphoma cell lines. Serum will be stored for future correlative studies.

8.5 Study Calendar

Time and Events Schedule for Protocol

Procedure	Screening/ Baseline	Day 1	Day 15 (± 5 days)	Day 30 (± 5 days)	Day 45 (± 5 days)	Day 60 (± 5 days)	Once a month (± 7 days)	Final Visit (+/- 7 days)
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Safety Assessments								
Physical Examination	X							
Targeted Physical Examination		X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Assessment of Signs and Symptoms		X	X	X	X	X	X	X
Adverse Events Assessment		X	X	X	X	X	X	X
Laboratory Monitoring	X	X	X	X	X	X	X	X
Electrocardiogram	X			X		X		
Chest X-ray	X							
Pregnancy Test	X							

Time and Events Schedule for Protocol

Procedure	Screening/ Baseline	Day 1	Day 15 (± 5 days)	Day 30 (± 5 days)	Day 45 (± 5 days)	Day 60 (± 5 days)	Once a month (± 7 days)	Final Visit (+/- 7 days)
Immune Correlative Blood Draw	X							

9. Data Collection and Reporting

9.1 Outcomes: All the transplant essential data are collected and reported to CIBMTR. The data management team of the BMT program also maintains an ACCESS Database which mirrors the data field collected for the CIBMTR. Additional data field will be created to capture the pertinent data pertaining to this study to include lymphocyte count, results of flow cytometry data (till LGL is confirmed) and t cell gene rearrangement analysis (performed after LGL is confirmed). Laboratory results will be monitored clinically by the treating physician but will not be transcribed into the CRF. If abnormal values are considered an AE, then they will be entered into the AE log.

9.2 Assignment of Adverse Event Intensity and Relationship to Dasatinib: All adverse events, including those that are serious, will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (eg, medical, surgical) to prevent one of the other

serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

- All pregnancies, regardless of outcome, must be reported to BMS, **including pregnancies that occur in the female partner of a male study subject. <u>All</u> pregnancies must be followed to outcome.**
- Although overdose and cancer are not always serious by regulatory definition, these events should also be reported in an expedited manner

NOTE: The following hospitalizations are **not considered SAEs**:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

Nonserious Adverse Events

Nonserious adverse events are all adverse events that are not classified as SAEs.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

9.3 Collection and Reporting Adverse Events: Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record. The investigator must supply BMS and the IRB/IEC with any additional information requested, notably for reported deaths of subjects.

9.3.1 Serious Adverse Events: Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue for 30 days after the last administration of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs, whether considered related or unrelated to dasatinib, must be reported to BMS (by the investigator or designee) within 24 hours of study personnel becoming aware of the event. 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 be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

For studies conducted under an **Investigator IND**, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible **and no later than 7 days** (for a death or life-threatening event) **or 15 days** (for all other SAEs) **after the investigator's or institution's initial receipt of the information.** BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/
All SAEs should simultaneously be e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Email: Worldwide.safety@bms.com

If the investigator believes that an SAE is not related to the investigational product but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the potential relationship should be specified in the narrative section of the SAE report.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent within 24 hours to BMS. As follow-up information becomes available it should be sent within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

9.3.2 Nonserious Adverse Events: The investigator will begin collecting nonserious adverse event (NSAE) information once administration of the investigational product is initiated.

All identified NSAEs must be recorded and described in the medical record. If an ongoing NSAE worsens in its intensity, or if its relationship to the investigational product changes, a new NSAE entry for the event should be completed. NSAEs

should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for NSAEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with NSAEs at study completion should receive post-treatment follow-up as appropriate.

9.3.3 Overdose: An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

9.3.4 Pregnancy: Sexually active WOCBP must use an effective method of birth control during the course of the study, in such a manner that the risk of failure is minimized. Before enrolling WOCBP in this study, investigators must review the BMS-provided information about study participation for WOCBP. The topics include the following:

General Information
Informed Consent Form
Pregnancy Prevention Information Sheet
Drug Interactions with Hormonal Contraceptives
Contraceptives in Current Use
Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and of the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving dasatinib. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive dasatinib and must not continue in the study.

In addition, all WOCBP must be instructed to contact the investigator and/or other study personnel immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

The investigator must immediately notify BMS if a study subject becomes pregnant.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not on an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and information on the outcome provided once it is available. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Note: Any pregnancy that occurs in a female partner of a male study subject must be reported to BMS using the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed for the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Information regarding the course of the pregnancy, including perinatal and neonatal outcome, must be reported to BMS on the Pregnancy Surveillance Form.

9.3.5 Handling of Expedited Safety Reports: In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union, an event meeting these criteria is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). BMS will send investigators an expedited safety report (ESR) to notify them of such an event.
Other important findings that BMS may report as ESRs include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or the decision by BMS to end or temporarily halt a clinical study for safety reasons.
Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, BMS will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. When BMS has a written agreement with a local IRB/IEC, BMS will directly submit ESR(s). The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
In addition, BMS will report suspected serious adverse reactions (whether expected or unexpected) to the relevant health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

10. Ethical Consideration

10.1 Good Clinical Practice: This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).
The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.
All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

10.2 Protocol Review/IRB: This protocol is to be reviewed by peer medical review committee (PMRC) of Karmanos Cancer Institute and the institutional review board (IRB) of WSU. Informed consent is to be signed by the participating subjects.

10.3 Informed Consent: Investigators will ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) before clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society

11. DATA AND SAFETY MONITORING

Monitoring and Personnel Responsible for Monitoring
The Bone Marrow Transplant Research Team consisting of the PI, Collaborating Investigators, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Scheduled meetings will occur monthly once patients are registered to the protocol. These meetings will include the Principal Investigator, co-investigators, research nurse, data managers, and anybody deemed important to attend by the Principal Investigator.

During these meetings following points will be reviewed and discussed:

1. Safety of protocol participants (AE reporting).
2. Validity and integrity of the data.
3. Enrollment rate relative to expectations and the characteristics of participants.
4. Retention of participants and adherence to the protocol (potential or real protocol violations).
5. Completeness of collected data.

Reports of these Data and Safety Monitoring meetings will be kept on file in the Clinical Trials Office of the Karmanos Cancer Institute/Wayne State University. The Principal Investigator or one of the Co-Investigators will sign these reports. Quarterly, the monthly reports will be provided to the Karmanos Cancer Institute Data and Safety Monitoring Committee for independent oversight monitoring of the protocol as well to determine whether significant benefits or risks are occurring that would warrant study closure or continuation.

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