# AN OPEN-LABEL, PHASE I/II STUDY OF TWO DIFFERENT SCHEDULES OF DASATINIB (SPRYCEL) AND DECITABINE (DACOGEN) USED IN COMBINATION FOR PATIENTS WITH ACCELERATED OR BLASTIC PHASE CHRONIC MYELOGENOUS LEUKEMIA (Protocol CA180357)

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# 1.0 OBJECTIVES AND ENDPOINTS

## 1.1 Objectives

### 1.1.1 Primary Objectives

a) For phase I: To define the maximally tolerated dose (up to the target dose) of the combination of dasatinib (Sprycel) and decitabine (5-aza-deoxycitidine; Dacogen) in patients with chronic myelogenous leukemia (CML) in the accelerated (AP) or blastic (BP) phases.

b) For phase II: To assess the efficacy, measured as the response to therapy during the first 3 months of therapy, of the combination of dasatinib and decitabine in patients with CML in AP or blastic BP phases.

### 1.1.2 Secondary Objectives

a) To determine the duration of response and survival with the combination of dasatinib and decitabine in advanced phase CML.

b) To establish the toxicity of the combination of dasatinib and decitabine therapy.

c) To determine the effects on gene methylation of decitabine given in combination with dasatinib.

## 1.2 Endpoints

### 1.2.1 Primary Endpoints

a) Phase I: To determine the MTD (up to the target dose) with the combination of dasatinib and decitabine in CML-AP or CML-BP.

b) Phase II: To determine the hematologic response (HR) rate with the combination of dasatinib and decitabine in CML-AP or CML-BP.

### 1.2.2 Secondary Endpoints

a) To document the rate of major cytogenetic response (MCyR), duration of response, and survival (overall survival and progression-free survival) of patients with CML-AP or CML-BP treated with dasatinib and decitabine.

b) To determine the nature, incidence, and severity of adverse events, as determined by physical exam and laboratory assessment, of the combination of dasatinib and decitabine.

c) Assessment of decitabine-induced demethylation of *p15*, *H19*, and *ABL1* genes in peripheral blood and/or marrow leukemic cells obtained from patients enrolled in the present study.

# 2.0 BACKGROUND

## 2.1 The Disease

CML is a fatal disease characterized by clonal expansion of myeloid progenitor cells. The worldwide incidence of CML is 1-2 cases per 100,000, and CML accounts for one-fifth of all leukemias.[1] In the United States there are almost 5000 new cases annually. The median age of diagnosis is between 45-55 years of age with approximately 10% of cases occurring before the age of 20. However one-third of patients are over the age of 60 making some treatment options more difficult. CML is slightly more prevalent in males than in females (1.3:1).[1-5]

As a consequence of the translocation of chromosomes 9 and 22 (the Philadelphia chromosome), the *BCR* (breakpoint cluster region) gene on chromosome 22 is fused to the *ABL1* gene on chromosome 9. The result is the generation of the hybrid *BCR-ABL1* oncogene, which encodes the fusion BCR-ABL1 oncoprotein. BCR-ABL1 acts as a constitutively activated tyrosine kinase whose activity is central in the pathogenesis of CML. In addition, the subcellular localization of this hybrid Abl tyrosine kinase is altered, resulting in its cytoplasmic location. The *BCR* breakpoint site varies creating fusion proteins of variable sizes. The p210BCR-ABL1 fusion protein is seen mainly in CML with a minority of CML patients having a p230BCR-ABL protein. A smaller p190BCR-ABL1 protein is found in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). [2, 6, 7]

Most patients with CML, about 85%, are diagnosed during the chronic phase (CML-CP) of the disease. Clinical presentation during this phase includes fatigue, weight loss, bleeding, purpura, splenomegaly, leukocytosis or thrombocytosis, and anemia. Left untreated, CML-CP lasts 3 to 5 years.[8, 9] Over time, cells bearing the *BCR-ABL1* fusion gene acquire additional genetic abnormalities (i.e., genomic instability) and undergo clonal expansion, thus setting the stage for CML progression. Whilst most patients may progress quite rapidly to CML-BP, most do somewhat more gradually, through an accelerated stage of the disease (i.e., CML-AP), which may last for months or years, before a CML-BP ensues.

During CML-AP, patients increase the percentage of blastic cells in both bone marrow and peripheral blood, and they become more symptomatic and frequently present with fever, bone pain, and hepatosplenomegaly. The duration of CML-AP is variable but frequently short-lived, lasting an average of 6 to 18 months. The clinical importance of CML-AP is that it quickly proceeds into blast crisis, the final aggressive stage of the disease. About a quarter of patients may rapidly progress from diagnosis of CML to CML-BP without evidence of AP.[3, 8]

CML-BP is defined by the presence of >30% blasts in the bone marrow and/or peripheral blood. Patients suffer from increasing symptoms of anemia, bleeding, infections, lymphadenopathy and leukostasis. Patients with CML-BP have an extremely poor prognosis with a median survival of only 3-6 months. CML-BP is clinically similar to acute leukemia, including a remarkable resistance to standard chemotherapeutic agents. In CML-BP, the bone marrow is hypercellular with blast cells. Interestingly blast crisis can have a myeloid (50%) phenotype, lymphoid (25%), or mixed phenotype (25%).[3, 8]

## 2.2 Treatment of CML

There are multiple treatment options for CML-CP. Hydroxyurea (500-2000 mg/day PO) or busulfan (2000-6000 mg/day PO) have been used for many years as oral chemotherapy to control high white blood cell counts, and prolong survival in patients with CML. Neither of these agents can prevent the progression from CML-CP to CML-BP.

Interferon-alfa-2a (IFN-α) has been shown in many trials to be effective in the treatment of CML. The exact therapeutic mechanism of IFN-α is not known. It is speculated that it may have an antiproliferative effect on CML progenitor cells or it may restore normal regulatory control of CML cells. IFN-α appears to be superior to chemotherapy. The 5-year survival of patients with CML treated with IFN-α was 57% and only 42% for those who received chemotherapy. In addition 80% of patients achieve a complete hematological response (CHR), 50% of patients achieve a cytogenetic response, and >25% of patients complete disappearance of Philadelphia chromosome-positive cells.[1, 10, 11] In CML-AP, IFN-α appears to have no added benefit. Hence, attempts have been made to combine IFN-α with ara-C for better efficacy, but unfortunately these have led to increased toxicity.[1, 10, 11]

Stem cell transplantation or bone marrow transplantation is another effective treatment for CML. In selected cases, it represents a curative treatment, but its use is associated with significant morbidity and mortality. Transplantation-related mortality varies from 5% to 50% depending on several factors including the age of the patient, CML phase, degree of compatibility, CMV status, and the experience of the center where the transplantation is performed. Most patients with CML are ineligible for transplantation, as a matched related or unrelated donor is not available. In addition, transplantation is less effective when used in advanced phase CML (i.e., CML-AP or CML-BP).[2, 12]

Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor (TKI) that specifically targets BCR-ABL1 kinase and results in remarkable clinical response rates.[13-15] While the drug is highly active in CML-CP, being associated with a >90% response rate, fewer responses are seen in CML-AP or CML-BC, with most of these responses being often transient in nature. In CML-BC, for example, 1-year survival is only 25% in patients treated with imatinib alone.[16] These data suggest that the drug is relatively ineffective in advanced phase CML, likely as a result of additional genetic and epigenetic changes.

Dasatinib (Sprycel) and Nilotinib (Tasigna) are second generation TKIs which are 300- and 30-fold respectively more potent than imatinib against BCR-ABL1 kinase.[17] Phase II studies of dasatinib and nilotinib have shown that most patients with CML-CP resistant or intolerant to imatinib therapy respond to second generation TKI therapy.[18, 19] In addition, therapy with either nilotinib or dasatinib has been associated with higher response rates compared with single-agent imatinib in patients with CML-AP and CML-BP.[20, 21]

### 2.2.1 Dasatinib in CML

Dasatinib is a multityrosine kinase inhibitor with activity against BCR-ABL1, the SRC family of kinases (SFKs), c-KIT, EPHA2, and platelet-

derived growth factor (PDGFR-β) at nanomolar concentrations.[17] Dasatinib was tested in phase I study in 84 patients with any phase of CML or Ph+ ALL and hematologic resistance or intolerance to imatinib.[22] Of these, 63 were dosed on a twice a day schedule with total daily doses ranging from 50 to 240 mg, and 21 received dasatinib once daily, with doses ranging from 15 to 180 mg. Over 40% of all treated patients attained major hematologic and/or cytogenetic responses, with most responses occurring at doses between 100 and 140 mg daily. The MTD was not defined, and the phase II dose (70 mg twice daily) was based primarily on efficacy rather than safety criteria.[22]

Four different ongoing single-arm phase II studies of dasatinib have enrolled a total of 445 patients. Most patients had received prior cytotoxic chemotherapy and were imatinib resistant. Therapy consisted of dasatinib 70 mg twice daily given continuously. The FDA Drug Application was based on interim analyses from these phase II studies, in which all patients had a minimum follow-up of 6 months.[23] Median duration of treatment ranged from 5.6 months for patients with CML-CP to 2.8 months for those with lymphoid CML-BP. The primary efficacy end-point for CML-CP was major cytogenetic response (MCyR), which comprises complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR). The primary efficacy end-point for CML-AP, CML-BP, and Ph+ ALL was major hematologic response (MHR), which comprises CHR and no evidence of leukemia (NEL). In CML-CP, the MCyR rate was 45% with a CCyR rate of 33%. MCyR rates were 59%, 32%, 31%, and 42% in patients with CML-AP, myeloid CML-BP, lymphoid CML-BP, and 42% in Ph+ ALL, respectively.

**Table 1. Efficacy of dasatinib in phase II single-arm trials**

| | **CP (n=186)** | **AP (n=107)** | **Myeloid BP (n=74)** | **Lymphoid BP (n=42)** | **Ph+ ALL (n=36)** |
|---|---|---|---|---|---|
| Response rate | | | | | |
| CHR (95% CI) | 90 (85-94) | 33 (24-42) | 24 (15-36) | 26 (14-42) | 31 (16-48) |
| MCyR (95% CI) | 45 (37-52) | 31 (22-41) | 30 (20-42) | 50 (34-66) | 58 (41-74) |
| CCyR (95% CI) | 33 (26-40) | 21 (14-30) | 27 (17-39) | 43 (28-59) | 58 (41-74) |

Despite the high response rate achieved in all phases, the duration of response is short for patients treated in accelerated or blast phase. While progression-free survival for patients in chronic treated with dasatinib is 80% at 2 years, it is only 46% for those treated in accelerated phase, and the median is only 3 to 6 months for those treated in blast phase.

The most common treatment-related adverse events were gastrointestinal (e.g., diarrhea, nausea, vomiting, anorexia, and abdominal pain), constitutional (e.g., pyrexia, headache, fatigue, and asthenia), fluid retention, and bleeding events. Myelosuppression was

common in all patient populations. Baseline grade 3-4 neutropenia and thrombocytopenia were reported in 7% to 31% and 1% to 58% of patients, respectively. Forty percent of the safety population experienced bleeding events of any type, and 10% experienced grade 3 or 4 bleeding. Fatal brain hemorrhages tended to occur in patients with blast-phase disease in the setting of grade 4 thrombocytopenia. Approximately 50% of the patients experienced fluid retention, which was grade 3-4 in 9%. Pleural effusion was reported in 22% of patients across all studies and was grade 3-4 in 5%. Grade 3-4 pericardial effusion, pulmonary edema, ascites, and generalized edema were each reported in 1%.

The FDA granted dasatinib accelerated approval for the treatment of adults with CML in all phases with resistance or intolerance to prior therapy including imatinib. The approval was based on cytogenetic or hematologic responses.[23]

### 2.2.2 Decitabine

Decitabine is a deoxycytidine analog with demonstrated antineoplastic activity against murine leukemias, which is more potent than ara-C, against murine leukemias. Decitabine is phosphorylated to its nucleotide prior to DNA incorporation.[24] Once incorporated, it produces marked DNA hypomethylation (superior to Azacytidine in this effect) via inhibition of DNA methyltransferase. At high doses, it appears to cause DNA synthesis arrest due to covalent linkage with DNA-Methyltransferases (Mtase), which results in cytotoxicity and apoptosis. At low doses, however, minimal cytotoxicity is observed, and the treated cells exhibit marked reduction in Mtase activity, reduced overall and gene-specific DNA methylation and reactivation of silenced genes. This is associated with tumor suppressor gene activation, induction of cellular differentiation, and inhibition of clonogenic growth of leukemia progenitors. Decitabine also 1) induces a stable increase of HLA-class I RNA transcripts and 2) interacts additively or synergistically with several biological modifiers such as IFN-α and retinoic acid in induction of differentiation and loss of clonogenicity.

**Clinical Experience with Low-Dose Decitabine at M.D. Anderson Cancer Center**

Based on *in vitro* data suggesting greater hypomethylating activity at lower doses, a phase I biological study of decitabine was initiated at M.D. Anderson Cancer Center that accrued 48 patients with myeloid malignancies (35 AML, 7 MDS, 5 CML, 1 ALL) over a period of two years.[25] In order to maximize the hypomethylating effects of decitabine, multiple low dose schedules in patients with relapsed/refractory myeloid malignancies were tried. Initially, patients were treated at 5 mg/m$^2$ IV over 1 hour daily for 10 days (dose 30 folds lower than the reported MTD). The dose was then escalated to 10, 15 and 20 mg/m$^2$ daily for 10 days. Finally, a group of patients received 15 mg/m$^2$ daily for 15 days then 20 days. Of the 39 patients enrolled onto the study, 3 did not complete the first course (one due to sepsis and death on day 2 and two due to rapidly rising counts) and therefore were excluded from analyses.

Responses were seen at all dose levels, but 15 mg/m$^2$ appeared to induce the most responses, with no further benefit for increasing the dose or duration of administration. The overall response rate was 32%, including 9 complete remissions (CR; 18%) and 1 partial remission (PR; 2%). Seven additional patients had significant reductions in peripheral and/or bone marrow blasts but did not recover normal hematopoiesis. Responses were seen in refractory/relapsed acute myeloid leukemia (AML; 10/30), myelodysplastic syndrome (MDS; 3/4), and CML (2/2). These responses were confirmed in an additional cohort of 10 patients treated at 15 mg/m$^2$ in the phase II component of the study. Overall, 5 patients with CML were treated. Two were in BP, refractory to imatinib, and one of these had a CHR and PCyR after one cycle. Of the other three patients (previously untreated with imatinib), one had a partial response, one had a CHR and CCyR and one was taken off study early and is not evaluable for response. In most patients who responded, there was a very gradual diminution of blasts over 2-4 weeks, and eventual recovery of normal hematopoiesis at 4-5 weeks, suggesting a non-cytotoxic mode of action for this regimen Response duration ranged from 2 months to 10+ months. Of the 6 patients who achieved a clinical response and had baseline and on-treatment samples available, only 2 were methylated (1 had a CR, 1 had a PR), and these had not changed methylation at days 5 or 12 after therapy. Therefore low-dose decitabine is an effective agent in myeloid malignancies. The effective low dose administration schedule derived from this phase I study is 15 mg/m$^2$ IV over 1 hour daily for 10 days.

In a recent study, three different schedules of decitabine aimed at delivering a dose of 100 mg/m$^2$ have been investigated in 95 patients with MDS following a Bayesian adaptive design: (1) 10 mg/m$^2$ intravenously over 1 hour daily for 10 days; (2) 20 mg/m$^2$ intravenously over 1 hour daily for 5 days; and (3) 20 mg/m$^2$ subcutaneously daily for 5 days. In this study, decitabine was given every 4 weeks (rather than 6 to 8 weeks) regardless of counts, as long as there was persistent disease and no significant myelosuppression-associated complications. Importantly, therapy was continued for at least 3 courses before evaluating response or failure on therapy. The 5-day IV schedule was selected as the optimal single-agent dose, with 39% of patients achieving a complete remission, compared with 21% in the 5-day subcutaneous arm and 24% in the 10-day IV arm ($p<0.05$). The high dose-intensity arm was also superior at inducing hypomethylation at day 5 and at activating *p15* expression. Grade 3-4 drug-related extramedullary toxicities were uncommon, and included transient liver toxicities (mostly elevations of liver enzymes) in 4 patients (4%) and other in 1 patient (1%). Myelosuppression-related complications occurred in approximately 15% of patients.

**Clinical Experience with Decitabine in CML at M.D. Anderson Cancer Center**

A phase II trial of decitabine was conducted in 123 with Ph-positive CML (64 BP, 51 AP, 8 CP) and 7 with Ph-negative CML at M.D. Anderson Cancer Center.[26] Initially, patients were treated at 100 mg/m$^2$ q12h for

5 days (1000 mg/m$^2$ per course) but the dose had to be reduced initially by 25% and eventually by 50% (100 mg/m$^2$) because of prolonged myelosuppression.

**Table 2. Number of patients treated at each dose schedule of decitabine by CML phase (n=130)**

| Decitabine (mg/m$^2$ IV over 6 hrs q12hrs for 5 days) | No. treated | | | | |
|---|---|---|---|---|---|
| | BP | AP | CP | Ph-negative | Total |
| 100 | 9 | 4 | 0 | 0 | 13 |
| 75 | 13 | 17 | 0 | 3 | 33 |
| 50 | 42 | 30 | 8 | 4 | 84 |

Most patients (n=84) received decitabine at 50 mg/m$^2$, including 42 patients with CML-BP and 30 CML-AP. Table 3 illustrates the responses obtained with decitabine by CML phase.

**Table 3. Response to decitabine by CML phase in a phase II clinical trial**

| Response | CML Phase | |
|---|---|---|
| | AP | BP |
| | No. (%) | No. (%) |
| Complete hematologic response | 12 (24) | 6 (9) |
| Cytogenetic response | | |
| Complete | 3 (6) | 0 (0) |
| Partial | 3 (6) | 2 (3) |
| Minor | 3 (6) | 3 (5) |
| Partial hematologic response | 1 (2) | 2 (3) |
| Hematologic improvement | 10 (20) | 7 (11) |
| Second chronic phase | 3 (6) | 3 (5) |
| Induction death | 3 (6) | 3 (5) |
| Primary resistance | 0 (0) | 20 (31) |
| Secondary resistance | 7 (14) | 23 (36) |

Unique features of decitabine in this setting were (1) a slow pattern of reduction of blasts, (2) a rapid rise in platelets following therapy and (3) occasional responses late into therapy (after 2 cycles). These suggested that responses to decitabine might involve a differentiation component, similar to what was observed with other differentiating agents in leukemia. A subset analysis of older (>50) patients in CML-BP showed that decitabine therapy resulted in a better survival than historical controls treated with combination chemotherapy.

In a subsequent phase II study, a low-dose of decitabine (15 mg/m$^2$ IV over 1 hour daily, 5 days a week for 2 weeks) was administered to 35

patients with imatinib-resistant or –intolerant CML (12 CP, 17 AP, and 6 BP).[27] CHR was reported in 12 (34%) patients and partial hematologic response in 7 (20%) patients, for an overall hematologic response rate of 54% (83% in CP, 41% in AP, and 34% in BP). McyR was observed in 6 (17%) patients, and mCyR in 10 (29%) patients, for an overall cytogenetic response rate of 46%. Median response duration was 3.5 months (range, 2 to 13+ months). Neutropenic fever was reported in 28 (23%) of 124 decitabine courses. LINE1 methylation decreased from 71.3% ±1.4% to 60.7% ±1.4% after 1 week, 50.9% ±2.4% after 2 weeks, and returned to 66.5% ±2.7% at recovery of counts (median, 46 days). At day 12, the decrease in methylation was 14.5% ±3.0% vs 26.8% ±2.7% in responders vs nonresponders ($p$= .007).[27]

In an attempt to improve on the response rates obtained with decitabine as single-agent, a phase II study was conducted in which low-dose decitabine was combined with the BCR-ABL1 kinase inhibitor imatinib mesylate.[28] Twenty-eight patients were treated (25 with imatinib resistance; 18 in AP, 10 in BP) with decitabine 15 mg/m$^2$ IV daily, 5 days per week for 2 weeks and imatinib 600 mg orally daily. A median of 2.5 cycles per patient were administered. Hematologic responses were observed in 43% of patients (32% with CHR), with a median duration of response 18 weeks (range, 4 to 107). A major cytogenetic response was attained by 18% of patients. A decrease in methylation assessed by long interspersed nucleotide element (LINE) bisulfite/pyrosequencing assay tended to be greater in nonresponders than in responders on days 5 and 12.[28] Hematologic responses were significantly more frequent in patients with no BCR-ABL1 kinase mutations (53%) than in those with mutations (14%), suggesting that synergy between decitabine and imatinib may depend on residual sensitivity to imatinib.

### 2.2.3 Rationale for the Combination Use of Dasatinib and Decitabine

In previous studies we have shown that single-agent decitabine is an active therapy in CML-AP and CML-BP.[26] We have also shown that responses to decitabine in advanced phase CML are accompanied by demethylation and reactivation of the p15 cyclin-dependent kinase inhibitor. Furthermore, these responses can be achieved with low-dose decitabine.[26] The activity of dasatinib, a potent BCR-ABL1 and SFKs, is currently being investigated in phase II and III studies in patients with CML in all phases. Dasatinib has proved the most effective single agent in patients with CML-BP.[21] In addition, synergy has been reported between dasatinib and TKI (particularly imatinib) in imatinib-resistant cell lines.[29] Based on these data, we propose the hypothesis that the combination of dasatinib and decitabine will be a more effective regimen in CML-AP and CML-BP than either drug alone, by targeting different aspects of the biology of advanced phase CML simultaneously. We propose that decitabine is active in advanced phase CML through its ability to demethylate and reactivate genes silenced during disease progression, while dasatinib is most effective against CML cells whose proliferation is highly dependent on the activity of the BCR-ABL1 kinase. Furthermore, dasatinib has shown remarkable activity against CML-AP and CML-BP (particularly in patients with lymphoid CML-BP), and it is possible that its potent inhibitory effect against SFKs may play a role.[21]

In addition, decitabine may cause epigenetic (DNA demethylation) changes, which may enhance the sensitivity of CML cells to TKIs such as dasatinib. We then propose to combine the two drugs and test the hypothesis that the combination will result in a higher response rate and more durable responses than either drug alone. We will also measure toxicity and induction of demethylation as well as gene reactivation by this combination. In the clinical trial of decitabine + imatinib in imatinib resistant patients, the greatest clinical benefit was seen in those patients without mutations, suggesting that residual sensitivity to the TKI greatly enhances the response rate to the combination. Because dasatinib is more active in most patients with BCR-ABL mutations, the combination of decitabine + dasatinib would be predicted to be particularly effective.

## 3.0 BACKGROUND DRUG INFORMATION

### 3.1 Dasatinib

Dasatinib is manufactured and distributed by Bristol-Myers Squibb. It has been approved by the FDA for the treatment of all phases of CML after failure of imatinib therapy, and for patients in chronic phase as initial therapy.

Pharmaceutical Data: dasatinib is provided by Bristol-Myers Squibb as 70 mg, 50 mg, and 20 mg capsules packaged in bottles. Medication labels will comply with the legal requirements of each country and will be printed in the local language

Stability and Storage Requirements: the storage conditions for dasatinib will be described on the medication label. Bottles must be stored in a safe, secure location at 25°C (77°F).

Route of Administration: Oral.

Special Precautions: dasatinib is a local irritant and must be taken in a sitting position with a large (250 mL) glass of water. This direction is noted on the medication label.

Known Side Effects and Toxicities: dasatinib was generally well-tolerated in phase II studies involving patients with CML in all phases. The most frequently encountered side effects include fluid retention syndromes, diarrhea, headache, skin rash, nausea, hemorrhage, fatigue, dyspnea, bone and joint aches, and vomiting.

Drug Disposal: Unused/expired drug will be disposed of onsite following institutional guidelines.

**Table 4. Adverse effects reported in more than 10% of all patients in clinical studies of dasatinib**

| Adverse reaction | All patients (n=2182) | | CP (n=1150) | AP (n=502) | Myeloid BP (n=280) | Lymphoid BP and Ph+ALL (n=250) |
|---|---|---|---|---|---|---|
| | All grades | Grade 3-4 | Grade 3-4 | Grade 3-4 | Grade 3-4 | Grade 3-4 |
| Fluid retention | 37 | 8 | 6 | 7 | 13 | 7 |
| Local superficial edema | 20 | <1 | <1 | 1 | 1 | <1 |
| Pleural effusion | 22 | 5 | 4 | 5 | 10 | 6 |
| Other fluid retention | 10 | 3 | 3 | 3 | 6 | 2 |
| Generalized | 3 | <1 | <1 | 1 | <1 | 1 |
| Congestive heart failure | 2 | 1 | 2 | <1 | 2 | 1 |
| Pericardial effusion | 3 | 1 | 1 | 1 | 2 | 0 |
| Pulmonary edema | 2 | 1 | 1 | 1 | 1 | 1 |
| Ascites | <1 | <1 | 0 | 0 | 1 | <1 |
| Pulmonary hypertension | 1 | <1 | <1 | 0 | 1 | 1 |
| Diarrhea | 31 | 3 | 3 | 4 | 5 | 4 |
| Headache | 24 | 1 | 1 | 1 | 1 | 2 |
| Skin rash | 22 | 1 | 1 | 1 | 1 | 1 |
| Nausea | 22 | 1 | 1 | 1 | 2 | 2 |
| Hemorrhage | 21 | 6 | 2 | 11 | 12 | 8 |
| Gastrointestinal | 7 | 4 | 1 | 8 | 9 | 5 |
| CNS | 1 | <1 | 0 | <1 | <1 | 2 |
| Fatigue | 21 | 2 | 2 | 3 | 1 | 2 |
| Dyspnea | 20 | 4 | 5 | 4 | 5 | 2 |
| Musculoskeletal pain | 14 | 1 | 2 | 1 | 1 | <1 |
| Pyrexia | 13 | 1 | 1 | 2 | 3 | 1 |
| Vomiting | 13 | 1 | 1 | 1 | 1 | 2 |
| Abdominal pain | 10 | 1 | 1 | <1 | 1 | 2 |

## 3.2 Decitabine

Decitabine is manufactured by MGI Pharma, Inc. It has been approved by the FDA for the treatment of myelodysplastic syndrome.

Description: decitabine is an analog of 2'-deoxycytidine with a nitrogen atom substituted for carbon at the 5-position of the ring.

Other Names: deoxyazacytidine; 5-aza-2'deoxycytidine, DAC.

How Supplied: freeze-dried power for injection, 50 mg in 20 ml vials.

Solution Preparation: when reconstituted with 10 mL of sterile water for injection each ml will contain 5mg of decitabine and 6.8 mg of $KH_2PO_4$. The reconstituted solution can be further diluted in 0.9% sodium chloride intravenous infusion B.P., which has been cooled to a temperature of 4-8°C.

Decitabine will be administered at a dose of 15 mg/m$^2$ (or the modified dose as per protocol) infused over approximately 1 hour daily for 10 days.

Storage: Vials should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). After reconstitution, use decitabine within 15 minutes. If diluted with cold (2°C to 8°C) fluids, the diluted solution is stable for up to 7 hours if stored between 2°C and 8°C (36°F and 46°F).

Pharmaceutical data
Decitabine sterile powder is a freeze-dried preparation. Each 20 ml vial contains 50 mg decitabine. The vials should be stored at 2-8°C and are stable for at least 2 years. Chemical instability of decitabine is a major problem encountered in the clinical formulation, leading to drug solutions of a decreasing potency upon storage. Reconstitution of the powder results in a rapidly decomposing solution. The concentration of decitabine decreases by about 10% after 4 hours at 25°C and by about 10% after 24 hours at 4°C. Thus the solution should be prepared at least twice a day and kept in a refrigerator (4-8°C), for a maximum period of 11 hours, until administration. The solution can be infused over maximally 3 hours if kept in the refrigerator for less than 10 hours. The solution can be infused over maximally 2 hours if kept in the refrigerator for more than 10 hours.

Precautions
Drug handling precautions will be strictly followed. Skin contact with the solution should be avoided and protective (chemotherapy) gloves should be worn. Drug spilling can be inactivated by 2 M sodium hydroxide solution. The skin should be treated with a borax buffer solution pH 10 and after that thoroughly washed with water and soap.

Drug supply and distribution
Both dasatinib and decitabine are commercially available.

The supply of vials for the treatment of patients should be available and kept up to date.

### 3.1.5 Human Toxicology

In the Phase I and Phase II studies of solid tumors the primary toxic reaction has been hematologic. Leukopenia has, in general, been more pronounced than thrombocytopenia. The median WBC nadir was day 21 (range 7-31) and median day to recovery was day 34 (range 13-50). No cumulative myelosuppression was documented in these studies. Other common toxicities have included mild to moderate nausea and vomiting. Rare occurrences of diarrhea, fever, mucositis and peripheral neuropathy have been recorded. At the higher dose schedules in leukemia neurotoxicity and gastrointestinal toxicity were a problem. In a randomized open-label, multicenter, phase III trial, 170 patients with International Prognostic Scoring System (IPSS) high-risk, intermediate-2, and intermediate-1 MDS were randomized to receive decitabine (15 mg/and best supportive care (n=89) or to receive best supportive care alone (n=81). The most commonly occurring adverse reactions were neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia. The

adverse reactions most frequently resulting in treatment discontinuation included thrombocytopenia, neutropenia, pneumonia, Mycobacterium avium complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, and abnormal liver function tests.

## 4.0 PATIENT ELIGIBILITY

### 4.1 Inclusion Criteria

**4.1.1** Patients age 18 years of age or older with CML-AP, CML-BP or Philadelphia chromosome-positive acute myeloid leukemia defined as follows:

- CML-AP is defined by the presence of 15-29% blasts in peripheral blood (PB) or bone marrow (BM), ≥20% basophils in PB or BM, ≥30% blasts plus promyelocytes (with blasts <30%) in PB or BM, <100 x$10^9$/L platelets unrelated to therapy, or by clonal cytogenetics evolution (i.e., the presence of cytogenetic abnormalities other than the Philadelphia chromosome).

- CML-BP is defined by the presence of ≥30% blasts in the bone marrow and/or peripheral blood or the presence of extramedullary disease.

**4.1.2** Patients are eligible whether they have received or not prior TKI therapy. For the phase I portion of the study, patients who had received prior therapy with dasatinib should have been able to tolerate the dose equivalent to the starting dose of dasatinib in the dose level at which the patient is being entered. Patients who previously received dasatinib but never at the dose being proposed are eligible provided they tolerated the maximum dose they were prescribed with no grade 3-4 toxicity not responding to optimal management.

**4.1.3** ECOG performance status 0-3.

**4.1.4** Men and women of childbearing potential should practice 2 methods of contraception; 1 method must be highly effective and a second method must be either highly effective or less effective. . Men and women of childbearing potential are defined as: a male that has not been surgically sterilized or a female that has not been amenorrheic for at least 12 consecutive months or that has not been surgically sterilized. Patients must use birth control during the study and for 3 months after the last dose of study drug if they are sexually active.

**4.1.5** Women of childbearing potential must have a pregnancy test at screening.

**4.1.6** Signed informed consent.

**4.1.7** Patients must have been off all prior therapy for CML for 2 weeks prior to start of study therapy and recovered from the toxic effects of that therapy. Exceptions to these are hydroxyurea and TKIs (including but not limited to imatinib, nilotinib, and bosutinib) which should be discontinued ≥24 hrs prior to the start of therapy. Patients who are

receiving dasatinib prior to enrollment do not have to discontinue this agent prior to start of study therapy.

**4.1.8** Adequate organ function:

- Serum creatinine ≤2.0 mg/dl or creatinine clearance ≥60 mL/min
- Total bilirubin ≤1.5xULN (unless considered due to Gilbert's syndrome or hemolysis)
- Alanine aminotransferase (ALT) ≤3xULN unless considered due to leukemic involvement.

## 4.2 Exclusion Criteria

**4.2.1** NYHA cardiac class 3-4 heart disease.

**4.2.2** Cardiac disease including:

- Uncontrolled angina within 3 months.
- Diagnosed or suspected congenital long QT syndrome.
- Any history of clinically significant ventricular arrhythmias (eg, ventricular tachycardia, ventricular fibrillation, or Torsades de pointes).
- Prolonged QTc interval on pre-entry electrocardiogram (> 470 msec) on the Fridericia's correction.
- Uncontrolled hypertension (defined for this protocol as sustained systolic BP ≥150 and diastolic ≥100).
- Patients currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes (see Appendix F).

**4.2.3** Serious uncontrolled medical disorder or uncontrolled active systemic infection or current unstable or decompensated respiratory or cardiac conditions which makes it undesirable or unsafe for the patient to participate in the study.

**4.2.4** Patients with known, clinically significant pericardial or pleural effusion.

**4.2.5** History of significant bleeding disorder unrelated to cancer, including diagnosed congenital bleeding disorders (e.g., von Willebrand's disease), or diagnosed acquired bleeding disorders within one year (e.g., acquired anti-factor VIII antibodies).

**4.2.6** Subject is receiving potent inhibitors of CYP3A4; for such medications, a wash-out period of >/= 7 days is required prior to starting dasatinib unless discontinuation or substitution of such an inhibitor is not in the best interest of the patient as determined by the investigator. These include the following medications: itraconazole, ketoconazole, miconazole, voriconazole; amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir; ciprofloxacin, clarithromycin, diclofenac,

doxycycline, enoxacin, isoniazid, ketamine, nefazodone, nicardipine, propofol, quinidine, telithromycin. In instances where use of these agents is felt to be required for the best management of the patients, inclusion of such a patients should be discussed with PI and the rationale documented.

**4.2.7** Females who are pregnant or are currently breastfeeding.

**4.2.8** Patients that are eligible for (including having available donor) and willing to receive an allogeneic stem cell transplant within 4 weeks.

## 5.0 TREATMENT PLAN

**5.1** Therapy with decitabine may be administered on an outpatient or inpatient basis. Decitabine may be administered by local doctor or at MD Anderson. The maximum number of patients to be enrolled in this study is 84.

**Outside Physician Participation During Treatment**

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record

2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix K)

3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

6. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

8. Patients will return to MDACC every month for 1-2 months, then every 2-4 cycles for evaluation.

9. For patients who receive the first cycle at home, a phone call will be placed to the patient on day 14 (+/- 5 days) of the first cycle to assess toxicity.

10. Patients receiving therapy at home will return to MDACC for assessment before the start of each cycle for the 1st 3 cycles, then every 3 cycles (+/- 1 cycle) until 1 year from start of therapy, then every 6 months (+/- 1 month).

**5.2** The first 3 patients will be treated on schedule A, dose level 0 (See Table on section 5.3.4). If DLT is identified in 0 of 3 or ≤1/6 patients, the next 3 patients will be assigned to schedule B. If DLT is identified in 0 of 3 or ≤1/6 of these patients, patients will be accrued to dose level +1 (ie, Target dose), first to Schedule A, and then to Schedule B using the same algorithm. If no MTD is identified at this dose level, phase II will start and all subsequent patients will be randomized to schedules A and B as described under statistical section. The initial dose is per dose level 0, and the target dose is dose level +1. If MTD has not been defined after completing dose level +1 for one or both arms, all subsequent patients will be randomized to this dose level, or the MTD for each dose level if lower than +1. If MTD is exceeded at dose level 0, dose levels -1, -2 and -3 will be explored. If dose level -3 exceeds MTD, additional dose levels might be explored after discussion with sponsor and approval of amendment by IRB. The phase II portion of the study will commence once an MTD is defined for both schedules or, if no MTD is identified, when 0/3 or ≤1/6 patients treated at the Target Dose have experienced DLT with each schedule where MTD has not been determined at a lower level. The dose to be used for the phase 2 portion of the study is the one declared as MTD or the target dose (dose level +1) if no MTD was defined at a lower dose, whichever is lowest.

For the phase I aspect of the protocols: Subjects will not be enrolled into a higher dose level until all subjects in the current cohort have completed the first cycle of treatment. Prior to changing dose levels a cohort summary will be completed and submitted to the Clinical Research monitor in the IND Office.

**5.3 Dose Schedules:**

*Dasatinib and Decitabine administration will start at the same time.

**5.3.1** Dasatinib will be administered at a starting dose of 100 mg once daily. During the first cycle, dasatinib will be administered for the first 2 weeks only. Patients with rapidly proliferative disease and/or a high peripheral blood blast count (e.g. >2 x $10^9$/L) may continue dasatinib uninterrupted. In subsequent cycles, dasatinib may continue uninterrupted in the absence of adverse events that require treatment interruption.

**5.3.2** The starting dose of decitabine for Schedule A will be 10 mg/$m^2$ IV over approximately 1 hour daily for 10 days. The starting dose of decitabine for Schedule B will be 20 mg/$m^2$ IV over approximately 1 hour daily for 10 days. Administration of decitabine can be divided into 5 days weekly for two consecutive weeks if weekend administration or other logistical issues prevent administration in 10 consecutive days.

**5.3.2.1** Decitabine will be dosed based on actual body weight. However, at the treating physician's discretion an adjusted

body weight may be used, if actual body weight is >40% over ideal body weight. Adjusted body weight = ((Actual body weight – Ideal body weight) 0.4) + Ideal body weight

**5.3.3** Treatment will be repeated every 28 days (±7 days). Patients with rapidly proliferating disease may have therapy started earlier (but not earlier than day 14). The start of subsequent cycles may be delayed to allow for recovery of any adverse events as specified below. Patients with rapidly proliferating disease may start subsequent cycles early, but not earlier than day 14. In such instances, the observation period for DLT will be until the start of cycle 2.

**5.3.4 Dose Adjustment Levels*:**

| | | Decitabine | |
|---|---|---|---|
| **Dose level** | **Dasatinib** | **Schedule A** | **Schedule B** |
| +2** | 140 mg PO QD | 40 mg/m$^2$ IV over 1 hour daily for 5 days | 40 mg/m$^2$ IV over 1 hour daily, 5 days/week for two consecutive weeks |
| +1 (Target dose) | 140 mg PO QD | 10 mg/m$^2$ IV daily for 10 days | 20 mg/m$^2$ IV daily for 10 days |
| 0 (Starting dose) | 100 mg PO QD | 10 mg/m$^2$ IV daily for 10 days | 20 mg/m$^2$ IV daily for 10 days |
| -1 | 70 mg PO QD | 7.5 mg/m$^2$ IV daily for 10 day | 15 mg/m$^2$ IV daily for 10 days |
| -2 | 50 mg PO QD | 5 mg/m$^2$ IV daily for 10 day | 10 mg/m$^2$ IV daily for 10 days |
| -3 | 20 mg PO QD | 5 mg/m$^2$ IV daily for 5 days | 7.5 mg/m$^2$ IV daily for 10 days |

* Dose levels are described for induction. For maintenance, the daily dose is unchanged but decitabine will be administered for only 5 days.

** Dose level +2 to be used only for dose escalation as described in section 5.3.8

**5.3.5 Definition of Dose-Limiting Toxicity (DLT)**

**5.3.5.1** DLT will be defined by events that are clinically significant and at least possibly related to study drug occurring during the first 4 weeks (1 cycle) of therapy. In patients with rapidly proliferating disease who start cycle #2 early, the observation period to determine DLT will be until start of cycle 2.

**5.3.5.2** Non-hematologic DLT is defined as ≥ grade 3 (NCI common criteria, version 4.0) that is clinically significant and considered to be at least possibly related to the study drug. Grade 3 or 4 nausea, vomiting and diarrhea will be considered DLT only if not controlled by optimal therapy.

**5.3.5.3** Grade 3 or greater biochemical abnormalities (e.g., lipase or bilirubin elevation) will only be considered DLT if accompanied by clinical consequences. Grade 3 or greater electrolyte abnormalities will only be considered DLT if at least possibly related to study drug and not corrected by optimal replacement therapy.

**5.3.5.4** Hematologic DLT is defined as grade ≥3 neutropenia and/or thrombocytopenia with a hypocellular bone marrow with <5% bone marrow blasts lasting for 6 weeks or more after the start of a course. Hypocellular bone marrow with <5% blasts has to be confirmed with another bone marrow aspiration and/or biopsy within 7 -14 days to be counted as DLT. Once one bone marrow study is obtained that meets this criteria, dasatinib should be stopped and a repeat bone marrow aspiration and/or biopsy done within 7-14 days. If this bone marrow is confirmed hypocellular and with <5% blasts, a DLT is defined. The confirmation bone marrow aspiration and/or biopsy might occur after the 6 week threshold. (In case of a normocellular bone marrow with <5% blasts, 8 weeks with pancytopenia will be considered DLT). Anemia will not be considered for the definition of DLT.

**5.3.6 Definition of Maximally Tolerated Dose (MTD)**

**5.3.6.1** MTD will be defined as the highest dose at which 0 of 3 or ≤1/6 patients experience a first cycle DLT. If no MTD is identified at dose level +1 (ie, the Target dose) for each arm, this dose will be explored further in the phase II portion of the study and no further exploration of an MTD will be pursued.

**5.3.7** For the phase II portion of the study, patients who had received prior dasatinib and have demonstrated non-hematologic toxicity to a dose of 140mg daily (or lower) requiring dose reductions, will be treated at the highest dose they had tolerated before.

**5.3.8** If no significant anti-leukemic effect is observed after the first cycle of therapy and in the absence of grade 3 or higher clinically significant non-hematologic toxicity that is related to the study drugs, patients may be dose-escalated to the next dose level, provided it has been already deemed safe according to the phase I dose escalation rules. Dose level +2 is provided only for the purposes of dose escalation during the phase II portion of the study. For phase II portion of the study, if at any time patients need to be escalated to dose level +2, if at any time 33% or more of patients experience DLT at this dose level during the first cycle they receive at this dose, this would be considered to have exceeded MTD and should not be used any further.

**5.3.9** Dose adjustments of only one of the two agents is allowed if judged in the best interest of the patient (e.g., in patients with risk factors for

pleural effusion secondary to dasatinib or grade 1 or 2 pleural effusion at lower doses)

**5.4** Treatment cycles with decitabine will start every 28 days (± 7 days). Dasatinib will be continued uninterrupted. One cycle is defined as 28 days of therapy or until the start of the next course of decitabine in instances where this occurs before day 28.

**5.4.1** Subsequent cycles will be started once neutrophils recover to ≥1 $x10^9$/L and platelets to ≥70 $x10^9$/L (if above these levels before the start of the cycle).

**5.4.2** Patients with persistent leukemia (eg, blasts >5% in peripheral blood or bone marrow) may start the next cycle in the absence of full recovery of the bone marrow and/or peripheral blood counts provided they have recovered from non-hematologic toxicity as discussed below.

**5.4.3** Delays in beginning the next course of therapy for other reasons might be acceptable. The rationale should be discussed with the principal investigator and documented.

**5.4.4** Subsequent courses may be instituted early if there is evidence of early recovery of neutrophils (to ≥1 $x10^9$/L) and platelets (to ≥70 $x10^9$/L) and/or increasing blast count, but not earlier than 14 days from the start of the prior cycle.

**5.4.5** In instances where it is considered appropriate to delay therapy with one agent, administration of the other agent may continue as planned (eg, pleural effusion due to dasatinib)

**5.5** **Maintenance Therapy:** Patients that achieve a major hematologic response or are back to chronic phase may receive maintenance chemotherapy as follows:

**5.5.1** **Dasatinib:** 100 mg daily or the highest dose tolerated before.

**5.5.2** **Decitabine:** at the maximum dose tolerated before but for 5 days only.

**5.5.3** **P**atients that show increased proliferative activity (eg, increase blasts, rapid increase of WBC, etc) can revert back to the induction schedule.

**5.5.4** Dose adjustments for the maintenance therapy can be made following the same principles detailed below.

**5.6 Dose Adjustments**

**5.6.1** Patients who exhibit no significant anti-leukemic effect (e.g., failure to decrease the WBC count by at least 50% if initial WBC >$10x10^9$/L, or failure to decrease the peripheral blood blast percentage by at least 50% if initial WBC <$10x10^9$/L) after 6 courses of therapy will be taken off study.

**5.6.2** Patients who develop grade 3 or 4 drug-related clinically significant non-hematologic toxicity [except for a) nausea, vomiting or diarrhea unless uncontrolled by optimal therapy, or b) electrolyte abnormalities, unless uncontrolled by optimal supplementation or associated with clinical consequences] possibly related to the study drugs may have therapy interrupted until resolution of toxicity to grade ≤1, then therapy can be reinitiated at the next lower dose.

**5.6.2.1** If toxicity is clearly attributable to one of the drugs (eg, pleural effusion with dasatinib, arthralgias with decitabine) interruptions may apply to that drug alone while continuing the other agent. Resumption of the drug responsible for the toxicity will follow the guidelines mentioned above.

**5.6.2.2** Missed doses will not be made up.

**5.6.3** Patients with neutropenia or thrombocytopenia as a consequence of the disease prior to the start of therapy do not require treatment interruptions for myelosuppression. Dose-reductions and treatment interruptions in these patients should be considered in an individual case and discussed with the PI. The following guidelines can be used for these patients:

**5.6.3.1** Patients with a response and pre-course counts of neutrophils $>1x10^9$/L and platelets $>50$ $x10^9$/L who have sustained low counts of neutrophils $<0.5$ x $10^9$/L or a platelet count $<25$ x $10^9$/L for more than 2 consecutive weeks in the current cycle, with <5% blasts in the bone marrow, may receive a subsequent course at 1 dose level reduction. A reduction of 2 dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.

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

**5.6.3.3** If WBC is 5 to 10 x $10^9$/L or absolute blast 0.5 to 2 x $10^9$/L and platelet count $\leq 20$ x $10^9$/L, may continue treatment at same dose unless platelet count represents a decrease of >50%. If platelets $<20$ x $10^9$/L and <50% from baseline, may decrease dose by 1 dose-level.

**5.6.3.4** If WBC is $<5$ x $10^9$/L and absolute blast $<0.5$ x $10^9$/L and platelet count $\leq 20$ x $10^9$/L, may interrupt therapy until platelets $\geq 50$ x $10^9$/L. Then re-start therapy with a dose reduction by 1 dose-level. If WBC increases to $>10$ x $10^9$/L or blasts to $\geq 5$ x $10^9$/L before platelets recover, may re-start therapy with a 1 dose level reduction.

**5.6.4** Since the effect of decitabine may be delayed for up to 4 weeks, patients with high WBC counts (i.e., $>10x10^9$/L) may receive hydroxyurea prior to study entry. The use of hydroxyurea will be allowed during the first 4

cycles of therapy if necessary to control rapidly proliferating disease. The use of hydroxyurea will not be permitted after the first 4 cycles of therapy.

**5.6.5** Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale.

**5.6.6 Dose Escalation:** Patients with persistent disease (ie, not hematologic response after 1 cycle or no CCyR after 3 cycles) that are showing no evidence of unacceptable toxicity may have their dose escalated by one dose level per cycle up to dose level +2.

**5.6.6.1** Dose escalation of only one of the drugs is allowed if it is considered, based on the outcome with prior cycles that higher doses of one agent are not likely to be tolerated.

## 5.7 Duration of Therapy

**5.7.1** Patients achieving hematologic remission may continue receiving therapy with decitabine and dasatinib for as long as the treatment is judged to be beneficial to the patient, that is, if they maintain a response in the absence of intolerable toxicity.

**5.7.2** If needed, subsequent courses of decitabine will be adjusted to the immediate lower dose level to try to maintain granulocyte count approximately $>0.5x10^9$/L and platelet count approximately $>20x10^9$/L for most of the 28 days of each cycle.

**5.8** A minimum of 2 full courses will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. Patients who fail to complete 2 full courses of therapy will be replaced to reach the planned patient accrual. All patients receiving at least one dose of decitabine will be considered evaluable for toxicity. Patients achieving a partial response or with stable disease may continue on therapy until definite evidence of disease progression.

**5.9 Concurrent Administration of Other Medications.** Hematopoietic growth factors will not be routinely used. However, their use is permitted when clinically indicated. Other approved medications to treat concurrent medical problems and/or infections are allowed as clinically indicated.

**5.9.1** The use of investigational medications is not allowed during study.

**5.9.2** Concurrent administration of intrathecal chemotherapy is allowed for patients with evidence of CNS disease as clinically indicated.

**5.9.3** Caution is warranted when administering dasatinib to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. Systemic exposures to these medications could be increased while receiving dasatinib. In *in vitro* studies, dasatinib is a strong inhibitor of the human CYP3A4 enzyme and a weak inhibitor of CYP1A2, CYP2D6 and CYP2C19. dasatinib shows time-dependent inhibition of CYP3A4; however, there appears to be a

low probability for drug-drug interactions due to metabolism-dependent CYP3A4 inactivation. Results from an *in vitro* hPXR trans-activation study suggest that dasatinib has little potential to induce CYP3A4 through the activation of hPXR.

**5.9.4** CYP3A4 inhibitors and inducers should be used with caution (but are not prohibited) since they could alter the systemic exposure to dasatinib. Incubations with recombinant human CYP450 isozymes suggest that dasatinib is primarily metabolized by the CYP3A4 enzyme. Many other enzymes appear capable of metabolizing dasatinib, including CYP1A1, 2C9, 2E1, FMO3, 1B1, 2B6, 2A6, 2C8, and 4A1; however, it is unknown at this time what contributions these enzymes may have to the total metabolic clearance of dasatinib. A list of drugs that are inducers, inhibitors or substrates of CYP3A4 can be found at http://medicine.iupui.edu/clinpharm/ddis/.

## 6.0 METHYLATION STUDIES (Optional)

Gene-specific methylation assays: *in vitro*, decitabine efficiently inhibits gene-specific (promoter CpG island) methylation allowing for gene reexpression. This methylation can be quantitatively measured using either Southern blot analysis or bisulfite treatment of DNA followed by PCR and restriction enzyme digestion, or pyrosequencing. We have previously shown that decitabine therapy is associated with demethylation and reexpression of *p15*, which appears to be associated with response to the drug. Some degree of demethylation was also observed for *ABL1*, but no demethylation was observed for *H19*, a gene frequently found methylated in CML. In the present trial, we will measure the methylation status of *p15*, *H19*, and *ABL1* (as well as other disease specific genes) before or on the first day of treatment (day 0 or day 1) in blood and/or bone marrow, at the end of the first 5 doses of decitabine (day 5) in blood, at the end of the treatment course (day 12) in blood, and at recovery of counts in blood by pyrosequencing (Cycle 1 only). For all patients, we will also measure methylation at either complete remission, or at exit from the protocol if the regimen did not provide substantial benefit. When more than one gene is used (and methylated at baseline), each gene will be considered separately for all correlative endpoints. Global DNA methylation will also be measured by the LINE1 bisulfite pyrosequencing assay. In addition to methylation, we will also measure expression of *p15* and *p21* at these same time-points by real-time polymerase chain reaction (qPCR). The values obtained will be compared to our experience with single-agent decitabine and will also be correlated with response. All these studies will be performed by Dr. Jean-Pierre Issa at Temple University – Fels Institute.

Optional samples will also be obtained for decitabine pharmacokinetics and stored for subsequent analysis. Samples will be obtained at 0, 1, 4, 8, and 24 hours on Cycle 1 Day 1 and baseline only on Cycle 2 Day 1. All samples will be collected in the Leukemia Department clinic by accredited personnel. All pharmacokinetic studies will be performed at M.D. Anderson Cancer Center.

## 7.0 PRETREATMENT EVALUATION

All pretreatment evaluations with the exception of the Cytogenetics should be completed within 14 days (+/- 2 days) prior to start of protocol treatment.

**7.1** A complete history, physical, concomitant medications and performance status.

**7.2** CBC, platelet count, differential, SGPT, creatinine, bilirubin, HBV screening, potassium, magnesium.

**7.3** Bone marrow aspirate.

**7.4** Bone marrow cytogenetics if not done in previous 3 months.

**7.5** Urine pregnancy test for women of childbearing potential.

**7.6** EKG.

**7.7** Optional blood sample (12 cc) for methylation studies, to be sent to Dr. Jean-Pierre Issa's laboratory (215-707-4307). Optional samples will also be obtained for Decitabine pharmacokinetics.

## 8.0 EVALUATION DURING STUDY

**8.1** Physical exam, review of toxicity and concomitant medications before the start of cycle 2, and then every 2-4 cycles for the first year, then every 6 cycles.

**8.2** Patients will keep a study diary that will be reviewed at scheduled study visits.

**8.3** CBC, platelet count and differential (if WBC $>1x10^9$/L) weekly for the first 3 cycles, then Q2-4 weeks.

**8.4** SGPT, creatinine, bilirubin, potassium, magnesium Q1-2 weeks for the first 3 cycles then every 4-8 weeks.

**8.5** EKG approximately 1 week after the start of therapy.

**8.6** Bone marrow aspiration (to include cytogenetics) before the start of cycle 2 and every 3 cycles during the first year, then every 4-6 cycles as clinically indicated.

**8.7** Peripheral blood for PCR for bcr/abl every 1-3 months.

**8.8** Optional: Blood sample (12 cc) on days 0 (same sample as described in section 7.7), 5 and 12 (all days +/- 2 days) of treatment for methylation studies. The samples from days 5 and 12 will be collected during the first course of treatment. Samples to be sent to Dr. Jean-Pierre Issa's laboratory (215-707-4307).*

**8.9** Optional: Blood sample (12 cc) from all patients at either complete remission or when taken off study (if possible) (+/- 2 days). Samples to be sent to Dr. Jean-Pierre Issa's laboratory (215-707-4307).*

**8.10** Patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluation during study may be modified after discussion with the principal investigator. These include a decrease in the frequency of

bone marrow aspirations to every 6-12 months (or as clinically indicated), and laboratory tests once with every cycle.

**8.11** Optional: Blood sample (about 1 teaspoon) for Decitabine pharmacokinetics at 0, 1, 4, 8, 24 hrs on Cycle 1 Day 1 and baseline only on Cycle 2 Day 1.

* Missing occasional samples of optional correlative studies and for Decitabine pharmacokinetics will not be considered a protocol deviation.

## 9.0 CRITERIA FOR RESPONSE AND TOXICITY

### 9.1 Major Hematologic Response (HR)

#### 9.1.1 Complete Hematologic Response (CHR):

**9.1.1.1** WBC ≤ institutional upper limit of normal (ULN).

**9.1.1.2** Absolute neutrophils count (ANC) ≥1 $x10^9$/L.

**9.1.1.3** Platelets >100 $x10^9$/L.

**9.1.1.4** No blasts or promyelocytes in peripheral blood.

**9.1.1.5** < 5% myelocytes plus metamyelocytes in peripheral blood

**9.1.1.6** Peripheral blood basophils <5%

**9.1.1.7** No extra-medullary involvement including no splenomegaly or hepatomegaly

**9.1.1.8** ≤5% blasts in bone marrow

**9.1.2 No Evidence of Leukemia (NEL)** - meet the same criteria as CHR except for:

**9.1.2.1** WBC ≤ institutional upper limit of normal (ULN).

**9.1.2.2** No blasts or promyelocytes in peripheral blood.

**9.1.2.3** < 5% myelocytes plus metamyelocytes in peripheral blood

**9.1.2.4** Peripheral blood basophils <5%

**9.1.2.5** No extra-medullary involvement including no splenomegaly or hepatomegaly

**9.1.2.6** ≤5% blasts in bone marrow

**9.1.2.7** At least one of the following:

**9.1.2.7.1** 20 $x10^9$/L ≤ Platelets <100 $x10^9$/L

**9.1.2.7.2** 0.5 x$10^9$/L ≤ ANC <1 x$10^9$/L

**9.2** **Minor Hematologic Response (MiHR)** - meet all of the following:

**9.2.1** < 15% blasts in BM and PB

**9.2.2** < 30% blasts + promyelocytes in BM and PB

**9.2.3** < 20% basophils in PB

**9.2.4** No extra-medullary disease other than spleen and liver

**9.3** **Overall Hematologic Response (OHR)** is defined as CHR, NEL or MiHR

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

**9.5** **Cytogenetic Response (CyR)**: classified according to suppression of the Philadelphia chromosome (Ph) by cytogenetics (FISH if cytogenetic analysis not informative, e.g., insufficient metaphases)

**9.5.1** No cytogenetic response - Ph positive >95%

**9.5.2** Minimal cytogenetic response - Ph positive 66-95%

**9.5.3** Minor cytogenetic response - Ph positive 36-65%

**9.5.4** Partial cytogenetic response - Ph positive 1-35%

**9.5.5** Complete cytogenetic response - Ph positive 0%

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

**9.6** **Molecular Response**

**9.6.1** Major (MMR): BCR-ABL/ABL ratio ≤ 0.1% (IS). Currently, results form the MDACC laboratory can be converted to the IS by multiplying the BCR-ABL1/ABL1 ratio by 0.35.

**9.6.2** Complete: Undetectable BCR-ABL

**9.7** Duration of Response will be measured frome the date the given response is achieved to the date the response is first known to be lost.

**9.8** Overall survival will be measured from the date treatment is started to the date of death or last follow-up.

**9.9** Toxicities will be reported on a scale of 1-4 according to the NCI criteria Common Terminology Criteria for Adverse Events (CTCAE), Version 4

## 10.0 CRITERIA FOR REMOVAL FROM STUDY

**10.1** Patients with clinically significant progressive disease

**10.2** Unacceptable (grade 3-4) toxicity in the absence of significant antileukemic effect.

**10.3** Patient's request.

**10.4** If the patient does not derive any appreciable benefit and/or has better treatment options as judged by the investigator.

**10.5** Poor compliance with treatment or protocol procedures.

## 11.0 REGULATORY AND REPORTING REQUIREMENTS

### 11.1 Regulatory and Reporting Requirements

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.0 of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Version 4.0 of CTCAE.

Refer to Section 11.2 for Leukemia-Specific Adverse Event Recording Guidelines. The Principal Investigator will sign the PDMS/CORe Case Report Form toxicity pages per each patient at the completion of each course for the first 3 courses, then every 3-6 courses. The attribution of toxicity will be determined by the PI. Following signature, the Case Report Form will be used as source documentation for the adverse events.

### 11.2 Leukemia-Specific Adverse Event Recording and Reporting Guidelines

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events-definition of expected AE-" All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study treatment" and Guideline for Good Clinical Practice 4.11.1 "All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting".

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be

considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

Adverse Events (AEs) will be evaluated according to current CTC version in each protocol. Only unexpected AEs will be recorded in the Case Report Form (CRF). Expected events during leukemia therapy are:

1. Myelosuppression related events (due to disease or leukemia therapy)
   a. febrile or infection episodes not requiring management in the intensive care unit
   b. epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage
   c. anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis
2. Disease related events
   a. symptoms associated with anemia
      i. fatigue
      ii. weakness
      iii. shortness of breath
   b. electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)
   c. chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)
   d. coagulation abnormalities
   e. disease specific therapy (induction, maintenance, salvage, or stem cell therapy)
   f. alopecia
   g. bone, joint, or muscle pain
   h. liver function test abnormalities associated with infection or disease progression
   i. disease progression
3. General therapy related events
   a. catheter related events
   b. renal failure related to tumor lysis syndrome or antibiotic/ antifungal therapy
   c. rash related to antibiotic use

4. Hospitalization for the management of any of the above expected events

Abnormal hematologic values will not be recorded on the CRF. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF.

## 11.3 Serious Adverse Event Reporting (SAE)

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

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

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

**Reporting to FDA:**

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

  It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

**Investigator Communication with Supporting Companies:**

**All SAEs should be faxed or emailed to BMS at:**
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

## 12.0 STATISTICAL CONSIDERATIONS

**Phase I Stage**

A 3+3 design for dose escalation scheme will be used. For purposes of estimating the MTD, up to 2 schedules of combination Dasatinib/Decitabine treatment will be considered. These schedules are listed in the table below. Schedule A is a less intensive schedule of the combination while Schedule B is a more intensive schedule. To minimize the risk to patients we will proceed in a sequential manner using a 3+3 algorithm and starting the first cohort patients at Schedule A. The starting dose is defined by dose level 0 on section 5.3.4, with the target dose being dose level +1 for both schedules. If no MTD is identified at this dose level, the phase II stage will begin with this dose, or at the maximum dose resulting in <2/6 patients with DLT for each cohort. The phase II portion of the study will commence once and MTD is defined for both schedules, or when 0/3 or ≤1/6 patients treated at dose level +1 have been treated without experiencing DLT. Treatment escalation will be based on toxicities observed through 28 days of drug administration.

### 1 Schedules

| Schedule | Fixed Dose Dasatinib/Variable Decitabine |
|---|---|
| A (less intensive) | Dasatinib 100mg daily; Decitabine 10 mg/m$^2$ IV daily for 10 days |

| | |
|---|---|
| B (more intensive) | Dasatinib 100mg daily; Decitabine 20 mg/m$^2$ IV daily for 10 days |

Patients will be treated in cohorts of 3 using a 3+3 algorithm. The probability of escalating from one dose to the next dose given the true probability of toxicity is given in the table below. We can see that for low probabilities of toxicity we are likely to escalate while for high toxicity probabilities we are unlikely to escalate.

**2 Dose Escalation**

| Probability of Toxicity | Probability of Dose Escalation |
|---|---|
| 0.01 | 0.999 |
| 0.10 | 0.906 |
| 0.20 | 0.709 |
| 0.30 | 0.494 |
| 0.40 | 0.309 |
| 0.50 | 0.172 |
| 0.60 | 0.082 |
| 0.70 | 0.032 |
| 0.80 | 0.009 |

**Phase II Stage**

**Gehan Augmented Selection Design**

2.1 In this trial we will randomize patients to two treatment arms. The goal of this study is to evaluate the activity of the two arms. In the Gehan Stage of the design we will initially enroll 14 patients per arm and evaluate each arm independently for activity. An arm will be deemed active if we observe at least 1 of 14 patients with hematologic response (any hematologic response observed during the first 3 months of treatment) in a given arm. If we observe activity in both arms then the goal will be to accrue a total of 30 patients per arm and "select" the best arm, where the best arm is the arm in which more patients respond. We justify our power calculation below.

The test statistic to select treatment *s* over treatment *t* at the end of a trial is:

$$Z` = \frac{\hat{p}_s - \hat{p}_t}{\sqrt{\frac{p_s(1-p_s)}{m_s+n_s} + \frac{p_t(1-p_t)}{m_t+n_t}}}$$

Where

$$\hat{p}_s = \frac{x_s + X_s}{m_s + n_s}$$

$$\hat{p}_t = \frac{x_t + X_t}{m_s + n_s}$$

The variable $x_S$ is the data accumulated at the Gehan interim look for group s and $X_S$ is the future data that will accrue for group s. Note that $x_S$ is observed thus fixed.

The quantity $x_t$ is the accumulated data at the Gehan interim analysis for group t and $X_t$ is the future data that will accrue for group t. Note that $x_t$ is observed thus fixed.

Now define

$$\hat{p}_s(x_s) = \frac{x_s + x'_s}{m_s + n_s}$$

$$\hat{p}_t(x_t) = \frac{x_t + x'_t}{m_s + n_s}$$

$$\hat{\theta} = \hat{p}_s(x_s) - \hat{p}_t(x_t)$$

Given these definitions the probability of both arms advancing past the first stage of the Gehan design and then at the end of the trial declaring treatment *s* superior to treatment *t* is given as

$$\sum_{x_s=1}^{m_s}\sum_{x_t=1}^{m_t}\sum_{x'_s=0}^{n_s}\sum_{x'_t=0}^{n_t}\binom{m_s}{x_s}p_s^{x_s}(1-p_s)^{m_s-x_s}\binom{m_t}{x_t}p_t^{x_t}(1-p_t)^{m_t-x_t} \cdot \times\binom{n_s}{x_s}p_s^{x'_s}(1-p_s)^{n_s-x'_s}\binom{n_t}{x'_t}p_t^{x'_t}(1-p_t)^{n_t-x'_t} I\left(0<\hat{\theta}\right)$$

Based on these probabilities the chance of selecting *s* over *t* if the response rate is 25% in for treatment *s* and 5% for treatment *t* is 97.0%. The chance of selecting *s* over *t* if the response rate is 40% in the *s* arm and 25% for the *t* arm the power is 86.8%.

If only one arm proceeds to the second stage of the Gehan design, we will accrue a total of 20 patients in the second stage. For example if treatment *s* stops in stage 1 because of 0 of 14 patients experienced hematologic response, then treatment *t* will accrue only 7 more patients.

**Toxicity Monitoring**

An arm will stop if unexpected grade 3-4, treatment-related toxicity exceeds 33% at any time in the trial.

## 13.0 REFERENCES

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