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PHASE II STUDY OF COMBINATION OF HYPER-CVAD AND DASATINIB IN PATIENTS WITH PHILADELPHIA (PH) CHROMOSOME POSITIVE AND/OR BCR-ABL POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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PROTOCOL SUMMARY

Objectives:

1. To evaluate the clinical efficacy (event-free survival) of an intensive short-term chemotherapy regimen (Hyper-CVAD program) given in combination with the tyrosine kinase inhibitor dasatinib for Philadelphia (Ph)-positive and/or BCR-ABL-positive acute lymphoblastic leukemia-ALL).

2. To evaluate other clinical efficacy (overall response rate and survival) and safety of an intensive short-term chemotherapy regimen (Hyper-CVAD program) given in combination with the tyrosine kinase inhibitor dasatinib for Philadelphia (Ph)-positive and/or BCR-ABL-positive acute lymphoblastic leukemia-ALL).

Rationale:

At least 70% of children with ALL can be cured. Adult ALL has a worse outcome, with expected CR rates of around 75%, and long-term event-free survival (EFS) rates ranging from 20% to 35%.The outcomeof patients with newly diagnosed Ph-positive ALL treated at MD Anderson Cancer Center who were treated with hyper-CVAD alone was recently reviewed. The CR rate was 90% with no induction deaths observed. The median survival was 16 months, and median CR duration (CRD) was 10 months. When compared to VAD or other conventional chemotherapy programs, hyper-CVAD was clearly superior in terms of CR rate (90% vs 55%, p=.002), failure rate (10% vs 37%, p=.014), and median disease-free survival (42 vs 29 weeks, p=.008). However, the event-free survival (EFS) rate was 14% and the 3-year survival and DFS rates were both less than 10%. Combination of hyper-CVAD with the tyrosine kinase inhibitor, imatinib mesylate, in Ph+-ALL has been evaluated and appears to be highly effective. Dasatinib (BMS-354825) is a potent, broad spectrum ATP-competitive inhibitor of several tyrosine kinases including BCR-ABL and SRC. Dasatinib is ~500-fold more potent than imatinib in inhibiting BCR-ABL by binding to both active and inactive conformations of c-ABL, whereas imatinib only binds to the inactive state. In in vitro studies, dasatinib demonstrated curative efficacy against several advanced human CML xenografts in severe combined immunodeficiency (SCID) mice, including an imatinib “acquired-resistance” model completely insensitive to imatinib. Furthermore, early clinical studies of dasatinib have demonstrated its high activity and limited toxicity in treating patients with Ph+-leukemias including patients with refractory Ph+-ALL. As such, it is expected that combinations of chemotherapy regimens used to treat patients with ALL and dasatinib are likely to be associated with better response rates and higher likelihood of eradication of minimal residual leukemia than those reported with imatinib.

Eligibility:

Inclusion:

1. Diagnosis of one of the following:

I - Previously untreated Ph-positive ALL [either t(9;22) and/or bcr-abl positive] (includes patients initiated on first course of hyper-CVAD before cytogenetics known)

II - After 1-2 courses of chemotherapy with or without imatinib mesylate (Gleevec)

- If they achieved CR, they are assessable only for event-free and overall survival, or
- If they failed to achieve CR, they are assessable for CR, event-free, and overall survival

III – Patients with relapsed Ph-positive ALL [either t(9;22) and/or bcr-abl positive] or lymphoid blast phase of chronic myeloid leukemia failing any therapy other than dasatinib.

These groups will be analyzed separately.

2. Age ≥ 18 years.

3. Zubrod performance status ≤ 2 (ECOG Scale, Appendix G).

4. Adequate liver function (bilirubin ≤ 3.0 mg/dl, unless considered due to tumor), and renal function (creatinine ≤ 3.0 mg/dl, unless considered due to tumor).

5. Adequate cardiac function as assessed clinically.

6. Signed informed consent

Exclusion:

1. An active serious infection not controlled by oral or intravenous antibiotics.

2. Treatment with any investigational antileukemic agents or chemotherapy agents in the last 7 days before study entry, unless full recovery from side effects has occurred or patient has rapidly progressive disease judged to be life-threatening by the investigator.

3. Active secondary malignancy other than skin cancer (e.g., basal cell carcinoma or squamous cell carcinoma) that in the investigator's opinion will shorten survival to less than 1 year.

4. Active Grade III-V cardiac failure as defined by the New York Heart Association Criteria (Appendix H).
   Uncontrolled angina, or MI within 6 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 (> 470 msec) unless corrected after electrolyte replacement
   Patients currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes (unless these can be changed to acceptable alternatives)

5. Prior history of treatment with dasatinib.

6. Pregnant and lactating women will not be eligible; women of childbearing potential should have a negative pregnancy test prior to entering on the study and be willing to practice methods of contraception. Women do not have childbearing potential if they have had a hysterectomy or are postmenopausal without menses for 12 months. 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.

7. 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)

8. Patients with documented significant pleural or pericardial effusions unless they are thought to be secondary to their leukemia

Treatment/Study Plan:

Hyper-CVAD plus dasatinib [Odd courses 1, 3, 5, 7]:

Cyclophosphamide (CTX) 300 mg/m^2 IV over 3 h every 12 hrs x 6 doses days 1,2,3 (total dose 1800 mg/m^2).
MESNA 600 mg/m^2/d IV continuous infusion daily for 24 hrs, starting approximately 1 hour prior to CTX and completing by approximately 12 hrs after the last dose of CTX.
Doxorubicin 50 mg/m^2 IV over 24 hrs via central venous catheter on day 4 after last dose of CTX given (infuse over 48 hrs in patients with reduced ejection fractions < 50%). May be given by shorter infusion if difficulty with central venous access.
Vincristine 2 mg IV on day 4 plus/minus 2 days and day 11 plus/minus 2 days.
Dexamethasone 40 mg IV or p.o. daily on days 1-4 plus/minus 2 days and days 11-14 plus/minus 2 days.
Dasatinib 100 mg po daily days 1-14 for course 1 (may shift +/- 4-5 days if therapy changed once results of cytogenetics known). For subsequent courses 3, 5, and 7 dasatinib 70 mg po daily continuously without interruptions unless due to toxicity.
GCSF 10 mcg /kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes > 1.0 x 10^9/L.
For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 on days 1 and 11 of cycles 1 and 3.
CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) on day 2 plus/minus 2 days. Cytarabine 100 mg intrathecally on day 7 plus/minus 2 days.

High-dose Methotrexate and cytarabine plus dasatinib [Even courses 2,4, 6, and 8]:

Methotrexate (MTX) 200 mg/m^2 IV over 2 hrs followed by 800 mg/m^2 over 22 hrs on day 1.
Solumedrol 50 mg IV approximately every 12 hrs for 6 doses days 1 to 3.
Dasatinib 70 mg po daily continuously without interruptions unless due to toxicity in courses 2, 4, 6, and 8.
Cytarabine 3 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2,3.
Reduce to 1 g/m2 IV over 2 hrs every 12 hrs for 4 doses on days 2 and 3 for:

Neurotoxicity
Age 60 years or greater.
Creatinine greater than or equal to 1.5 mg/dL.
Citrovorum rescue 50 mg IV or PO followed by 15 mg IV every 6 hours for 8 doses beginning 12 hrs +/- 2 hrs post MTX completion, i.e. approximately 36 hours from start of MTX.
GCSF 10 mcg/kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes greater than or equal to 1.0 x 10^9/L.
For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 on days 1 and 8 of cycles 2 and 4.
CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) day 2 plus/minus 2 days. Cytarabine 100 mg intrathecally day 7 plus/minus 2 days.

Maintenance, Intensifications, and Post-Remission Therapy
Maintenance therapy with dasatinib plus vincristine and steroids.
Maintenance chemotherapy with vincristine, and prednisone for approximately 24 months beginning at level 0 or lower dose level if prior toxicity required dose reduction of agents (titrate to keep ANC > 0.5 x 109/L and platelet count ≥ 30 x 109/L):
Vincristine 2 mg IV day 1 approximately every 28 days
Prednisone 200 mg P.O. daily days 1 to 5 approximately every 28 days with vincristine
dasatinib 100 mg po daily as tolerated.

Intensifications interrupting maintenance phase as follows:
1. Two intensifications with one course of hyper-CVAD plus dasatinib 100 mg po daily on days 1-14 or 70 mg po every day depending on tolerance, months 6 and 13 of maintenance.
2. Intensifications may be eliminated if the bone marrow PCR for bcr-abl is negative, or prior toxicity with intensive chemotherapy prohibits administration, or for other reasons judged valid by the Principal Investigator.
3. Dasatinib may be continued indefinitely after the 24 months of therapy at a dose tolerated by the patient.
4. For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 on days 1 and 11 of the intensification cycles in months 6 and 13. If patients do not receive the intensification cycles (due to reasons specified in 2. above), they may receive Rituximab alone 375 mg/m^2 on days 1 and 11 of maintenance cycle in months 6 and 13.

Disease Group: Leukemia

Treatment Agent: Adriamycin, Cyclophosphamide, Cytarabine, Dasatinib, Dexamethasone, Methotrexate, Vincristine, Prednisone, and Sulumedrol

Statistical Considerations:

1. The major study objective is to evaluate the event-free survival after hyper-CVAD plus dasatinib and achieve a 2-year EFS rate > 60% (based on reported data from hyperCVAD plus imatinib)[21]. The study is expected to accrue 115 patients (previously untreated, or after having received one or two prior course of chemotherapy, or relapsed) over approximately 2 years (referral pattern of 15 to 20 patients/year, accrual completed in 12 to 24 months), with an additional 12 months of follow-up. This will allow estimates of CR rates and disease-free survivals. Disease-free survival is the time from documented CR until relapse or death. Event-free

survival is the time from treatment until any failure (resistant disease, relapse, or death). The results will be compared descriptively to historical controls in terms of response, survival, toxicity, etc. (recently published data). A 95% confidence interval width will be approximately 11% for the CR rate estimated with 115 patients.

2. It is expected that the addition of dasatinib will achieve an efficacy superior to that obtained with the hyper-CVAD program alone and superior to hyper-CVAD plus imatinib mesylate. The trial will be monitored for possible early termination if there is evidence that the rate of response is not at least equivalent to that observed on the previous hyper-CVAD trial (26 CR of 29 patients). Observation of the following number of responses or fewer per number of patients evaluated will be regarded as evidence for termination: 2/5, 6/10, 10/15, 14/20, 18/25, 21/30, 25/35, 29/40, 33/45, 37/50, 41/55, 45/60, 49/65, 53/70, 57/75, 61/80, 65/85, 69/90,73/95,77/100,81/105, 85/110, or 89/115 on the basis that there is < 5% probability that efficacy is superior to that of hyper-CVAD. Using these guidelines, simulation results indicate the following expected results for several values of CR rate:

True rate of CR	Probability of early termination recommendation	Expected median sample size (25%, 75%)
0.6	>0.99	5 (5, 10)
0.7	0.98	15 (10, 35)
0.8	0.50	110 (20,115)
0.85	0.16	115 (115, 115)
0.9	0.03	115 (115, 115)
0.95	<0.01	115 (115, 115)

The molecular CR rate with hyper-CVAD is not known. Quantification of bcr-abl will be measured prospectively and analyzed by descriptive statistics.

3. Hyper-CVAD alone has very low toxicity (<5%). In this combination trial, if the toxicity rate is too high (Pr[Toxicity rate > 5%|Data] > 0.9), then the trial will be stopped (toxicity is defined at the beginning of this section). Specifically, the trial will be stopped if the number of patients experiencing unacceptable (as defined in section 9.0) toxicities /total number of patients is greater than or equal to 2/5, 3/12, 4/24, 5/37, 6/51, 7/65, 8/79, 9/100, or 10/109. The probability to stop the trial early is 0.02, 0.12, 0.73, 0.98 or >0.99 when the true toxicity rate is 0.03, 0.05, 0.10, 0.15 or 0.20 respectively.

4. A separate analysis will be carried out for previously treated patients (who have received one or two prior course of therapy). The historical number of Philadelphia-positive patients presenting after failure of one course of chemotherapy is one of 204 patients (< 1%). The historical rate of patients who achieved a CR after one course of chemotherapy continuing on hyper-CVAD at MDACC is 4 of 208 patients (2%). None were Ph-positive. Thus, the expected number of patients in this category is expected to be small. Patients who have failed one course of non-hyper-CVAD chemotherapy will be assessed for CR rate (historical CR rate for ALL overall is 5 of 6 [83%]) and disease-free survival. Patients presenting in CR will be assessed for disease-free survival and toxicity only.

5. A separate analysis will also be carried out for patients with relapsed disease, i.e. those with Ph-positive ALL or lymphoid blast phase of chronic myeloid leukemia who have failed (after achieving an initial response) prior therapy which does not include dasatinib. It is expected that

40 patients will be enrolled in this category alone. Patients will be evaluated for response, toxicity, event-free survival and disease-free survival.

6. Despite best efforts, the expected rate of allogeneic transplant is at best 20%, with failure due to lack of a suitable donor, age or performance status characteristics, comorbid conditions, or relapse of their disease prior to planned transplant. Patients who successfully undergo allogeneic transplant will be censored for disease-free survival at the time of transplant. Those patients who successfully complete allogeneic transplant prior to completion of the program will be replaced.

1. INTRODUCTION

1.0 BACKGROUND

1.1 Acute Lymphoblastic Leukemia (ALL)

Significant improvements in outcome for childhood acute lymphoblastic leukemia (ALL) have been observed, with complete response (CR) rates exceeding 90% with modern chemotherapy regimens.[1,2] At least 70% of children with ALL can be cured. Adult ALL has a worse outcome, with expected CR rates of around 75%, and long-term event-free survival (EFS) rates ranging from 20% to 35%.[3-7] Prognosis is influenced by age, performance status, organ function, white blood cell count, ALL phenotype (CALLA, T-cell, B-cell, Burkitt's or Burkitt's-like), karyotype [t(1; 19), t(4; 11), Philadelphia (Ph) chromosome], and time to achieve CR.

TABLE I. OUTCOME OF ALL PATIENTS BY RISK CATEGORY

Risk Category	% patients	% Event free survival
Standard (good)	25	50-60
Poor (WBC ≥ 5 x 10^9/L, ≥ 1 course therapy until CR)	75	≤ 20
Ph (+)	15	≤ 10

Kantarjian et al reported the overall results of hyper-CVAD in adult ALL,[8,9] with the subsets of Burkitt's type ALL and lymphoblastic lymphoma (LL) being detailed separately.[10,11] The outcome in both these subtypes has been significantly improved with CR rates of 81% and 96% in Burkitt's and LL, respectively. Overall survival for the LL group was improved to 75% at 3 years, with two-thirds of the patients remaining disease-free at 3 years compared to previously employed standard ALL regimens.[11]

Overall, the group had a median age of 40 years (range 15-90 years); 20% of the patients were aged 60 or older.[9] The majority of patients were considered high-risk for systemic relapse (74%) or CNS relapse (55%). Compared to the VAD (vincristine, doxorubicin, dexamethasone) program (DM85-43, DM88-015, DM88-150, DM89-123), the outcome with hyper-CVAD was significantly improved with respect to CR rate and overall survival.[8,9]

The overall CR rate with hyper-CVAD for all subtypes of ALL (n=288) was 92% with an induction mortality of 5% (all due to infections). Eleven percent of the patients required 2 courses to achieve CR; only 3% of the patients failed to achieve a remission with persistence of the leukemia. Leukocytosis and karyotypic abnormalities were not prognostic for achieving CR with the hyper-CVAD. Patients with poor performance status, hypoalbuminemia, hyperbilirubinemia and hepatomegaly had lower CR rates (in the range of 68% to 82%)mostly because of high induction mortality rate.[9] Side effects were similar to those reported in the recent update of the hyper-CVAD program in Burkitt's type ALL.[9,10]

Multivariate analysis identified the following factors to be adverse independent factors for CR duration ($P < 0.05$): age ≥45 years; leukocytosis ≥50 × 10^9/L; poor performance (ECOG score of 3-4); Ph-positive disease; FAB L2 morphology; > 1 course to CR; and bone marrow blasts > 5%

on Day 14. Central nervous system relapse was low, with a 7% incidence in low-risk patients (given 4 prophylactic intrathecal [IT] treatments), 1% in high-risk patients (I6 prophylactic ITs), and 6% in patients with unknown CNS relapse risk (8 prophylactic ITs).[9] The 5-year continuous CR rate was 35% with a 5-year survival of 36%. On multivariate analysis, pre-treatment factors associated with a shorter survival included older age, poor performance status, presence of hepatomegaly, high leukocyte count ($\geq 50 \times 10^9$/L), low platelet count, and presence of Ph+ disease. When compared to other published standard regimens of MSKCC,[5] SWOG,[6] Hoelzer et al,[4] and Larson et al,[7] the outcome was comparable even though the MDACC patients were older and prognostically less favorable.

1.2 Hyper-CVAD in Ph-positive ALL

The outcome with hyper-CVAD in newly diagnosed Ph-positive ALL was recently reviewed by Faderl et al.[12] Twenty-nine patients were treated with the regimen
from 1992 to 1997. Their median age was 41, and median leukocyte count was 23×10^9/L. The CR rate was 90% with no induction deaths observed. The median survival was 16 months, and median remission duration (CRD) was 10 months. When compared to VAD [n=32] (or other conventional chemotherapy programs, n=6), the hyper-CVAD was clearly superior in terms of CR rate (90% vs 55%, p=.002), failure rate (10% vs 37%, p=.014), and median disease-free survival (42 vs 29 weeks, p=.008). The event-free survival (EFS) rate was 14%. Despite improvements in CR rate and median CRD compared to earlier and other published conventional ALL programs, the 3-year survival and DFS rates were both less than 10%.

1.3 Single Agent Imatinib Mesylate in Chronic Myelogenous Leukemia and Ph-positive ALL

Imatinib mesylate is an inhibitor of a number of protein-tyrosine kinases including Bcr-Abl, the platelet-derived growth factor (PDGF) receptor and c-Kit, but not of other members of the Type III receptor kinase family, such as Flt-3 and Fms. Chronic myeloid leukemia (CML) represents an ideal disease for therapy with Imatinib mesylate given that the Bcr-Abl kinase plays a dominant role in the deregulated myeloid cell proliferation which is the hallmark of this disease. Inhibition of the Bcr-Abl kinase is most likely to have anti-leukemic effects during the chronic phase of CML since additional chromosomal abnormalities may drive the malignant process during accelerated phase and blast crisis. However, activity has already been observed during these later phases of the disease.

Imatinib mesylate shows selectivity for the Abl protein-tyrosine kinase at the in vitro, cellular and in vivo level.[13] The compound specifically inhibits proliferation of Bcr-Abl expressing cells. In colony forming assays using ex vivo peripheral blood and bone marrow samples, imatinib mesylate shows selective inhibition of Bcr-Abl positive colonies from CML patients[13] and ALL patients.[14] Beran et al also demonstrated significant suppression of phosphorylation of $p190^{bcr-abl}$.[14] In animal models, the compound shows potent anti-tumor activity against Bcr-Abl and v-Abl expressing cells at tolerated doses.[15]

Multiple studies have demonstrated the efficacy and safety of Imatinib mesylate in the treatment of all phases of chronic myeloid leukemia and have established it as the therapy of choice in this disease.[16-19]

Although the single agent response rate with imatinib mesylate in relapsed or refractory Ph+ALL is encouraging, ongoing maintained responses (after short follow-up) were observed in only a small number of patients treated by Ottmann et al.[20] They treated 56 patients with relapsed or refractory Ph(+) acute lymphoblastic leukemia (ALL; 48 patients) or chronic

myelogenous leukemia in lymphoid blast crisis (LyBC; 8 patients). Imatinib was given once daily at 400 mg or 600 mg. Imatinib induced complete hematologic responses (CHRs) and complete marrow responses (marrow-CRs) in 29% of ALL patients (CHR, 19%; marrow-CR, 10%), which were sustained for at least 4 weeks in 6% of patients. Median estimated time to progression and overall survival for ALL patients were 2.2 and 4.9 months, respectively. CHRs were reported for 3 (38%) of the patients with LyBC (one sustained CHR). Grade 3 or 4 treatment-related nonhematologic toxicity was reported for 9% of patients; none of the patients discontinued therapy because of nonhematologic adverse reactions. Grade 4 neutropenia and thrombocytopenia occurred in 54% and 27% of patients, respectively. Imatinib therapy resulted in a clinically relevant hematologic response rate in relapsed or refractory Ph(+) acute lymphoid leukemia patients, but development of resistance and subsequent disease progression were rapid.[20]

Several investigators have conducted in vitro assays to determine the effects of imatinib mesylate in combination with various antileukemic agents such as interferon-alpha, hydroxyurea, daunorubicin, and cytarabine. The combination of imatinib mesylate was additive or synergistic with interferon-alpha, daunorubicin, and cytarabine. Therefore, strategies such as combination imatinib with an effective ALL regimen such as hyper-CVAD have been evaluated.[21,22]

1.4 HyperCVAD plus tyrosine kinase inhibitors

Thomas et al have reported on the results of a phase II clinical trial of concurrent hyper-CVAD and imatinib to improve the above results of combination chemotherapy. The initial regimen of imatinib 400 mg orally daily days 1-14 of each course (fractionated cyclophosphamide, vincristine [VCR], doxorubicin and dexamethasone alternating with high dose methotrexate and cytarabine) was followed by imatinib, VCR and prednisone maintenance with intensifications months 6 and 13. Allogeneic stem cell transplant (SCT) was performed in CR if feasible. Preliminary results of first 20 patients treated were encouraging.[21] Recent modifications included increasing the dose of imatinib to 600 mg daily days 1-14 of course 1, then daily if tolerated with courses 2-8. Maintenance was extended to 24 months with imatinib indefinitely. At the time of the report, 43 patients with Ph+ ALL had been treated from April 2004 to July 2005. Thirty-six patients had active disease, either untreated (n=31) or refractory (n=5) to one induction course without imatinib; 7 patients were in CR after one induction course without imatinib. Of 35 evaluable patients, 33 (94%) achieved CR (1 induction death, 1 failed to meet platelet criteria for CR). Median time to response was 21 days. 13 patients underwent allogeneic SCT within a median of 3 months from start of therapy (range, 1-12). After a median follow-up of 3 years (range 1-48 months), 1 primary refractory patient relapsed at 12 months, 1 de novo patient had isolated CNS relapse, 2 patients relapsed after allogeneic SCT (no post SCT imatinib) and 2 patients changed therapy for persistent Ph+ metaphases (1 relapsing). Deaths in CR included 5 older patients without allogeneic SCT (1 osteomyelitis, 1 mucormycosis, 1 C. difficile colitis, 1 sudden death, 1 GNR sepsis) and 4 patients after allogeneic SCT (3 graft-versus-host disease, 1 GNR sepsis). Outcome with the hyper-CVAD and imatinib regimen continues to demonstrate favorable disease-free survival rates compared with hyper-CVAD alone, particularly for the de novo group. Use of higher dose imatinib concurrently appears to be feasible. Molecular response rates appear to be improved with the higher dose imatinib.

Dasatinib (BMS-354825) is a potent, broad spectrum ATP-competitive inhibitor of several tyrosine kinases including BCR-ABL and SRC. Dasatinib is ~260fold more potent than imatinib in inhibiting BCR-ABL by binding to both active and inactive conformations of c-ABL, whereas imatinib only binds to the inactive state. In in vitro studies, dasatinib demonstrated curative efficacy against several advanced human CML xenografts in severe combined immunodeficiency

(SCID) mice, including an imatinib "acquired-resistance" model completely insensitive to imatinib. Furthermore, early clinical studies of dasatinib have demonstrated its high activity and limited toxicity in treating patients with Ph+-leukemias including patients with refractory Ph+-ALL. As such, it is expected that combinations of chemotherapy regimens used to treat patients with ALL and dasatinib are likely to be associated with better response rates and higher likelihood of eradication of minimal residual leukemia than those reported with imatinib.

In a recently reported study (ASH 2005), a total of 78 patients with either Ph+ ALL (n=36) or CML in lymphoid blast phase (n=42) were treated with dasatinib. An overall hematological response rate of 73% including a complete hematological response rate of 52% was reported (31% in Ph+ ALL and 21% in CML lymphoid blast phase). Another 18% had no evidence of leukemia but with inadequate count recovery for a response. Complete cytogenetic responses were noted in 21 (58%) of Ph+ ALL patients and 15 (43%) of patients with CML in lymphoid blast phase. Therefore, dasatinib appears to be highly active in this setting and merits further investigation in combination with standard chemotherapy.

1.5 Summary of Results of Investigational Program for Dasatinib

Dasatinib has been administered to over 2000 subjects; the majority with CML refractory or intolerant to imatinib. Other target populations studied include Ph+ ALL and metastatic solid tumors. Additional background information on preclinical pharmacology, toxicology and pharmacokinetics may be found in the Investigator Brochure.[38]

1.5.1 Preclinical Anti-tumor Activity

1.5.1.1 In Vitro Molecular Studies

Dasatinib competes with ATP for the ATP-binding site in the kinase domain of selected protein tyrosine kinases (PTKs) and has been shown to inhibit at least five protein tyrosine kinases/kinase families: SRC family kinases, BCR-ABL, c-KIT, EPHA2 and the PDGFβ receptor. Dasatinib is much more potent than imatinib mesylate.

1.5.1.2. Cellular Studies

Dasatinib inhibits the BCR-ABL kinase with an *in vitro* IC_{50} of 3 nM, a potency that was 260-fold greater than that of imatinib mesylate (IC_{50} = 790 nM). In cellular assays, dasatinib killed or inhibited the proliferation of all BCR-ABL dependent leukemic cell lines tested to date. Dasatinib also demonstrated undiminished antitumor activity against several preclinically- and clinically-derived models of imatinib mesylate resistance. Evidence that SRC family kinase over expression 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.[38]

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.

1.5.2. In Vivo Studies

The activity of dasatinib against CML cells *in vitro* was reproduced *in vivo* against several human CML xenograft models grown subcutaneously in SCID mice. Against the K562/imatinib mesylate/R CML model, dasatinib was curative in 100% of the treated animals. In contrast, at its optimal dose and schedule, imatinib mesylate was inactive.

1.5.2.1. Preclinical Toxicology

Single or repeated oral administration of dasatinib principally affected the gastro-intestinal (GI) tract, including the liver, the 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 affect the immune system and bone turnover.

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, respirations and heart rate, blood pressure, or arterial oxygen saturation in single-dose, 10-day, or 1-month oral toxicity studies in monkeys.

Dasatinib was found to exhibit a profile of broad-spectrum platelet inhibition best typified by anti-platelet 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. This effect could potentially result in an increase in bone mineral density and a phenotype analogous to osteopetrosis.[38]

1.5.2.2. Clinical Pharmacokinetics

The pharmacokinetics of oral dasatinib have been extensively studied in normal volunteers and in subjects with leukemia. Studies in subjects with solid tumors are currently in progress.

After an oral dose of 70 mg, the recommended dose in recurrent CML, a peak level of 50 – 60 ng/mL is attained at 1 – 1.5 hours followed by an mean plasma half-life of 4 – 5 hours. Good bioavailability of the clinical tablet formulation has been documented. No accumulation has been observed in any schedule. Dose proportionality was documented over the entire dose range from 15 – 240 mg/day, although substantial interpatient variability has been observed. No significant effect of age, gender, race or disease state has been detected. No clinically-significant food effect was found, but antacid treatment markedly reduced exposure. Plasma protein binding has been estimated at 96% based on *in vitro* studies, and distributes freely into red blood cells (blood:plasma ratio ~1.8); estimated volume of distribution is approximately 9-fold greater than total body water.

Metabolism is primarily via CYP3A4, followed by biliary excretion; renal excretion is minimal. Clinically-significant increases in dasatinib exposure were observed with concomitant ketoconazole (a CYP3A4 inhibitor) and decreases with concomitant rifampicin (a CYP3A4 inducer). For additional detail, see the Investigator Brochure, Appendix I.

1.5.3. Experience in CML

Clinical experience with dasatinib in chronic phase (CP) CML is considered more applicable to patients with solid tumors than that in advanced-phase CML or Ph+ ALL, and will be summarized briefly.

One phase I study in CML, which included 40 subjects with progressive CP CML, was open for accrual from November, 2003, to April, 2005. Two Phase II studies in subjects with imatinib-resistant or –intolerant CP CML were open from February to July, 2005 (CA180013; n=424) and February to September, 2005 (CA180017; n=150). A Phase III randomized study in CP CML (CA180034; n=670) was open for accrual from July, 2005 to March, 2006.

In addition, over 1,000 subjects with recurrent advanced-phase CML or Ph+ ALL have been studied in Phase I (CA180002, n=44), Phase II (CA180005, CA180006, and CA180015, n=420), and Phase III (CA180035, n=613).[39,40,41,42,43,44]

Myelosuppression is part of the natural history of most hematologic malignancies and is also a common side effect of most chemotherapeutic agents. Thus, the level of hematologic toxicity observed may partly be the result of the underlying leukemic diagnosis and the extensive prior therapies in these patient populations.

Subsequently, two randomized phase III studies were launched (CA1800034 and CA1800035) to compare efficacy and safety of QD vs BID schedules in all phases of CML and of different daily dose in chronic phase CML. These studies have closed to accrual.

Two Phase I trials are in progress in patients with recurrent or progressive solid tumors, one with a BID and one with a QD schedule. To date, the safety profile in solid tumor subjects has been similar to that in CP CML subjects with the exception that myelosuppression (attributable to suppression of the Bcr-Abl-driven clone) has not been observed in solid tumor patients. No MTD has been reached in these studies.

1.5.4. Overall Risk/Benefit Assessment

The most common side effects of dasatinib are skin rash, fluid retention including pleural effusion, headache, fever, fatigue or weakness, gastrointestinal symptoms including bloating or flatulence, diarrhea or nausea, and discomfort in muscles or joints. Less common side effects include pneumonitis, constipation or abdominal pain, hypocalcemia, shortness of breath, neurologic changes such as tingling, confusion or dizziness. Minimal myelosuppression has been observed in subjects with solid tumors treated with dasatinib.

1.5.5. Phase II Experience

Subjects with AP CML, MyBP CML and LyBP CML or Ph+ ALL were enrolled in three Phase II studies using a dose of 70 mg BID. These studies are closed to enrollment. Data from 35 subjects on the START-A Study for Accelerated Phase CML have been reported.[38] Most patients were extensively treated with imatinib. Cytogenetic responses were documented in 13/24 patients, including 4 complete and 2 partial responses. Molecular response data is not yet available. Profound myelosuppression (Grade 4 thrombocytopenia and Grade 4 neutropenia) were reported in 20 and 17 patients respectively. Non-hematologic toxicities included diarrhea

(10 patients), nausea (5 patients), headache (5 patients), peripheral edema (3 patients) and pleural effusion (2 patients) all Grade 1 or 2.

Data from the first 34 patients from the START-B Study for CML, Myeloid Blast Crisis have been reported.[38] Major hematologic responses were seen in 16/29 (55%) of patients, with 7 complete hematologic responses and 9 with no evidence of leukemia. Cytogenetic responses were seen in 13 (45%) [21% complete, 12% partial). Molecular response data is not yet available. Grade 4 neutropenia occurred in 59% and grade 4 thrombocytopenia occurred in 56% of patients. Other non hematologic toxicity, usually Grade 1-2, included diarrhea (8 pts), rash (4 pts), nausea (3pts), peripheral edema (3pts) and pleural effusion (4 pts).

Data from the first 28 (13 CML-LBC and 13 Ph+ ALL) patients accrued to the START-L Study for CML Lymphoid Blast Crisis or Ph+ ALL have been reported.[38] Seventy seven patients were enrolled to the study. Thirteen patients had a MHR (7 CHR and 6 no evidence of leukemia). Twelve (12) patients had a cytogenetic response within 1-3 months (11 complete, 1 minor). The majority of patients had Grade 3 or 4 myelosuppression, in some cases pre-existing to study participation. Grade 4 hematologic toxicities include neutropenia (64%) and thrombocytopenia (71%), Non-hematologic toxicity included Grade 1-2 peripheral edema (3 pts), Grade 1 facial edema (2 pts), GI intolerance was infrequent.

More recent trials have demonstrated that once daily dosing is associated with a lower toxicity and similar efficacy.[45]

1.5.6 CD20 expression and rituximab

Immunophenotypic classification of acute lymphoblastic leukemia (ALL) has well recognized prognostic implications. The significance of CD20 expression has been evaluated in childhood precursor B-lineage ALL with conflicting results. In a recently published report, our group retrospectively analyzed the influence of CD20 expression on outcome in 253 adults with *de novo* precursor B-lineage ALL treated with either conventional (VAD/CVAD) or intensive (hyper-CVAD) frontline regimens in the pre-rituximab era. Overall, CD20 positivity > 20% was associated with lower 3-year rates of complete remission duration (CRD) (20% *vs* 55%, p<.001) and overall survival (OS) (27% *vs* 40%, p=.03). In the CD20 negative subset, the 3-year rates for CRD (58% *vs* 42%, p=.04) and OS (60% *vs* 28%, p<.001) were superior for hyper-CVAD compared with VAD/CVAD; rates were particularly favourable for the CD20 negative younger age group (68% and 85%, respectively). In contrast, 3-year CRD and OS rates were uniformly poor for the CD20 positive group regardless of therapy (27% or less). Multivariate analysis for event-free survival identified older age, leukocyte count >30 x 10^9/L, presence of Philadelphia chromosome, high systemic risk classification, and CD20 positivity as independent predictors of worse outcome. The authors concluded that CD20 expression in *de novo* adult precursor B-lineage ALL appears to be associated with a poor prognosis and suggested that the incorporation of monoclonal antibodies directed against CD20 into frontline chemotherapy regimens warrants investigation.[46] Another report by our group has demonstrated that the addition of rituximab to hyper-CVAD may improve outcome in adult BL or B-ALL, particularly in elderly patients.[47] Within our database we have seen that approximately 45% of patients with Ph+ ALL express the CD20 antigen.

2. STUDY OBJECTIVES

2.1. To evaluate the clinical efficacy (event-free survival) of an intensive short-term chemotherapy regimen (Hyper-CVAD program) given in combination with the tyrosine kinase inhibitor dasatinib for Philadelphia (Ph)-positive and/or BCR-ABL-positive acute lymphoblastic leukemia-ALL.

2.2. To evaluate other clinical efficacy (overall response rate and survival) and safety of an intensive short-term chemotherapy regimen (Hyper-CVAD program) given in combination with the tyrosine kinase inhibitor dasatinib for Philadelphia (Ph)-positive and/or BCR-ABL-positive acute lymphoblastic leukemia-ALL.

3. SELECTION OF PATIENTS

Patients will be selected from those referred to the Leukemia department at M D Anderson Cancer Center through the normal of process of referral. Eligible patients will be registered after the process of consenting on the MD Anderson protocol and data monitoring system.

3.1 Inclusion Criteria

1. Diagnosis of one of the following:

I - Previously untreated Ph-positive ALL [either t(9;22) and/or bcr-abl positive] (includes patients initiated on first course of hyper-CVAD before cytogenetics known)
II - After 1-2 courses of chemotherapy with or without imatinib mesylate (Gleevec)

- If they achieved CR, they are assessable only for event-free and overall survival, or
- If they failed to achieve CR, they are assessable for CR, event-free, and overall survival

III – Patients with relapsed Ph-positive ALL [either t(9;22) and/or bcr-abl positive] or lymphoid blast phase of chronic myeloid leukemia failing any therapy other than dasatinib.

These groups will be analyzed separately.

2. Age $\geq$ 18 years.

3. Zubrod performance status $\leq$ 2 (ECOG Scale, Appendix G).

4. Adequate liver function (bilirubin $\leq$ 3.0 mg/dl, unless considered due to tumor), and renal function (creatinine $\leq$ 3.0 mg/dl, unless considered due to tumor).

5. Adequate cardiac function as assessed clinically by physical examination.

6. Signed informed consent

3.2 Exclusion Criteria

1. Active serious infection not controlled by oral or intravenous antibiotics.

2. Treatment with any investigational antileukemic agents or chemotherapy agents in the last 7 days before study entry, unless full recovery from side effects has occurred or patient has rapidly progressive disease judged to be life-threatening by the investigator.

3. Active secondary malignancy other than skin cancer (e.g., basal cell carcinoma or squamous cell carcinoma) that in the investigator's opinion will shorten survival to less than 1 year.

4. Active Grade III-V cardiac failure as defined by the New York Heart Association Criteria (Appendix H).
   Uncontrolled angina, or MI within 6 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 (> 470 msec) unless corrected after electrolyte replacement
   Patients currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes (unless these can be changed to acceptable alternatives)

5. Prior history of treatment with dasatinib.

6. Pregnant and lactating women will not be eligible; women of childbearing potential should have a negative pregnancy test prior to entering on the study and be willing to practice methods of contraception. Women do not have childbearing potential if they have had a hysterectomy or are postmenopausal without menses for 12 months. 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.

7, 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)

8. Patients with documented significant pleural or pericardial effusions unless they are thought to be secondary to their leukemia.

4. TREATMENT OF SUBJECTS

4.1. Variations in dose reductions of the individual chemotherapy or the administration of dasatinib or supportive care dose schedules other than those suggested below are allowed in the best interest of patients. Such patients should be discussed with the principal investigator. Dose escalations for the intensive chemotherapy courses above those outlined in the protocol; however, are not allowed.

4.2. General Considerations

1. The hyper-CVAD (odd courses) will alternate with high dose methotrexate and cytarabine (even courses) administered on 21 or later day cycle (as count recovery allows), or earlier if count recovery allows.
    - Anti-emetic therapy with each course of intensive chemotherapy as needed.
    - G-CSF will be administered with each course after the completion of chemotherapy.
    - Next course may be started when granulocytes > 1.0 x $10^{9/}$L and platelets ≥ 50 x 10^9/L, following discontinuation of G-CSF. Courses may be started with dose reductions prior to full platelet recovery, if the treatment is delayed (e.g., greater than 28 days from last course).
    - Prophylactic antibiotics may be given with each course until neutrophil recovery to 500/μL or greater (or other antibiotics if being treated for active infection). Suggestions include: Levaquin 500 mg p.o. daily (or other quinolone) or trimethoprim-sulfamethoxazole double strength one tablet p.o. b.i.d. or other appropriate antibacterial agent. Fluconazole 200 mg p.o. daily or itraconazole 200 mg p.o. bid. or other appropriate antifungal agent. Valacyclovir 500 mg p.o. daily or acyclovir 200 mg p.o. b.i.d. or other appropriate antiviral agent.
    - Dasatinib 100 mg po daily will be given days 1 to 14 of the first course of intensive chemotherapy (course 1 doses may be adjusted ± 4-5 days if therapy changed from frontline protocol once cytogenetics known). For subsequent courses 2, 3, 4, 5, 6, and 7 dasatinib 70 mg po daily will be given continuously without interruptions unless due to toxicity.
    - Patients who enter the program in CR or with partial response after one course of therapy may start this program either with course 1 or 2 depending on their prior therapy, with the decision made by the Principal Investigator at study entry.
    - For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 on days 1 and 11 of cycles 1 and 3, and days 1 and 8 of cycles 2 and 4. For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 on days 1 and 11 of the intensification cycles in months 6 and 13. If patients do not receive the intensification cycles, they may receive Rituximab alone 375 mg/m^2 on days 1 and 11 of maintenance cycle in months 6 and 13.
    - In general 8 cycles of chemotherapy (4 hyperCVAD, 4 methotrexate plus cytarabine) will be administered in approximately 3 to 4 week intervals (depending on the recovery of blood counts). This will be followed by approximately 24 months of maintenance chemotherapy. Thereafter, dasatinib may be continued indefinitely. Modifications thought to be in the best interest of the patient are allowed after discussion with the principal investigator. Patients will be followed indefinitely for relapse and survival.
    - All patients should have a chest radiograph before each course of methotrexate and cytarabine; methotrexate dose will be adjusted as indicated below for pleural effusions.

2. Total number of prophylactic intrathecal treatments for newly diagnosed patients will be as follows (2 intrathecals of methotrexate on day 2 ± 2 days and cytarabine day 7 ± 2 days with each course of chemotherapy until total number reached):
    - Indeterminate or high-risk disease: 8 intrathecals Serum lactate dehydrogenase (LDH) > 1400 U/L; or Proliferative index %S + G2M ≥ 14%; or De novo LDH and/or proliferative index unknown
    - Low-risk disease: 6 intrathecals
      None of the above features

- If the patient has been previously treated, and has had prior intrathecal therapy, or prior CNS disease, discuss management of CNS with the principal investigator.
- If active CNS disease: Consider methotrexate alternating with cytarabine (see sections 5.3 and 5.4) twice weekly until CSF clear; then once weekly for 4 weeks, then back to prophylactic schedule. Consider XRT to the base of the skull, particularly with cranial nerve root involvement (cranial nerve palsies). Alternative methods of treating CNS disease are allowed if appropriate for the patient (e.g., intrathecal liposomal cytarabine, or others). Modifications to the regimen thought to be necessary for administration of XRT are allowed after discussion with the principal investigator.
- CSF specimens obtained during therapeutic and diagnostic lumbar punctures will be evaluated for presence of minimal residual leukemia and β-2 microglobulin: (1) first spinal tap at M D Anderson, (2) first lumbar puncture after CR is documented (3) last spinal tap during the consolidation therapy. Variations in these time-points are permitted if felt to be appropriate by the treating physician.
- CSF specimens obtained during therapeutic and diagnostic lumbar punctures will be evaluated for dasatinib concentrations. Up to 3 specimens per patients will obtained during any of the scheduled lumbar punctures and sent to the laboratory of Dr Merrill Egorin, MD at the University of Pittsburg Cancer Institute.

3. Maintenance phase chemotherapy will be given after completion of the 8 courses of intensive chemotherapy as outlined in Section 4.6.
   Patients may be moved from the intensive chemotherapy to the maintenance phase prior to completion of 8 cycles of chemotherapy (or for transitional treatment prior to allogeneic bone marrow transplant) if intolerant after discussion with the Principal Investigator.

4.3. Hyper-CVAD plus dasatinib [Odd courses 1, 3, 5, 7]:

- Cyclophosphamide (CTX) 300 mg/m^2 IV over 3 h every 12 hrs x 6 doses days 1,2,3 (total dose 1800 mg/m^2).

- MESNA 600 mg/m^2/d IV continuous infusion daily for 24 hrs, starting approximately 1 hour prior to CTX and completing by approximately 12 hrs after the last dose of CTX.

- Doxorubicin 50 mg/m^2 IV over 24 hrs via central venous catheter on day 4 after last dose of CTX given (infuse over 48 hrs in patients with reduced ejection fractions < 50%). May be given by shorter infusion if difficulty with central venous access.

- Vincristine 2 mg IV on day 4 $\pm$ 2 days and day 11 $\pm$ 2 days. Vincristine is not myelosuppressive and may be given while patients are receiving G-CSF; no known adverse effects have been observed with the 2 agents given together.

- Dexamethasone 40 mg IV or p.o. daily on days 1-4 $\pm$ 2 days and days 11-14 $\pm$ 2 days.

- Dasatinib 100 mg po daily days 1-14 for course 1, (may shift $\pm$ 4-5 days if therapy changed once results of cytogenetics known).). For subsequent courses 3, 5, and 7 dasatinib 70 mg po daily continuously without interruptions unless due to toxicity.

- GCSF 10 mcg /kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes > 1.0 x 10^9/L. G-CSF may be stopped earlier for bone pain or other related toxicity. Minimum time allowed between courses is 14 days.

- For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 on days 1 and 11 of cycles 1 and 3.

- CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) on day 2 (± 2 days). Cytarabine 100 mg intrathecally on day 7 (± 2 days). Administer in 3 to 5 cc of preservative-free normal saline.

4.4. High-dose Methotrexate and cytarabine plus dasatinib [Even courses 2,4, 6, and 8]:

- Methotrexate (MTX) 200 mg/m^2 IV over 2 hrs followed by 800 mg/m^2 over 22 hrs on day 1. Total duration of administration is 24 hours (2 plus 22 hours).

- Solumedrol 50 mg IV approximately every 12 hrs for 6 doses days 1 to 3.

- Dasatinib 70 mg po daily continuously without interruptions unless due to toxicity in courses 2, 4, 6, and 8.

- Cytarabine 3 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2,3.
  Reduce to 1 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2 and 3 for:
    - Neurotoxicity (≥ grade 2 cerebellar or other cytarabine-related CNS toxicity as per Appendix F), or
    - Age 60 years old or greater.
    - Creatinine ≥1.5 mg/dL.

- Citrovorum rescue 50 mg IV or PO followed by 15 mg IV or PO every 6 hours for 8 doses beginning 12 hrs ± 2 hrs post MTX completion, i.e. approximately 36 hours from start of MTX.

- Check MTX levels around time 0h, 24h and 48h post completion of MTX unless methotrexate cleared:
    1. if > 20 μM at time 0, hold cytarabine and repeat level; if continues to be > 20 μM reduce cytarabine to 1 g/m^2 IV over 2 hours every 12 hours for 4 doses on days 2,3. Begin citrovorum rescue as described above.

    2. if > 1 μM at 24hrs or > 0.1 μM at 48 hours, increase citrovorum rescue to 50 mg IV or PO every 6 hrs until serum methotrexate level is < 0.1 μM. Clearance to levels 0.15 μM or less is acceptable in patients with normal renal function.

    3. Citrovorum rescue may be increased further for elevated methotrexate levels or delayed clearance

- GCSF 10 mcg/kg (rounded) subcutaneously daily (or 5 mcg /kg twice daily) until post-nadir granulocytes ≥ 1.0 x 10^9/L. G-CSF may be stopped earlier for bone pain or other related toxicity. Minimum time allowed between courses is 14 days (e.g., day 14).

- For patients with CD20 expression (≥ 20% by flow cytometry) Rituximab 375 mg/m^2 on days 1 and 8 of cycles 2 and 4.

- CNS prophylaxis: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) day 2 ± 2 days. Cytarabine 100 mg intrathecally day 7 ± 2 days. Administer in 3 to 5 cc of preservative-free normal saline.

4.5. Suggested Standard Dose Reductions/modifications:

1. Cytarabine 1 g/m^2 IV over 2 hrs every 12 hrs for 4 doses on days 2 and 3.

    - Creatinine ≥ 1.5 g/dL.
    - Time "0" MTX level > 20 μM (on repeat level). Follow the directions outlined in section 4.4, Bullet #4.
    - Age ≥ 60 years.
    - Grade 2 or greater CNS toxicity.

2. Vincristine 1 mg IV days 4 and 11 (50% reduction).

    - Bilirubin > 2.0 g/dl and ≤ 3.0 g/dl
    - Clinically significant grade 2 peripheral neuropathy persisting greater than 2 weeks.
    - Eliminate vincristine for grade 3-4 peripheral neuropathy, including grade 3-4 ileus suspected to be related to vincristine, bilirubin > 3.0 g/dL.

3. Doxorubicin:

    - Reduce by 50% for bilirubin 2 to 3 g/dl, by 75% for bilirubin 3 to 5 g/dl. Eliminate if bilirubin > 5 g/dL.
    - Administer over 48 hours in patients with borderline reduced (< 50%) ejection fractions.
    - Contraindicated in patients with prior history of known Type I hypersensitivity or anaphylactic reactions to doxorubicin.

4. Methotrexate:

    - Consider reduction by 25%-50% for grade 3 or worse mucositis with previous methotrexate course.
    - Reduce by 50% for calculated creatinine clearance 10-50 ml/min, if < 10 ml/min, hold methotrexate.
    - Reduce by 25% to 75% for delayed excretion and/or nephrotoxicity with previous methotrexate course.
    - Reduce by 50% for pleural effusion or ascites (drain effusion if possible). All patients should have a chest radiograph prior to each course of methotrexate and cytarabine.

5. Dasatinib

    - Grade III-IV non-hematological toxicity:
      Consider holding until grade I or less.
      May consider resuming at 70 mg po daily (if the patient is receiving 100 mg po daily in the first cycle) or resuming at 50 mg po daily (if the patient is receiving 70 mg po daily in the subsequent cycles) for grade III or IV non-hematological toxicity; consider discontinuing if grade III or IV non-hematological toxicity recurs.
    - Other modifications should be discussed with the Principal Investigator

    - During intensive phase of chemotherapy, consider holding dasatinib if ANC not > 1.0 x 10^9/L or if platelet count not > 30,000 by day 21 of the cycle. Resume dasatinib upon recovery to ANC > 1.0 x 10^9/L and platelet count ≥ 50,000 (without need for G-CSF or platelet transfusions) if able to tolerate. Resume dasatinib at the dose of 70 mg po daily if time to recovery < 1 week. Resume dasatinib at 50 mg po daily if time to recovery > 1 week.

    - If there is inadequate response to dasatinib 70 mg po daily and in the absence of significant (grade III or IV toxicity) may consider increasing the dose of dasatinib to 100 mg po daily or 70 mg twice daily or 140 mg po daily.

    - Dasatinib may be administered once or twice daily if felt to be in the patient's best interest; once daily is likely to be associated with reduced toxicity.

6. Dose reductions exceeding those above or in other agents, e.g., citrovorum, antibiotics, antiemetics, etc., are allowed after discussion with the Principal Investigator.

4.6. Maintenance, Intensifications, and Post-Remission Therapy

- Maintenance therapy with dasatinib plus vincristine and steroids.

Maintenance chemotherapy with vincristine, and prednisone for approximately 24 months beginning at Dose level 0 or lower dose level if prior toxicity required dose reduction of agents (titrate to keep ANC > 0.5 x 10^9/L and platelet count ≥ 30 x 10^9/L) (See table below):

Vincristine 2 mg IV day 1 approximately every 28 days
Prednisone 200 mg P.O. daily days 1 to 5 approximately every 28 days with vincristine
dasatinib 100 mg po daily as tolerated.

- Suggested maintenance chemotherapy dose adjustments are as below:

Level	VCR (mg)	Prednisone (mg)	Dasatinib (mg)
+1	2	200	70 bid or 140 po daily
0	2	200	100 po daily
-1	1	100	70 po daily
-2	0	50	50 po daily

1. Prednisone
   Dose should remain at 200 mg unless steroid myopathy or other significant toxicity occurs.

Prednisone not required to be dose adjusted for hyperglycemia.

2. Vincristine
   Decrease by one dose level for grade 2 peripheral neuropathy persisting longer than 2 weeks.
   Discontinue for grade 3 or greater peripheral neuropathy persisting longer than 2 weeks.
3. Dasatinib
   Grade III-IV non-hematological toxicity:
   Consider holding until grade I or less.
   May resume at dose of 70 mg po daily for grade III or IV non-hematological toxicity; consider discontinuing if toxicity recurs.
   Other modifications should be discussed with the principal investigator.
   If ANC < 0.5 x 10^9/L or platelets < 30 x 10^9/L:
   Hold until ANC > 1 x 10^9/L and platelet count > 50 x 10^9/L, and wait for recovery.
   If recovery occurs in < 2 weeks, resume at same dose.
   If recovery occurs > 2 weeks, resume at 80 mg po daily level.
   Recurrent neutropenia may be managed with dose modifications after discussion with the Principal Investigator.
   If there is inadequate cytogenetic/molecular response, the dose of dasatinib may be increased to 70 mg twice daily or 140 mg po daily.

- Intensifications interrupting maintenance phase as follows:

1. Two intensifications with one course of hyper-CVAD plus dasatinib 100 mg po daily on days 1-14 or 70 mg po every day depending on tolerance, months 6 and 13 of maintenance.

2. Intensifications may be eliminated if the bone marrow PCR for bcr-abl is negative, or prior toxicity with intensive chemotherapy prohibits administration, or for other reasons judged valid by the Principal Investigator.

3. Dasatinib may be continued indefinitely after the 24 months of therapy.

4.7. Monitoring Plan

The hyper-CVAD regimens have been conducted since 1992, and have accrued over 500 patients on similar induction-consolidation-maintenance phases. The treatment-associated side-effects, both myelosuppressive and extramedullary are well-known, and have been described and reported. Known and anticipated side effects of this regimen (Appendix E) will not be reported as individual ADRs, according to the Code of Federal Regulations and ICH guidelines BCGP Section 4.1 I. I,p. 24. This also complies with the NCI CTEP-CTC guidelines which state that for expected events grade 4 myelosuppression or other grade 4 events that do not require expedited reporting will be specified in the protocol (Section 12.0).

The trial will be closely monitored for any adverse effect of dasatinib on the expected toxicity and CR rate for the first 10 patients. An accrual rate of 1 to 2 patients per month is expected. The first 10 patients will receive their entire 8 courses of chemotherapy treatment in Houston in order to be closely monitored. Early stopping for excessive toxicity will be considered if early induction mortality exceeds 20%. Thus the study will be stopped if deaths/treated patients is >1/5 or >2/10. The trial will also be stopped if the number of patients experiencing unacceptable toxicities (as

defined in section 9.0)/total number of patients is greater than or equal to 2/5, 3/12, 4/24, or 5/37. The continuation of study at the above doses will be dependent on clear evidence that the addition of dasatinib will not adversely affect these parameters as compared to previous regimens including hyperCVAD and hyperCVAD plus gleevec.

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Recognizing there will be instances where patient cannot receive all of their therapy at M.D. Anderson, the following monitoring plan will be implemented as feasible:

All patients who enter therapy with active disease will receive their first course of therapy at M. D. Anderson, and will be monitored until CR or failure to respond.

Subsequent courses of therapy may be given by a local physician under direction of the M. D. Anderson Cancer Center treating physician or the principal investigator (The first 10 patients will receive their entire 8 courses of therapy at M D Anderson). The patient will be given a copy of the protocol, instructions, and the M. D. Anderson contact numbers for the principal investigator and research nurse, with telephone and fascimile numbers. The referring physician will be identified, contacted and the protocol details discussed. It will be detailed that therapy should not be administered unless carrying out handwritten chemotherapy orders compiled by the principal investigator or treating physician at M. D. Anderson. A recent weight to calculate BSA, review of laboratory data, review of compliance with dasatinib, and review of toxicities will be performed. Orders will be written by M. D. Anderson treating physician or the principal investigator after discussion of the patient's status with the treating physician.

Physicians will be requested to sign a letter stipulating these items, and indicating their willingness to defer all decisions regarding the chemotherapy and dasatinib to MDACC. Documentation will be requested from outside physicians, including drug administration records to ensure that the orders were followed. Outside physicians will be asked to contact MDACC for prior approval of any decisions or changes related to the chemotherapy or dasatinib administration.

5. CONCOMITTANT MEDICATIONS

Short-acting antacid agents may be taken, but it is recommended that these not be taken from 2 hours before to 2 hours after dosing of dasatinib.

Dasatinib may be taken with meals. The dosing time may be adjusted as required (for bid schedules recommend skipping doses that are missed by 6 hours, for qd dosing recommend skipping doses that are missed by more than 12 hours). If doses are missed for toxicity, they should not be replaced. If vomiting occurs within 30 minutes of intake, that dose may be repeated. If needed, tablets should be dissolved in strong juice rather than crushed.

Patients currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes (including: 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) should change these to acceptable alternatives.

Medications that inhibit platelet function (i.e., aspirin, dipyridamole, epoprostenol, eptifibatide, clopidogrel, cilostazol, abciximab, ticlopidine, and any non-steroidal anti-inflammatory drug) or

Anticoagulants (warfarin, heparin/low molecular weight heparin [e.g., danaparoid, dalteparin, tinzaparin, enoxaparin]) should be avoided as much as possible.

Exceptions include low-dose warfarin for prophylaxis to prevent catheter thrombosis, and for heparin-flushes for IV lines. If patients develop deep vein thrombosis during the course of therapy or are receiving anticoagulation for indications such as recent thrombosis or artificial heart valves these drugs may be continued with close monitoring of the patients.

When used concomitantly with drugs known to be CYP3A4 inducers such as rifampin, consider increasing the dose of dasatinib with careful monitoring for toxicity. When used concomitantly with strong CYP3A4 inhibitors, such as ketoconazole, consider decreasing the dasatinib dose.

Proton pump inhibitors may be administered concomitantly with dasatinib if felt to be in the patient's best interest.

6. STUDY PROCEDURES

6.0. PRETREATMENT EVALUATION

1. History and physical examination, documentation of disease.
2. CBC, platelet count, differential, total bilirubin, creatinine, SGPT, uric acid.
3. Bone marrow aspirate and cytogenetics. Quick Philadelphia screen is acceptable.
4. EKG
5. Pregnancy test in patients of appropriate age and menopausal state
6. Echocardiogram or MUGA scan to assess cardiac function

6.1. EVALUATION DURING STUDY

1. 1-2 times weekly CBC, platelet count and differential for course 1 (if in CR at study entry every 1-3 weeks), then every 1-3 weeks during 8 cycles of chemotherapy then every 4-6 weeks during maintenance.
2. Total bilirubin, SGPT, creatinine weekly for course 1, then every 1-4 weeks during intensive chemotherapy cycles, then every 4-8 weeks during maintenance.
3. Bone marrow aspiration for course 1 (in patients enrolled with active marrow disease) on day 14 $\pm$ 5 days and day 21 $\pm$ 5 days (or at the time of hematologic recovery) if day 14 bone marrow with residual leukemia.
4. Evaluate for toxicity assessment
5. EKG – Recommended at baseline and week 4
6. A chest radiograph should be performed at baseline and before each course of methotrexate to evaluate for the presence of pleural effusions

	Intensive treatment plus dasatinib								
Odd: hyperCVAD Even: MTX/Cytarabine Dasatinib days 1-14	Pre-Rx	1	2	3	4	5	6	7	8
Informed consent	X								
EKG	X		X						
History + physical	X								
CBC/Diff/Platelet	X	X	X	X	X	X	X	X	X
SGPT, Bili, creat	X	X	X	X	X	X	X	X	X
Marrow, CG	X								
Pregnancy test (If indicated)	X								
Chest X-ray	X		X		X		X		X
Toxicity assessment		X	X	X	X	X	X	X	X

7. EFFICACY AND SAFETY ASSESSMENTS

7.0. CRITERIA FOR RESPONSE

1. Complete Remission (CR): Normalization of the peripheral blood and bone marrow with 5% or less blasts in normocellular or hypercellular marrow with a granulocyte count of 1 x 10^9/L or above, and platelet count of 100 x 10^9/L. Complete resolution of all sites of extramedullary disease is required for CR.
2. Molecular CR: Same as for CR with RT-PCR negativity for bcr-abl.
3. Partial Response (PR): As above for CR except for the presence of 6-25% marrow blasts.
4. Relapse and resistant disease will be defined based on morphological assessment of bone marrow and peripheral blood.

7.1. EVALUATION OF TOXICITY

1. Toxicities will be graded according to the NCI Common Toxicity Criteria for Adverse Event Reporting Version 3.0 (Appendix B). The toxicity of the regimen will be monitored continuously during the course of the study.

7.2. CRITERIA FOR REMOVAL FROM THE STUDY

1. Unacceptable toxicity judged to be related to therapy by the investigator, as defined by the NCI Common Toxicity Criteria (Appendix B). (Irreversible or prolonged (greater than 42 days) grade 4 hematological toxicity or grade 4 non-hematological toxicity thought to be related to dasatinib).
2. Non-compliance by the patient with protocol requirements or patient's request to be removed from the study.

7.3 DEFINITION OF STUDY END-POINTS

1. Disease-free survival is the time from documented complete response until relapse or death.

2. **Event-free survival** is the time from the first day of treatment until any failure (resistant disease, relapse, or death).

3. Overall response rate is defined as the percentage of patients achieving complete remission and partial remission as defined above.

4. Overall survival is defined as the time from the first day of treatment to time of death from any cause.

8. STUDY DRUG(S)

8.0 The background drug information for the following agents is attached as an appendix to the back of this protocol (Appendix F).

Vincristine
doxorubicin
G-CSF
cyclophosphamide
methotrexate
cytarabine
Mesna

8.1. Dasatinib

8.1.1. Introduction

Dasatinib (BMS-354825) is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinases/kinase families: BCR-ABL, SRC, c-KIT, PDGFR, and ephrin (EPH) receptor kinases, each of which has been strongly linked to multiple forms of human malignancies. BCR-ABL is a constitutively active protein tyrosine kinase (PTK) present in >90% of patients with CML and 15-30% of adult patients with ALL. Numerous studies have demonstrated that BCR-ABL activity is required for the transforming ability of this protein.[23,24] With the approvals of imatinib mesylate (Gleevec®, Glivec®, STI-571), inhibition of BCR-ABL has proven effective in management of CML, particularly chronic phase where the hematologic response rate is >90%. However, patients with advanced disease are much less sensitive to imatinib, and experience less frequent and transient responses.[16] Clinical refractoriness to imatinib has been associated with the development of multiple mechanisms of drug resistance, including BCR-ABL gene mutation/over-expression and activation of selected SRC kinases.[25,26] Dasatinib is ~260fold more potent than imatinib in inhibiting BCR-ABL by binding to both active and inactive conformations of c-ABL, whereas imatinib only binds to the inactive state. This difference in binding may be responsible for the vastly increased potency of dasatinib over imatinib.

Dysregulation of SRC function has been strongly linked to the pathogenesis of human cancers. Tumor cells with increased metastatic potentials have been shown to have activated SRC kinase, providing strong evidence linking SRC activation with tumor progression and metastasis.[27] In epithelial cancers, SRC promotes metastasis by disrupting and/or weakening the normally strong cell-cell adhesions. At the same time, SRC increases the cell-matrix interaction and enhances cell migration.[28,29]

c-KIT is the receptor for stem-cell factor (SCF).[30] Binding of SCF to the KIT receptor results in autophosphorylation and activation of its kinase activity. These initial events trigger several down-stream signaling cascades that regulate cellular activities such as proliferation, apoptosis, and motility.[31] Specific somatic mutations in c-KIT resulting in kinase activation have been shown to cause certain forms of cancer and have been strongly implicated in the pathogenesis of gastrointestinal stromal tumors (GIST).[32,33] Imatinib, which inhibits mutant forms of c-KIT found in GIST, has been effective in the treatment of GIST.[34] Another type of mutation, involving the receptor kinase domain, is found in most cases of adult sporadic mastocytosis, germ cell tumors, acute myelogenous leukemia (AML), and sinonasal natural killer/T-cell lymphoma.[35] This latter form of mutant KIT has been shown to be insensitive to imatinib. Other types of tumors in which c-KIT dysregulation has been implicated include small cell lung cancer (SCLC), neuroblastoma, melanoma, ovarian carcinoma, and breast carcinoma.[35]

Dysregulations of PDGF and PDGFR expression and function have been implicated in many forms of solid tumors, including glioblastoma, meningiomas, melanomas, neuroendocrine tumors, ovarian, pancreatic, gastric, lung, and prostate cancer.[36] There is strong evidence supporting autocrine PDGF stimulation of tumor cell growth and paracrine PDGF stimulation of tumor angiogenesis as the underlying drivers of the oncogenic potential of PDGF and its receptors.[37]

8.1.2. Nonclinical Studies

Dasatinib has been extensively studied in vivo and in vitro. In vivo, at doses well below maximum tolerated dose (MTD), dasatinib demonstrated curative efficacy against several advanced human chronic myelogenous leukemia (CML) xenografts in severe combined immunodeficiency (SCID) mice, including an imatinib “acquired-resistance” model completely insensitive to imatinib. Dasatinib also demonstrated antitumor efficacy against several susceptible cancer models in nude mice, and is a potent inhibitor of vascular endothelial growth factor (VEGF)-stimulated proliferation and migration in human umbilical vein endothelial cells (HUVECs). In cellular assays, dasatinib killed BCR-ABL dependent leukemic cell lines, including a number that are resistant to imatinib whether due to mutations that affect drug binding or through overexpression of SRC kinases. Against 4 imatinib naive CML cell lines, cytotoxicity potency was 300-655 times higher for dasatinib than for imatinib. Dasatinib inhibited cellular proliferation of numerous cancer cell lines that express activated SRC or c-KIT.

8.1.3. Effects in Humans

Bristol-Myers Squibb Company (BMS) began Phase 1 clinical development of dasatinib in November 2003. Since then, dasatinib has been studied in more than 900 patients with CML and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) resistant or intolerant to imatinib, and a number of solid tumors. Preliminary clinical pharmacokinetic (PK) data indicate that dasatinib has good oral absorption, is >90% protein bound and is predicted to have a large volume of distribution. Comparable dosing interval exposures are seen regardless of whether dasatinib is administered once daily (QD) or twice daily (BID). Dasatinib’s overall

mean terminal half-life is around 4 hours in patients and it is expected to be eliminated mainly through metabolism.

Dasatinib has an acceptable safety profile. None of the patients who were intolerant to imatinib became intolerant to dasatinib or developed adverse events similar to those that precluded treatment with imatinib. Most chronic phase CML patients had some degree of myelosuppression, most importantly, severe thrombocytopenia. In cases of severe myelosuppression, recovery generally occurred following short dose interruptions. Other severe hematologic toxicities were uncommon. In advanced CML and Ph+ ALL, severe myelosuppression was noted in most patients. In solid tumor patients, however, there was no clinically important myelosuppression. Nonhematologic toxicities consisted primarily of gastrointestinal (GI) intolerance, which typically was mild and easily manageable in chronic phase CML patients and mild to moderate in patients with advanced disease. In patients with advanced disease, especially blast phase, there was evidence of fluid retention, pleural and pericardial effusion. In all CML and Ph+ ALL patients, there were very few changes in blood chemistries and there were no instances of severe drug-related hepatic dysfunction. ECG measurements suggest a moderate QTc prolongation (4 chronic, 2 advanced patients had >60 msec increase from baseline in QTc).

Major cytogenetic response and complete hematologic response have been observed in a large number of imatinib resistant and intolerant patients in all phases of disease. The complete hematologic response rate in chronic phase CML was 90% (36/40) and was similar with QD and BID schedules. The major hematologic response rate was 71% (30/42) in patients with CML and Ph+ ALL. Cytogenetic responses were documented in 52% (22/42), including major cytogenetic responses in 7 of 21 with BCR/ABL mutations reported to confer resistance to imatinib.

Recently Sawyers et al presented an update of a Phase I dose-escalating study, initiated in November 2003, of dasatinib in imatinib-resistant/intolerant patients with CML in late chronic phase (CP) or advanced disease (accelerated phase [AP], myeloid blast crisis [MBC] or lymphoid blast crisis [LBC]) or with Ph+ ALL. Data were available for 84 patients (40 CP, 10 AP, 23 MBC, 11 LBC/Ph+ ALL). At the time of the report, 40 CP patients, with 8 years median duration of CML (range: 1–17 yrs), had been treated with dasatinib (15–180 mg/day, once-daily [QD] or twice daily [BID]) for a median of 13 months. The rate of complete hematologic response (CHR) in CP was 88% (35/40). Major cytogenetic responses (MCyR) were observed in 40% (16/40), with complete CyR (CCyR) in 33% (13/40). In advanced disease, 44 patients have been treated with dasatinib (70–240 mg/day, BID) for a median of 3–7 months; 2 patients (1 MBC and 1 LBC) were not evaluable for response, but were included in the analysis of time to progression. The rate of major hematologic response (MHR) (bone marrow blasts <5%) was 80% (8/10) in AP, 77% (17/22) in MBC and 60% (6/10) in LBC/Ph+ ALL. The CHR rate (<5% bone marrow blasts, with recovery of peripheral blood counts) is 50% (5/10) in AP, 18% (4/22) in MBC and 50% (5/10) in LBC/Ph+ ALL. The overall rates of MCyR and CCyR in advanced disease were 36% (15/42) and 21% (9/42), respectively. Cytogenetic responses were seen in patients with a wide spectrum of BCR-ABL mutations, as well as in patients with minimal or no prior CyR with imatinib. Treatment was well tolerated. Reversible grade 3–4 myelosuppression was observed in all cohorts [CP (38%); AP (70%); MBC and LBC/ Ph+ ALL (91%)]. 8 patients developed unexplained pleural effusions (2 CP; 6 BC), which were easily managed without treatment discontinuation. No patients have gone off study for toxicity. Responses were durable in CP and AP patients, but relapses had occurred in the MBC and LBC/Ph+ ALL cohorts, often due to dasatinib-resistant BCR-ABL mutations. Their data support the therapeutic potential of dasatinib in patients with imatinib-resistant or -intolerant CML/Ph+ ALL. In summary, dasatinib has an acceptable safety profile and demonstrated evidence of activity in all phases of CML and Ph+ ALL.

Talpaz et al also reported the preliminary results from a Phase II trial in CML patients in myeloid blast crisis (MBC), which was initiated in December 2004. This open-label study was carried out in 37 centers worldwide between December 2004 and May 2005. A total of 74 imatinib-resistant (IM-R) or imatinib intolerant (IM-I) MBC pts were accrued (41 male, median age 56 years [range

21-71]). Preliminary data were available on the first 34 patients (29 IM-R and 5 IM-I). Dasatinib was administered orally, at a dose of 70 mg twice daily (BID) in a continuous daily dosing schedule; dose escalation to 100 mg BID was permitted for patients who did not achieve hematologic response and dose reduction to 50 mg and 40 mg BID was allowed in the presence of persistent toxicity. Complete blood counts were performed weekly and bone marrow assessment, including cytogenetic analysis, was performed monthly. Mutations in the BCR-ABL domain were assessed in all patients. Pretreatment characteristics of these 34 patients included: 71% male, median age 54 years (range 21 – 71). Median duration of CML from first diagnosis was 49.3 months (range 5.6 – 215.5). Prior therapy included bone marrow transplant (5 pts, 15%) and interferon (18 pts, 53%). In 44% of pts, the highest IM dose was >600 mg/day and 41% of pts received IM for >3 years. Best responses to IM were complete hematologic response (CHR) in 82% of patients and major cytogenetic response in 39% of patients (complete in 27%, and partial in 12%). At baseline, 35% of pts had a WBC count ≥20 x 10^3/mm^3, 71% had a platelet count <100 x 10^3/mm^3 and 24% had ≥50% bone marrow blasts. BCR-ABL mutations were documented in 4/10 patients. Dasatinib doses were increased in 32% of patients while dose reductions were required in 21% of patients, mostly due to persistent thrombocytopenia. Major hematologic responses were documented in 16/29 (55%) patients with 7 CHR and 9 no evidence of leukemia (CHR without complete recovery of PMN or platelets). There were 13 (45%) cytogenetic responses, including 6 (21%) complete (0% Ph+) and 5 (17%) partial (1 – 35% Ph+). Dasatinib therapy was associated with rapid and profound myelosuppression. PMN <500/μl occurred in 59% of patients and platelets <25 x 10^3 /μl in 56% of pts. Non-hematologic toxicities were uncommon and usually grade 1 or 2, with diarrhea in 8 patients, rash in 4 patients, nausea in 3 patients (1 grade 3) and peripheral edema in 3 patients. 4 patients had pleural effusion. This preliminary data provided further evidence of the activity of dasatinib in CML patients with MBC and of its acceptable safety profile.

8.1.4. Formulation and chemical properties

Dasatinib is supplied for clinical research as 20 mg and 50 mg film-coated tablets and commercially as 70 mg film-coated tablets containing dasatinib with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate. The tablet coating consists of hydromellose, titanium dioxide, and polyethylene glycol. Tablets for clinical studiesare supplied in high-density polyethylene bottles containing a desiccant and cotton; the bottles are heat-induction sealed with child-resistant caps. The recommended storage condition is 15°C - 25°C. The tablet descriptions are as follows:
20 mg tablet - white to off-white, biconvex, round, film-coated with “20” debossed on one side and “527” on the other side
50 mg tablet -white to off-white, biconvex, oval, film-coated with “50” debossed on one side and “528” on the other side
70 mg tablet (commercial tablet) - is white to off-white, biconvex, round, film-coated with “BMS” debossed on one side and “524” on the other side

The chemical name for dasatinib is N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is C22H26ClN7O2S • H2O. The formula weight for the monohydrate is 506.02 and for the anhydrous free base is 488.01.
Dasatinib is a white to off-white powder, which may contain lumps, and has a melting point of 280°C - 286°C. The drug substance is insoluble (United States Pharmacopeia [USP] definition) in water (0.008 mg/mL) at 24 ± 4°C. The pH of a saturated solution of dasatinib in water is about 6.0. Two basic ionization constants (pKa) (6.8 and 3.1) and one weakly acidic pKa (10.8) were

determined. The solubility (USP definition) of dasatinib in various solvents at 24 ± 4°C are as follows: slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol; very slightly soluble in acetone and acetonitrile, and practically insoluble in corn oil.

Clinical experience in more than 900 patients has identified several safety concerns with dasatinib. There is a potential for myelosupression (in addition to that produced by the underlying disease), fluid retention, pleural and pericardial effusion, QTc prolongation, skin rashes, respiratory events, GI/CNS hemorrhage and tumor lysis syndrome. Due to these events, patients are prohibited from taking anticoagulants or medications that inhibit platelet function while on dasatinib therapy. An exception to this may be the use of anagrelide for CML patients with significantly elevated platelet counts.

8.1.5 Dasatinib Product Identification

The following investigational product, BMS-354825-03 (dasatinib), will be supplied by Bristol-Myers Squibb Pharmaceutical Research Institute in two different strengths:

BMS-354825-03 20 mg film coated tablets, biconvex, round, white to off-white in appearance with “BMS” or “20” debossed on one side and “527” on the other side.

BMS-354825-03 50 mg film coated tablets, biconvex, oval, and white to off-white in appearance with “BMS” or “50” debossed on one side and “528” on the other side.

8.1.6 Packaging and Labeling

Dasatinib will be labeled in open-label fashion. Each bottle will be labeled with a two-panel label. Description of the contents, batch number, container number, storage conditions and caution statements required by country regulations will be on the label. The second panel will have batch number, container number.

8.1.7 Handling and Dispensing of Investigational Product

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.

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.

Dasatinib should be administered as an oral dose as per the protocol. Subjects do not require fasting at the time of dasatinib consumption. Grapefruit juice should not be consumed during study drug therapy, as P450 enzyme inhibition may increase drug exposure.

If a scheduled dose is missed by more than 6 hours, this dose should be omitted. Missed doses should not be made up. Subjects should be provided with a diary in which to record any changes in dosing of study drug.

Bristol-Myers Squibb will be responsible for assuring that the quality of BMS-354825-03 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**. Re-supply requests need to be submitted at-least 2 weeks before the expected delivery date.

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 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 accordance with the environmental conditions (temperature, light and humidity) as determined by the Sponsor and defined in the Investigator Brochure or SmPC/reference label.

8.1.8 Investigational Product Records at Investigational Site(s)

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.

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.

Amount transferred to another area/site for dispensing or storage.

Non-study disposition (e.g., lost, wasted, broken).

Amount returned to Sponsor.

Amount destroyed at study site, if applicable.

Retain samples sent to third party for bioavailability/bioequivalence, if applicable.

Investigational product dispensing record/inventory logs and copies of signed packing lists must be maintained at the investigational site. Batch numbers for BMS-354825-03 must be recorded in the drug accountability records.

8.1.9 Return and Destruction of Investigational Product

8.1.10 Return of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to BMS, if not authorized by BMS to be destroyed at the site.

All investigational products returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers. Empty containers should not be returned to BMS. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational product(s) should be arranged by the responsible Investigator at the site.

8.1.11 Destruction of Investigational Product

If investigational products are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for disposal and written authorization has been granted by BMS, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained. The unused investigational products can only be destroyed after appropriate instruction by BMS.

9. ADVERSE EVENTS

1. See Appendices A and E for guidelines for reporting ADR's.
2. Adverse Events Requiring Expedited Reporting: Serious unexpected adverse events (SAEs) considered associated therapy should be reported to the Principal
Investigator [Farhad Ravandi, MD, Telephone (71 3) 745-0394 within 48 hours of observing or learning of the event.
3. Expected therapy-related events include those known toxicities or side effects related to the components of the chemotherapy as indicated in the Guidelines for AE Reporting for Leukemia Phase 2/3 studies (Appendix E). These grade 4 or less events will not be reported as individual SAEs, but will be summarized in the annual report to the IRB: Hyperglycemia Electrolyte abnormalities, changes in serum lactate dehydrogenase. Renal failure related to tumor lysis syndrome, methotrexate, or antibiotic therapy (e.g, AmBisome, aminoglycosides) Cytarabine related central nervous system toxicity Catheter-related deep venous thrombosis Coagulation

abnormalities during induction chemotherapy (e.g. chemical DIC or hypofibrinogenemia) Ileus related to vincristine Hepatotoxicity related to methotrexate Post lumbar puncture headaches
All serious, unusual, life-threatening, or lethal experience which may be due to dasatinib drug toxicity will be reported within 24 hrs by telephone to Bristol-Myers Squibb and must be followed by a written report which must be received within 10 business days. Information about all serious adverse events will be collected and recorded on the Bristol Myers Serious Adverse Event Report Form. To ensure patient safety, each serious adverse event must also be reported to Bristol Myers within 24 hours of learning of its occurrence.
Events not considered to be serious events are hospitalizations for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition. Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen. Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.
Pregnancy, although itself not a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities. Any serious adverse event occurring in a patient after providing informed consent, while receiving study drug and until 30 days after stopping study drug must be reported on the Medwatch Form. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated. All serious adverse events must also be reported for the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication.

A ***serious AE*** is any untoward medical occurrence that at <u>any dose</u>:

results in death,

is life-threatening (defined as an event in which the patient 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,

results in persistent or significant disability/incapacity,

is a congenital anomaly/birth defect,

results in the development of drug dependency or drug abuse,

is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) **For reporting purposes, also consider the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events.**

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

- All serious AEs whether related or unrelated to investigational product, must be immediately reported to BMS (or designee) by confirmed facsimile transmission. If only

limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

- For studies that are IND Exempt, any event that is both serious and unexpected must be reported to BMS as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information.

  All SAEs should be faxed to Bristol-Myers Squibb at:

  Global Pharmacovigilance & Epidemiology
  Bristol-Myers Squibb Company
  Fax Number: 609-818-3804

- For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. Bristol-Myers Squibb will be provided with a simultaneous copy via facsimile of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, or other institutional or group form.

  SAEs should be sent to the FDA at:

  MEDWATCH
  5600 Fishers Lane
  Rockville, MD 20852-9787
  Fax: 1-800-FDA-0178 (1-800-332-0178)

  All SAEs should simultaneously be faxed to Bristol-Myers Squibb at:

  Global Pharmacovigilance & Epidemiology
  Bristol-Myers Squibb Company
  Fax Number: 609-818-3804

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

  - An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting

purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event (see Serious Adverse Events).

- In BMS supported trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE that may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

10. STATISTICAL METHODOLOGY

1. The major study objective is to evaluate the event-free survival after hyper-CVAD plus dasatinib and achieve a 2-year EFS rate > 60% (based on reported data from hyperCVAD plus imatinib)[21]. The study is expected to accrue 115 patients (previously untreated, or after having received one or two prior course of chemotherapy, or relapsed) over approximately 2 years (referral pattern of 15 to 20 patients/year, accrual completed in 12 to 24 months), with an additional 12 months of follow-up. This will allow estimates of CR rates and disease-free survivals. Disease-free survival is the time from documented CR until relapse or death. Event-free survival is the time from treatment until any failure (resistant disease, relapse, or death). The results will be compared descriptively to historical controls in terms of response, survival, toxicity, etc. (recently published data). A 95% confidence interval width will be approximately 11% for the CR rate estimated with 115 patients.

2. It is expected that the addition of dasatinib will achieve an efficacy superior to that obtained with the hyper-CVAD program alone and superior to hyper-CVAD plus imatinib mesylate. The trial will be monitored for possible early termination if there is evidence that the rate of response is not at least equivalent to that observed on the previous hyper-CVAD trial (26 CR of 29 patients). Observation of the following number of responses or fewer per number of patients evaluated will be regarded as evidence for termination: 2/5, 6/10, 10/15, 14/20, 18/25, 21/30, 25/35, 29/40, 33/45, 37/50, 41/55, 45/60, 49/65, 53/70, 57/75, 61/80, 65/85, 69/90,73/95,77/100,81/105, 85/110, or 89/115 on the basis that there is < 5% probability that efficacy is superior to that of hyper-CVAD. Using these guidelines, simulation results indicate the following expected results for several values of CR rate:

True rate of CR	Probability of early termination recommendation	Expected median sample size (25%, 75%)
0.6	>0.99	5 (5, 10)
0.7	0.98	15 (10, 35)
0.8	0.50	110 (20,115)
0.85	0.16	115 (115, 115)
0.9	0.03	115 (115, 115)
0.95	<0.01	115 (115, 115)

The molecular CR rate with hyper-CVAD is not known. Quantification of bcr-abl will be measured prospectively and analyzed by descriptive statistics.

3. Hyper-CVAD alone has very low toxicity (<5%). In this combination trial, if the toxicity rate is too high (Pr[Toxicity rate > 5%|Data] > 0.9), then the trial will be stopped (toxicity is defined at the

beginning of this section). Specifically, the trial will be stopped if the number of patients experiencing unacceptable (as defined in section 9.0) toxicities /total number of patients is greater than or equal to 2/5, 3/12, 4/24, 5/37, 6/51, 7/65, 8/79, 9/100, or 10/109. The probability to stop the trial early is 0.02, 0.12, 0.73, 0.98 or >0.99 when the true toxicity rate is 0.03, 0.05, 0.10, 0.15 or 0.20 respectively.

4. A separate analysis will be carried out for previously treated patients (who have received one or two prior course of therapy). The historical number of Philadelphia-positive patients presenting after failure of one course of chemotherapy is one of 204 patients (< 1%). The historical rate of patients who achieved a CR after one course of chemotherapy continuing on hyper-CVAD at MDACC is 4 of 208 patients (2%). None were Ph-positive. Thus, the expected number of patients in this category is expected to be small. Patients who have failed one course of non-hyper-CVAD chemotherapy will be assessed for CR rate (historical CR rate for ALL overall is 5 of 6 [83%]) and disease-free survival. Patients presenting in CR will be assessed for disease-free survival and toxicity only.

5. A separate analysis will also be carried out for patients with relapsed disease, i.e. those with Ph-positive ALL or lymphoid blast phase of chronic myeloid leukemia who have failed (after achieving an initial response) prior therapy which does not include dasatinib. It is expected that 40 patients will be enrolled in this category alone. Patients will be evaluated for response, toxicity, event-free survival and disease-free survival.

6.Despite best efforts, the expected rate of allogeneic transplant is at best 20%, with failure due to lack of a suitable donor, age or performance status characteristics, comorbid conditions, or relapse of their disease prior to planned transplant. Patients who successfully undergo allogeneic transplant will be censored for disease-free survival at the time of transplant. Those patients who successfully complete allogeneic transplant prior to completion of the program will be replaced.

10A. Data Confidentiality Plan

Data from this clinical trial will be shared with which is a retrospective data analysis study. 2006-0478 new testing will be undertaken on any specimen. (See Waiver of Informed Consent.)

11. REFERENCES

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