

**National PBM Drug Monograph
Dasatinib (Sprycel™)
February 2007**

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Efficacy

- Dasatinib is a multikinase inhibitor of BCL-ABL, c-kit, PDGFR β , EPHA, and the Src family of kinases.
- Binding occurs on both the open and closed conformations of the ABL kinase domain, making it effective in most imatinib resistant diseases that are due to kinase mutations; the T315I kinase mutation is resistant to both imatinib and dasatinib.
- In Chronic Phase Chronic Myelogenous Leukemia (CML) patients resistant to or intolerant of imatinib, dasatinib produced major cytogenetic responses as well as some complete cytogenetic responses.
- When compared to high dose imatinib in this population in a randomized phase II trial, dasatinib produced more major and complete cytogenetic responses. Of note, 79% of high dose imatinib patients crossed over to dasatinib therapy because of intolerance or progressive disease.
- In general, patients with initial imatinib intolerance had more favorable responses to dasatinib than did patients with initial imatinib resistance.
- In advanced CML (accelerated phase, myeloid blast crisis) and lymphoid blast crisis/Ph+ ALL patients resistant to or intolerant of imatinib, dasatinib produced major hematologic responses. The durability of those responses is yet to be determined.

Safety

- Adverse events were reported in the majority of dasatinib treated patients.
- Common adverse events include: Diarrhea, nausea, abdominal pain, vomiting, fluid retention (peripheral edema, pleural effusion), constitutional symptoms: pyrexia, headache, fatigue, asthenia, anorexia
- Serious adverse events include: neutropenia, thrombocytopenia, anemia (less common in chronic phase CML) neutropenic fever (10%), bleeding events (10%), pyrexia, dyspnea, pleural effusion (5%), diarrhea
- Other precautions include: myelosuppression (neutropenia, thrombocytopenia, and anemia), fluid retention (pleural and pericardial effusions), bleeding risks (including CNS hemorrhage with some fatalities and severe gastrointestinal bleeds), QTc prolongation, and laboratory abnormalities (elevated transaminases, bilirubin, hypocalcemia, hypophosphatemia)
- Discontinuation due to Adverse Events: 4-6% in Chronic Phase CML and Accelerated Phase CML 13-15% in Myeloid Blast Phase CML, Lymphoid Blast Phase CML, Ph+ALL
- Dose adjustments: Dose reductions in 21-50% Dose interruptions in 68-82%

Recommendations/Place in Therapy

- Patients with Chronic Phase CML, Accelerated Phase CML, Myeloid Blast Crisis CML, Lymphoid Blast Crisis CML, or Ph+ALL who develop resistance to or are intolerant of imatinib therapy
- ECOG PS 0-2 with adequate hepatic/renal function; potassium/magnesium/calcium within normal limits
- Consider limiting trial to a 4-month period based on data that most responses occurred within the first 3-4 months of therapy.
- Exclusion Criteria include uncontrolled/significant cardiovascular disease, bleeding disorder unrelated to CML, life expectancy < 4 months, sexually active male or female who will not use adequate form(s) of contraception.

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating dasatinib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Dasatinib is a multikinase inhibitor of BCR-ABL, c-KIT0, PDGFR β (platelet-derived growth factor receptor), SRC family of kinases, and EPHA (ephrin A receptor kinases). It binds to both the active or opened conformation and the inactive or closed conformation of the ABL kinase domain of BCR-ABL. Imatinib is only able to bind to the inactive or closed conformation. This binding difference accounts for the activity of dasatinib in most imatinib resistant kinase mutations. Dasatinib is ineffective against the imatinib resistant ABL mutation at T315I.

Table #1 Pharmacokinetic Parameters

Parameter	Dasatinib
Metabolism	Hepatic, primarily by CYP3A4 to active metabolite; does not induce CYP3A4 and is a weak inhibitor of CYP3A4; <4% excreted in urine
Elimination	Primarily in feces
Half-life	Mean 4-6 hours
Protein Binding	94%
Absorption	14% increase in AUC after a high-fat meal with single dose; not clinically relevant

Special Populations

Hepatic Impairment- There are no clinical trials with dasatinib in patients with hepatic impairment

Renal Impairment- There are no clinical trials with dasatinib in patients with decreased renal function

Drugs that may increase dasatinib plasma concentrations:

CYP3A4 inhibitors like ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin

Drugs that may decrease dasatinib plasma concentrations:

CYP3A4 inducers like rifampicin

Antacids: In a nonclinical trial, pH affected solubility. When 30ml of aluminum hydroxide/magnesium hydroxide was administered 2 hours prior to dasatinib, C_{max} concentrations were increased 26% but there was no difference in the AUC. When the same was administered concomitantly with dasatinib, the C_{max} was reduced 58% and the AUC was reduced 55%.

Famotidine: Co-administration of dasatinib and famotidine in single dose studies showed a decrease of 63% in the C_{max} and a 61% decrease in the AUC.

Drugs altered by dasatinib

The C_{max} and AUC of simvastatin were reduced by 37% and 20%, respectively, in single dose co-administration studies.

FDA Approved Indication(s) and Off-label Uses

The treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. The effectiveness of dasatinib was based on response rates and not on demonstrating a clinical benefit (like improved symptom control or increased survival).

The treatment of adults with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

Off label: Gastrointestinal stromal tumors (GIST)

Current VA National Formulary Alternatives

High dose imatinib for imatinib resistant CML

Dosage and Administration

The recommended dose of dasatinib is 140 mg per day orally in two divided doses (70 mg twice a day, once in the morning and once in the evening without regards to meals). Do not crush or cut tablets; they should be swallowed whole.

Continue dosing until the disease progresses or until no longer tolerated. The effect of stopping once a complete cytogenetic response is obtained has not been studied.

Dose Modifications

Increase or decrease the dose in 20mg increments based on individual safety and tolerability.

CYP3A4 inducers like rifampicin have resulted in a decrease in the mean C_{max} and AUC of dasatinib by 81% and 82%, respectively. Selection of another medication with no or minimal enzyme induction ability is recommended. If no substitute exists, a dose increase of dasatinib is recommended with careful monitoring.

St. John's Wort may decrease dasatinib concentrations unpredictably, and should not be given concomitantly.

CYP3A4 inhibitors such as ketoconazole may increase dasatinib plasma concentrations. Selection of an alternative medication is recommended. If there is no alternative, it is suggested to decrease the dasatinib dose to 20-40 mg daily.

In Philadelphia positive CML and ALL patients, doses were increased to 90mg twice a day in chronic phase CML and to 100mg twice a day in advanced phase CML and ALL for patients who did not achieve a complete cytogenetic or hematologic response using the recommended dose.

Dose Modifications for Adverse Events**Table #2 Myelosuppression**

Disease	Peripheral Counts	Modifications
Chronic Phase CML (starting at 70mg twice a day)	ANC <0.5 x 10 ⁹ /L And/or Platelets <50 x 10 ⁹ /L	1. Stop dasatinib until ANC ≥1 x 10 ⁹ /L and platelets ≥50 x 10 ⁹ /L 2. Resume therapy at original starting dose 3. If platelets are <25 x 10 ⁹ /L and/or recurrence of ANC <0.5 x 10 ⁹ /L for >7 days, repeat Step 1 and resume dasatinib at reduced dose of 50mg twice a day (second episode) OR 40mg twice a day (third episode)
Accelerated Phase CML, Blast	ANC <0.5 x 10 ⁹ /L	1. Check if cytopenia related to leukemia (bone

Phase CML and Ph+ ALL (Starting dose 70mg twice a day)	And/or Platelets <10 x 10 ⁹ /L	marrow aspirate or biopsy) 2. If unrelated to leukemia, stop dasatinib until ANC ≥ 1 x 10 ⁹ /L and platelets ≥ 20 x 10 ⁹ /L and resume at original dose 3. If recurrence of cytopenia, repeat Step 1 and resume dasatinib at a reduced dose of 50mg twice a day (second episode) or 40mg twice a day (third episode) 4. If cytopenia is related to leukemia, consider increasing dose to 100mg twice a day.
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Non-hematologic adverse events:

If severe non-hematologic events develop, hold dasatinib until the event has resolved or improved. Resume treatment at a reduced dose depending on the initial severity of the adverse event.

Efficacy^{1,2,3}

Efficacy Measures

The primary endpoint in chronic phase CML was major cytogenetic response (MCyR). This was defined as either a complete cytogenetic response (CCyR) or partial cytogenetic response. A complete cytogenetic response refers to elimination of the Ph+ chromosome or 0% Ph+ metaphases. A partial cytogenetic response refers to a reduction in the Ph+ chromosome by at least 65% or 0-35% Ph+ metaphases.

The primary endpoint in accelerated, myeloid blast, lymphoid blast phases and Ph+ ALL was major hematologic response (MaHR). This was defined as complete hematologic response (CHR) or no evidence of leukemia (NEL) confirmed after 4 weeks. Minor hematologic response (MiHR), which is return to chronic phase, is defined as < 15% blasts in bone marrow and peripheral blood; < 30% blasts plus promyelocytes in bone marrow and < 30% blasts plus promyelocytes in peripheral blood; < 20% basophils in peripheral blood; no extramedullary disease other than spleen and liver.

CHR was further defined within each disease phase as follows:

Chronic CML: WBC ≤ institutional ULN, platelets < 450,000/mm³, no blasts or promyelocytes in peripheral blood, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood ≤ institutional ULN, and no extramedullary involvement.

Advanced CML/Ph+ ALL: WBC ≤ institutional ULN, ANC ≥ 1000/mm³, platelets ≥ 100,000/mm³, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5%, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood ≤ institutional ULN, and no extramedullary involvement.

NEL: same criteria as for CHR, but ANC ≥ 500/mm³ and < 1000/mm³, and/or platelets ≥ 20,000/mm³ and ≤ 100,000/mm³.

Summary of efficacy findings

Two Phase II trials were performed to determine the efficacy of dasatinib in patients with chronic phase CML who were either resistant or intolerant to imatinib.

A. Chronic Phase

- Study CA180013 was a single-arm, open-label, multicenter trial involving patients who either developed progressive disease on imatinib doses > 600mg/day; developed resistance on ≤ 600mg/day with mutations of the BCR-ABL gene associated with a high level of resistance or were intolerant to imatinib at any dose.
- Of a total of 186 participants, 59 were imatinib-intolerant and 127 were imatinib-resistant.
- Patients were treated with dasatinib 70mg BID initially, then increased to 90mg BID if no response or disease progression after 8 weeks of therapy.

- The primary endpoint was MCyR at 12 weeks. Secondary endpoints included durability and time to MCyR as well as rate, duration and time to CHR.
- MCyR at 12 weeks was noted in 45% of patients overall. Of those responders, 43 (73%) were imatinib-intolerant while 40 (31%) were imatinib-resistant. At the 6-month follow-up, MCyR was noted in 43 (80%) of imatinib-intolerant subjects and 40 (33%) of imatinib-resistant subjects.
- CCyR rate for imatinib-intolerant subjects was 56% and 22% in imatinib-resistant subjects. At the 6-month follow-up, CCyR was noted in 33 (61%) of imatinib-intolerant subjects and 28 (23%) of imatinib-resistant subjects.
- Time and duration of MCyR were secondary endpoints. Median time to MCyR was 85 days. Duration of MCyR could not be determined as all patients with MCyR were responding at the conclusion of study.
- Rate, duration and time to CHR were secondary endpoints. Overall, 90% of subjects achieved CHR. Imatinib-resistant subjects with abnormal blood counts at baseline appeared to have lower response rates 70/86 (81%) than those with normal baseline blood counts 39/41 (95%). Median time to CHR was 16 days and the median duration of response was 7.6+ months.
- Most patients (79%) required dose interruptions, while 52% required dose reductions. Only 3% of patients had dose increased to 90mg BID.

B. Chronic Phase

- Study CA180017 was an open-label, non-comparative Phase II trial involving patients that were resistant to imatinib 400 - 600mg daily. Patients were randomized in a 2:1 ratio to either dasatinib 70mg BID or imatinib 400mg BID.
- Dose escalations of dasatinib were permitted. No dose escalations were permitted for imatinib. A crossover to the alternative treatment with appropriate washout period was permitted for lack of response, disease progression or intolerance.
- The primary endpoint was MCyR at 12 weeks. Secondary endpoints included durability and time to MCyR as well as rate, duration and time to CHR.
- Of a total of 36 participants, 22 were initially treated with dasatinib and 14 were initially treated with imatinib.
- A total of 79% in the imatinib arm crossed over to the dasatinib arm within 12 weeks due to either intolerance or inadequate response. Within the dasatinib arm, 9% of patients crossed over to imatinib due to either intolerance or progressive disease.
- MCyR at 12 weeks was 45% in the dasatinib group and 21% in the imatinib group. CCyR rate at 12 weeks was 37% in the dasatinib group and 7% in the imatinib group. Cytogenetic response data is limited because of short follow-up after crossover.
- Rate, duration and time to CHR were secondary endpoints. At 12 weeks, 21/22 (95%) of patients treated with dasatinib achieved a CHR, while 12/14 (93%) of patients treated with imatinib achieved a CHR. Mean time to CHR was 15 days. Due to short follow-up, the duration of response could not be estimated.
- Reviewer's note that the authors attempted to define a comparator arm for dasatinib by increasing the imatinib dose to 400mg BID. They note that this attempt was not successful as 79% of patients left the imatinib arm within 12 weeks, either because of intolerance or lack of efficacy.
- Reviewer's also note that this study did not define the time or durability of cytogenetic response.

Endpoints for the accelerated phase, myeloid blast phase, lymphoid blast phase and ALL trials were different than those used in the chronic phase trials. Primary endpoints for studies CA180005, CA180006 and CA180015 include Overall Hematologic Response (OHR) and Major Hematologic Response (MaHR). Secondary endpoints include Minor Hematologic Response (MiHR), time and durability of OHR and MaHR, Complete Hematologic Response (CHR) and No evidence of leukemia (NEL).

C. Accelerated Phase

- Study CA 180005 was a Phase II open-label, single-arm, multicenter trial involving patients with accelerated phase CML who were resistant or intolerant to imatinib.
- Treatment included dasatinib 70mg BID until disease progression or toxicity. Dose escalation to 100mg BID was permitted for disease progression; dose reduction was permitted for toxicity.
- The primary endpoints were to estimate the Major Hematologic Response (MaHR) and Overall Hematologic Response (OHR) rates. Secondary endpoints included durability and time to hematologic response; assess hematologic, cytogenetic and molecular responses in the imatinib-intolerant group; measure health-related QOL; assess safety and tolerability of dasatinib.
- A total of 107 patients were included; 99 were considered to be imatinib-resistant; 8 were considered to be imatinib-intolerant.
- MaHR after a median follow-up of 6 months was 5/8(63%) in the imatinib-intolerant group and 58/99(59%) in the imatinib-resistant group for an overall response rate of 59%. Median time to MaHR was 57 days.
- OHR after a median follow-up of 6 months was 6/8(75%) in the imatinib-intolerant group and 80/99(81%) in the imatinib-resistant group for an overall response rate of 80%. Median time to OHR was 30 days.
- Durability and time to hematologic response were secondary endpoints. CHR was noted in 35/107 (33%) overall. CHR was noted in 2/8 (25%) of imatinib-intolerant patients and 33/99 (33%) of imatinib-resistant patients. Most responses occurred during the first 3 months of therapy.
- Dose reductions occurred in 52 (49%) patients due to hematologic toxicity (28/52) and non-hematologic toxicity (13/52). Non-hematologic toxicity included GI bleed (4), diarrhea (2), headache (2), asthenia (1), renal insufficiency (1), arrhythmia (1) and pneumonia (1). Dose interruptions occurred in 71 (66%) patients due to hematologic toxicity (35/71) and non-hematologic toxicity (31/71).
- No data was provided on other secondary endpoints which included measure of QOL and safety/tolerability of dasatinib.

D. Myeloid Blast Phase

- Study CA 180006 was a Phase II, open-label, multicenter trial that involved patients in myeloid blast phase CML and either imatinib-resistance or intolerance.
- Treatment included dasatinib 70mg BID until disease progression or toxicity. Dose escalation to 100mg BID was permitted for disease progression; dose reduction was permitted for toxicity.
- The primary endpoints were to estimate the Major Hematologic Response (MaHR) and Overall Hematologic Response (OHR) rates. Secondary endpoints included durability and time to hematologic response; assess hematologic, cytogenetic and molecular responses in the imatinib-intolerant group; assess cytogenetic and molecular responses in the imatinib-resistant group; measure health-related QOL; assess safety and tolerability of dasatinib.
- A total of 74 patients were included; 6 were considered to be imatinib-intolerant; 68 were considered to be imatinib-resistant.
- MaHR after a median follow-up of 6 months was 1/6 (17%) in the imatinib-intolerant group and 23/68 (34%) in the imatinib-resistant group for an overall response rate of 32%. Median time to MaHR was 57 days.
- OHR after a median follow-up of 6 months was 3/6 (50%) in the imatinib-intolerant group and 36/68 (53%) in the imatinib-resistant group for an overall response rate of 53%. Median time to OHR was 30 days.
- The secondary endpoint of CHR was noted in 1/6 (17%) of imatinib-intolerant patients; 17/68 (25%) of imatinib-resistant patients for an overall response rate of 24%.
- The secondary endpoint of NEL was noted in none of imatinib-intolerant patients; 6/68 (9%) of imatinib-resistant patients for an overall response rate of 8%.
- The secondary endpoint of MiHR was noted in 2/6 (33%) of imatinib-intolerant patients; 13/68 (19%) of imatinib-resistant patients for an overall response rate of 20%.
- Hematologic and cytogenetic responses occurred during the first 3 months of therapy.
- No data was provided on other secondary endpoints which included measure of QOL and safety/tolerability of dasatinib.

E. Ph+ ALL or Lymphoid Blast Phase

- Study CA 180015 was a Phase II, open-label, single-arm trial that involved patients in lymphoid blast phase CML and Ph+ ALL and either imatinib-resistance or intolerance.
- Treatment included dasatinib 70mg BID until disease progression or toxicity. Dose escalation to 100mg BID was permitted for disease progression; dose reduction was permitted for toxicity.
- The primary endpoints were to estimate the Major Hematologic Response (MaHR) and Overall Hematologic Response (OHR) rates. Secondary endpoints included durability and time to hematologic response; assess hematologic, cytogenetic and molecular responses in the imatinib-intolerant group; assess cytogenetic and molecular responses in the imatinib-resistant group; measure health-related QOL; assess safety and tolerability of dasatinib; explore role of gene expression and point mutations as surrogates of response.
- A total of 78 patients were included; 42 with lymphoid blast CML; 36 with Ph+ ALL.
- MaHR after a median follow-up of 6 months was 13/42 (31%) in the lymphoid blast group and 15/36 (42%) in the Ph+ ALL group. Median duration of response in the lymphoid blast group was 3.71 months; median duration of response in the Ph+ ALL group was 4.83 months.
- The secondary endpoint of MCyR was noted in 21/42 (50%) in the lymphoid blast group and 21/36 (58%) in the Ph+ ALL group.
- No data was provided on other secondary endpoints which included measure of QOL and safety/tolerability of dasatinib. Determination of molecular response was not included in the interim analysis.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page15).

Adverse Events (Safety Data)**Table #3 Adverse Events ≥10% in Clinical Trials**

Adverse Event	All Patients (n=911)		Chronic (n=488)	Accelerated (n=186)	Myeloid Blast (n=132)	Lymphoid Blast and Ph+ ALL (n=105)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
Fluid Retention	50	9	6	6	23	9
Superficial edema	36	1	0	2	3	2
Pleural effusion	22	5	3	3	14	8
Other retention	14	5	4	4	12	3
General edema	5	1	<1	0	2	1
CHF	4	2	3	1	5	1
Pericardial Effusion	4	1	<1	1	3	0
Pulmonary edema	4	1	1	2	0	1
Ascites	1	1	0	1	2	2
Pulmonary Hypertension	1	0	<1	1	2	0
Diarrhea	49	5	3	10	8	6
Headache	40	2	2	2	4	6
Hemorrhage	40	10	3	18	23	17
GI Bleed	14	7	2	12	14	10
CNS Bleed	2	1	0	1	2	2
Musculoskeletal Pain	39	4	2	3	6	13
Pyrexia	39	5	1	5	13	9
Fatigue	39	3	2	4	4	8
Skin Rash	35	1	1	1	1	4
Nausea	34	1	<1	0	5	2
Dyspnea	32	6	5	7	11	9
Cough	28	<1	<1	1	1	0
Infection Includes bacterial, viral, fungal, NOS	34	7	4	8	15	13
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infection/inflammation	26	1	1	1	5	1
Abdominal Pain	25	2	1	2	4	6
Pain	26	2	<1	1	5	4
Vomiting	22	1	1	2	2	2
Anorexia	19	1	<1	2	2	3
Asthenia	19	3	1	4	6	5
Arthralgia	19	1	1	0	3	2
Mucosal inflammation Includes mucositis	16	1	<1	0	4	1
Dizziness	14	<1	<1	0	0	0
Weight decrease	14	1	<1	1	1	0
Constipation	14	<1	<1	0	1	0
Chest Pain	13	1	<1	0	4	3
Neuropathy Includes peripheral	13	1	1	1	0	0
Myalgia	12	1	0	1	2	2
Abdominal distention	11	0	0	0	0	0
Weight Increase	11	1	<1	1	1	1
Arrhythmia	11	2	2	1	2	3
Chills	11	<1	0	1	0	0
Pruritis	11	0	0	0	0	0
Pneumonia Includes bacterial, viral, fungal	11	6	3	8	11	10
Febrile Neutropenia	9	8	2	11	17	20

Deaths and Other Serious Adverse Events (optional)

Hematologic: neutropenia, thrombocytopenia, anemia (less common in chronic phase CML)

Other: neutropenic fever (10%), bleeding events (10%), pyrexia, dyspnea, pleural effusion (5%), diarrhea

Deaths:

Chronic Phase CML: 3 deaths (1 CNS hemorrhage, pneumonia and progressive disease, renal failure)

Accelerated Phase CML: 4 deaths (1 disease progression with multi-organ failure, pneumonia possibly PCP, pneumonia, shock)

Myeloid Blast Phase CML: 22 deaths (13 due to progressive disease, 3 due to fatal bleeding, 5 due to infection, 1 due to respiratory distress with tumor lysis syndrome, 1 due to cardiac insufficiency)

Lymphoid Blast Phase/Ph+ALL: 25 deaths (9 due to disease progression, 10 due to infections including sepsis and pulmonary Aspergillosis, 1 due to pleural effusion, 1 due to CNS hemorrhage with neutropenia and thrombocytopenia, 1 due to constrictive pericarditis, 1 due to respiratory failure, 1 due to pulmonary hemorrhage, 1 due to sepsis and multi-organ failure)

Common Adverse Events

Diarrhea, nausea, abdominal pain, vomiting, fluid retention (peripheral edema, pleural effusion), constitutional symptoms: pyrexia, headache, fatigue, asthenia, anorexia

Edema of any type=40% Bleeding of any type=34%

Other Adverse Events

CNS hemorrhage in 6 patients- 5 fatal (all but 1 in patients with advanced disease)

Cardiac failure 4% (most with risk factors like hypertension)

QTc prolongation 3% (average increase over baseline 3-6 milliseconds)

Tolerability

Discontinuation due to Adverse Events:

4-6% in Chronic Phase CML and Accelerated Phase CML

13-15% in Myeloid Blast Phase CML, Lymphoid Blast Phase CML, Ph+ALL

Dose reductions in 21-50%

Dose interruptions in 68-82%

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Updated versions may be found at <http://www.pbm.va.gov> or <http://vaww.pbm.va.gov>

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 15).

Precautions/Contraindications

General

1. Myelosuppression: Treatment is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. It is more common in advanced CML or Ph+ALL than in chronic phase CML. Myelosuppression was generally reversible and managed by temporary dose interruption or dose reduction. Monitor CBC weekly for 2 months then monthly or as clinically indicated.

2. Bleeding Related Events: In humans, dasatinib causes thrombocytopenia and platelet dysfunction. CNS hemorrhages occurred in 1%, some with fatalities. Gastrointestinal bleeding occurred in 7% and generally required dose interruption and transfusions. Other cases of bleeding occurred in 4%. Most events were associated with thrombocytopenia. Caution if patients are required to take medications that inhibit platelet function or anticoagulants as these patients were excluded from clinical trials.

3. Fluid Retention: Fluid retention was severe in 9% and included pleural effusions (5%) and pericardial effusions (1%). Severe pulmonary edema was reported in 1% of patients. Patients with symptoms of pleural effusion (dry cough or dyspnea) should be evaluated with a chest X-ray. Severe pleural effusion may require treatment with a thoracentesis and oxygen. Fluid retention was generally managed with supportive care like diuretics or short courses of steroids.

4. QTc Prolongation: In single arm trials, QTc interval changes from baseline were 3-6 milliseconds; the upper 95% confidence interval was <8 milliseconds. Nine patients had prolonged QTc; in 3 patients the QTcF was >500 milliseconds. Administer dasatinib with caution to patients who have or may develop prolongation of QTc, including patients with hypokalemia or hypomagnesemia, congenital long QTc syndrome, patients taking certain antiarrhythmics or other drugs that may lead to prolongation of QTc, and cumulative high-dose anthracycline therapy. Correct hypokalemia or hypomagnesemia prior to dasatinib therapy.

Precautions

1. Hepatic impairment

There are no clinical studies with dasatinib in patients with impaired hepatic function. Caution is recommended in patients with hepatic impairment as dasatinib is mainly metabolized hepatically. Patients with ALT or AST >2.5 times the ULN and/or total bilirubin >2 times the ULN were excluded from clinical trials.

2. Renal impairment

There are no clinical trials with dasatinib in patients with impaired renal function. Renal excretion of dasatinib and its metabolites is <4%; a decrease in total clearance is not expected in patients with renal insufficiency. In clinical trials, patients with serum creatinine concentrations >1.5 times the ULN were excluded.

3. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis studies have not been performed.

Mutagenesis: dasatinib was clatogenic in Chinese hamster ovary cells, was not mutagenic in the Ames test, and not genotoxic in a rat micronucleus study.

Impairment of Fertility: Although not studied in humans, the results of repeat dose toxicity studies indicate a potential for impairment of reproductive function and fertility in several male and female animal models.

4. Pregnancy: Category D

5. Nursing mothers

Women taking dasatinib should not breast feed as it is unknown if dasatinib is excreted in breast milk.

6. Geriatric Use

In clinical trials, 23% of patients were over 65 years old and 13% were over 75 years old. There were no differences in efficacy and safety compared to younger patients, but greater sensitivity of some older patients cannot be ruled out.

7. Pediatric Use

The efficacy and safety in patients <18 years old has not been studied.

Contraindications

None known

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name dasatinib: erlotinib, imatinib, gefitinib, sorafenib, sunitinib

LA/SA for trade name Sprycel: Sprintec, Seroquel, Spiriva, Symmetrel

Drug Interactions

Drug-Drug Interactions

1. Drugs that may increase dasatinib concentrations:

CYP3A4 inhibitors: Dasatinib is a CYP3A4 substrate; concomitant use of drugs that inhibit CYP3A4 (for example ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin) may increase exposure to dasatinib and should be avoided. A dasatinib dose reduction and careful monitoring for adverse events are recommended if a potent CYP3A4 inhibitor cannot be avoided.

2. Drugs that may decrease dasatinib concentrations:

Drugs that induce CYP3A4 (including dexamethasone, phenytoin, carbamazepine, rifamicin, Phenobarbital) may decrease dasatinib plasma concentrations. If needed, alternative drugs with less enzyme induction potential should be considered. If a potent CYP3A4 cannot be avoided, consider a dose increase of dasatinib.

3. St. John's Wort may decrease dasatinib plasma concentrations unpredictably and should be avoided.

4. Antacids:

The solubility of dasatinib is pH dependent in nonclinical trials. Simultaneous administration with dasatinib should be avoided. If administration is needed, give the antacid at least 2 hours prior to or 2 hours after dasatinib.

5. H₂ blockers/Proton Pump inhibitors:

Long-term suppression of gastric pH is likely to reduce dasatinib exposure. The concomitant use with dasatinib is not recommended. The use of antacids should be considered in place of H₂ blockers or proton pump inhibitors.

6. Drugs that may be altered by dasatinib:

Dasatinib is a time-dependent inhibitor of CYP3A4. Drugs that are CYP3A4 substrates with narrow therapeutic indexes like alfentanil, astemizole, terfenidine, cisapride, cyclosporine, fentanyl, pimozone,

quinidine, sirolimus, tacrolimus, or ergot alkaloids should be used with caution in patients receiving dasatinib.

Drug-Lab Interactions

Table #4 CTC Grade 3/4 Laboratory Abnormalities (%)

Parameter	Chronic Phase	Accelerated Phase	Myeloid Blast Phase	Lymphoid Blast Phase and Ph+ALL
Hematology				
Neutropenia	49	74	83	81
Thrombocytopenia	48	83	63	83
Anemia	18	70	70	51
Biochemistry				
Hypophosphatemia	11	13	23	21
Hypocalcemia	2	9	20	15
Elevated ALT	1	4	7	11
Elevated AST	1	2	5	8
Elevated Bilirubin	<1	1	5	8
Elevated Creatinine	0	2	1	1
CTC Grades: neutropenia (Grade 3= \geq 0.5-1 x 10 ⁹ /L; Grade 4= $<$ 0.5 x 10 ⁹ /L); thrombocytopenia (Grade 3= \geq 10-50 x 10 ⁹ /L; Grade 4= $<$ 10 x 10 ⁹ /L); anemia (Grade 3=hemoglobin \geq 65-80 g/L; Grade 4= $<$ 65 g/L); creatinine (Grade 3= \geq 3-6 x ULN; Grade 4= $>$ 6 x ULN); bilirubin (Grade 3= \geq 3-10 x ULN; Grade 4= $>$ 10 x ULN); AST or ALT (Grade 3= \geq 5-20 x ULN; Grade 4= \geq 20 x ULN); hypocalcemia (Grade 3= $<$ 7-6 mg/dL; Grade 4= $<$ 6 mg/dL); hypophosphatemia (Grade 3= $<$ 2-1 mg/dL; Grade 4= $<$ 1 mg/dL)				

Acquisition Costs

Table #5 Comparative Acquisition Costs

Drug	Dose	Cost/Day/patient (\$)	Cost/Month/patient (\$)
Dasatinib	70 mg twice a day	97.23	2917.00
Imatinib	800mg/day	114.15	3424.54

Pharmacoeconomic Analysis

There are no published pharmacoeconomic analyses at this time.

Conclusions

Efficacy:

Dasatinib is a tyrosine-kinase inhibitor that binds to the ABL kinase domain in both active and inactive conformations. This is unlike its predecessor, imatinib, which binds to only the inactive (closed) conformation. It is thought that this difference in binding may overcome mutations that render imatinib ineffective.

Dasatinib provides a therapeutic option for patients in chronic, accelerated, or myeloid/lymphoid blast phase CML who have (1) developed resistance to imatinib as evidenced by progressive disease or (2) become intolerant to imatinib therapy, as evidenced by toxicity.

Overall, according to the available data at this time, the imatinib-intolerant population exhibits a greater response rate than the imatinib-resistant population. Responses typically occur within a 3-4 month time-frame. For this reason and cost of drug, would recommend documentation of response for continuation of therapy.

Safety:

A majority of patients experience adverse drug events during dasatinib therapy. Common adverse events include fluid retention (including pleural effusions), gastrointestinal events (nausea, diarrhea, abdominal pain, vomiting), and bleeding events.

The most frequent serious adverse events include pyrexia, pleural effusion, febrile neutropenia, gastrointestinal bleeding, pneumonia, thrombocytopenia, dyspnea, anemia, cardiac failure, and diarrhea.

Precautions for serious adverse events include: bleeding risks (severe CNS hemorrhage including fatalities and severe gastrointestinal bleeds), fluid retention (including pleural and pericardial effusions), QTc prolongation, myelosuppression (more frequent in patients with advanced CML and Ph+ALL), and laboratory abnormalities (including elevated transaminases and bilirubin, hypocalcemia, and hypophosphatemia).

Recommendations and Place in Therapy

1. Restricted to use by VA Hematology/Oncology Service
2. Patients with ECOG 0-2 performance status; adequate hepatic/renal function; age \geq 18 years; serum potassium/magnesium/calcium within normal limits.
3. Patients in chronic phase CML who develop progressive disease while receiving imatinib $>$ 600mg/day or are intolerant to imatinib at any dose.
4. Patients in Ph+ (or BCR/ABL+) accelerated phase or myeloid blast phase CML who develop progressive disease while receiving imatinib $>$ 600mg/day for at least 2-4 weeks or are intolerant to imatinib at any dose.
5. Patients with Ph+ (or BCR/ABL+) lymphoid blast phase CML who develop resistance to or are intolerant of imatinib therapy.
6. Patients with Ph+ ALL previously treated with standard induction or consolidation therapy and have either progression or lack of response to imatinib at doses \geq 600mg/day after a 4-week period.
7. Consider assessment of hematologic and cytogenetic response after a 4-month period to determine continuation of therapy, based on data that most responses occurred within the first 3-4 months of therapy.
8. Patients with any of the following conditions should NOT receive dasatinib:
 - ECOG performance status $>$ 2
 - Uncontrolled/significant cardiovascular disease
 - Significant bleeding disorder unrelated to CML
 - Life expectancy $<$ 4 months
 - Pregnancy or actively breastfeeding
 - Sexually active males/females who do not use adequate contraceptive methods

References

- ¹ Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in Imatinib-Resistant Philadelphia Chromosome-Positive Leukemias. *N Engl J Med* 2006; 354:2531-41.
- ² Center for Drug Evaluation and Research Application Number: 21-986 & 22-072 Medical Review; http://www.fda.gov/cder/foi/nda/2006/021986s000_Sprycel_MedR.pdf
- ³ Bristol-Myers Squibb Company. Sprycel™ Tablets product information. Princeton, NJ. 2006 June

Prepared February 2007. Contact person: Mark C. Geraci, Pharm.D., BCOP/Berni Heron, Pharm.D., BCOP

Appendix: Clinical Trials

Include a brief description of the methods used to perform the literature search (database, period, search strategy), inclusion criteria for studies, and sources of any other pertinent information on clinical trials (e.g., review of reference lists, manufacturer's formulary and AMCP dossier, medical reviews and transcripts on FDA Web site; conference abstracts—last resort if information is lacking or abstract is of major importance, etc.) This paragraph is optional. For example:

A literature search was performed on PubMed/Medline (1966 to August 2004) using the search terms <generic name> and <trade name>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Insert text here.

A summary of relevant clinical trials is presented in this section utilizing the example chart formats below. Randomized, placebo-controlled, blinded trials (Grade A evidence) should be reviewed in detail. If available, head-to-head trials against formulary or standard treatments are desired. Trials of low evidence (i.e. open-label, non-comparative, abstract form) should be mentioned with brief synopsis without going into great detail. For reviews including multiple trials a table or chart outlining level of evidence, results of primary efficacy measures and safety data is recommended for easier visual comparison.

Citation	Study CA180013																										
Study Goals	Determine the efficacy of dasatinib in chronic phase CML among patients who are defined as imatinib-intolerant or imatinib-resistant.																										
Methods	<p>Study Design: Phase II, single-arm, multicenter, open-label study Patients in chronic phase CML who were either resistant to imatinib or intolerant of imatinib at any dose.</p> <p>Treatment: dasatinib 70mg BID; dose escalation to 90mg BID permitted for those with lack of response or disease progression after 8 weeks of therapy</p> <p>Treatment continued until disease progression, intolerable toxicity or withdrawal from study</p> <p>Primary endpoint: MCyR at 12 weeks</p> <p>Secondary endpoints: durability and time to MCyR; rate, duration and time to CHR</p>																										
Criteria	<p>Inclusion criteria: men/women; age ≥ 18 yrs of age; with chronic phase CML; developed progressive disease on imatinib > 600mg/day with acquired or primary resistance; resistance to imatinib ≤ 600mg/day with genetic mutation associated with high level of resistance; intolerance of imatinib at any dose.</p> <p>Exclusion criteria : eligible/willing to undergo transplantation; women of childbearing potential unwilling/unable to use contraceptive methods; men whose partners are women of childbearing potential unwilling/unable to use contraceptive methods; pregnancy or breastfeeding; accelerated or blast phase CML; intolerance to imatinib; significant cardiovascular disease or bleeding disorder; concurrent incurable malignancy; BCR-ABL mutation</p> <p>A total of 186 patients in chronic phase CML, defined as either imatinib-intolerant (N=59) or imatinib-resistant (N=127), were included in the study. Chronic phase CML was defined as <15% blasts in peripheral blood (PB) and bone marrow (BM), <20% basophils in PB, < 30% blasts +promyelocytes in PB and BM, platelets ≥ 100,000/mm³ unless thrombocytopenia is due to recent therapy, and no extramedullary involvement (other than liver or spleen).</p>																										
Results	<table border="1" data-bbox="431 1367 1323 1682"> <thead> <tr> <th></th> <th>Imatinib-intolerant N=59</th> <th>Imatinib-resistant N=127</th> <th>Total N=186</th> </tr> </thead> <tbody> <tr> <td>CHR, N(%)</td> <td>57 (97)</td> <td>111 (87)</td> <td>168 (90)</td> </tr> <tr> <td>MCyR, N(%)</td> <td>43 (73)</td> <td>40 (31)</td> <td>83 (45)</td> </tr> <tr> <td>CCyR, N(%)</td> <td>33 (56)</td> <td>28 (22)</td> <td>61 (33)</td> </tr> <tr> <td>PCyR, N(%)</td> <td>10 (17)</td> <td>12 (9)</td> <td>22 (12)</td> </tr> <tr> <td>MCyR-20, N(%)</td> <td>42 (71)</td> <td>33 (26)</td> <td>75 (40)</td> </tr> </tbody> </table> <p>MCyR-20 rates based on ≥ 20 metaphases</p> <p>CHR (complete hematologic response); MCyR (major cytogenetic response); CCyR (complete cytogenetic response); PCyR (partial cytogenetic response)</p> <p>Most patients (79%) required dose interruptions; 52% required dose reductions: 3% escalated to 90mg BID</p>				Imatinib-intolerant N=59	Imatinib-resistant N=127	Total N=186	CHR, N(%)	57 (97)	111 (87)	168 (90)	MCyR, N(%)	43 (73)	40 (31)	83 (45)	CCyR, N(%)	33 (56)	28 (22)	61 (33)	PCyR, N(%)	10 (17)	12 (9)	22 (12)	MCyR-20, N(%)	42 (71)	33 (26)	75 (40)
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Conclusions	The authors note that given only 33% of patients achieved a MCyR with prior imatinib therapy, the MCyR rates with dasatinib (45%) are clinically valuable. The authors also note that 21 of 29 (72%) patients without a prior cytogenetic response on imatinib, achieved a MCyR with dasatinib.
Critique	<p>A strength of this trial is that they looked at subsets of responders (ie. those with BCR-ABL point mutations, imatinib-intolerant patients who never achieved a cytogenetic response).</p> <p>Most patients achieved MCyR after 12 weeks of treatment.</p> <p>MCyR was durable, as response was maintained during the 6-month follow-up.</p> <p>MCyR was higher among imatinib-intolerant, than imatinib-resistant patients (73% vs. 31%). This suggests that a mechanism causing imatinib-resistance may cause dasatinib-resistance as well.</p> <p>This study provides support for using dasatinib in patients who have either progressed on imatinib therapy, or were intolerant of imatinib. It also supports use of dasatinib in those patients who never achieved a response with imatinib.</p>

Citation	Study CA180017
Study Goals	Determine the efficacy of dasatinib in chronic phase CML among patients who were resistant to imatinib at doses of 400-600 mg/day.
Methods	<p>Study Design: Phase II, open-label, non-comparative study with 2:1 randomization of treatment arms.</p> <p>Patients in chronic phase CML resistant to imatinib 400mg – 600mg daily.</p> <p>Treatment: dasatinib 70mg PO BID vs imatinib 400mg PO BID; dasatinib dose-escalations were permitted in cases of disease progression/lack of response; dose-reductions were permitted for toxicity; imatinib dose-escalations were not permitted; dose-reductions to 600mg daily were permitted; crossover to alternative treatment was permitted after adequate washout period</p> <p>Primary endpoint: major cytogenetic response (MCyR) at 12 weeks</p> <p>Secondary endpoints: durability and time to MCyR; rate, duration and time to CHR.</p>
Criteria	<p>Inclusion criteria: men/women; age \geq 18 yrs of age; ECOG PS 0-1; with chronic phase CML; no previous treatment with imatinib $>$ 600mg/day; resistant to imatinib at doses 400-600mg/day; able to tolerate imatinib without \geq grade 3 or 4 toxicity; adequate hepatic/renal function; serum potassium/magnesium/calcium within normal limits</p> <p>Exclusion criteria: eligible/willing to undergo transplantation; women of childbearing potential unwilling/unable to use contraceptive methods; men whose partners are women of childbearing potential unwilling/unable to use contraceptive methods; pregnancy or breastfeeding; accelerated or blast phase CML; intolerance to imatinib; BCR-ABL mutation</p> <p>A total of 36 patients with a long history of chronic phase CML, and extensive pretreatment, were included. The median duration of CML was $>$ 5 years. Prior therapies included stem cell transplant, interferon and imatinib. Cross-over was permitted for insufficient response or intolerance to therapy.</p> <p>Baseline demographics: males/females equally represented in dasatinib arm; majority (93%) were female in imatinib arm; prior treatments were balanced, except dasatinib arm contained 5 patients with prior stem cell transplant; imatinib arm contained none.</p>

Results	Results at 12 weeks		
		Dasatinib N=22	Imatinib N=14
	CHR, N(%) [95% CI]	21 (95) [77.2-99.9]	13 (93) [66.1 – 99.8]
	MCyR, N(%)	10 (45) [24.4 – 67.8]	3 (21) [4.7 – 50.8]
	CCyR, N(%)	7 (32)	1 (7)
	PCyR, N(%)	3 (14)	2 (14)
	Crossover	2 (9)	11 (79)
	Reasons for crossover	1 intolerance; 1 PD	6 intolerance; 4 inadequate response; 1 PD
	CHR (complete hematologic response); MCyR (major cytogenetic response); CCyR (complete cytogenetic response); PCyR (partial cytogenetic response); PD (progressive disease)		
Conclusions	The authors note that dasatinib produced early and major cytogenetic response rates in patients resistant to conventional doses of imatinib, making it an effective therapeutic alternative to imatinib 800mg daily.		
Critique	<p>The majority (79%) of patients in the imatinib arm crossed over to the dasatinib arm within 12 weeks due to intolerance or lack of efficacy. Durability and time to cytogenetic response were not assessed.</p> <p>Hematologic response rates were comparable between arms; responses occurred quickly (median 15 days); unable to estimate duration of response due to short follow-up.</p>		

Citation	Study CA180005																						
Study Goals	Determine the efficacy of dasatinib in accelerated phase CML among patients who were resistant or intolerant to imatinib.																						
Methods	<p>Study Design: Phase II, open-label, single-arm, multicenter trial</p> <p>Patients in accelerated phase CML with primary or acquired resistance to imatinib</p> <p>Treatment: dasatinib 70mg PO BID until disease progression or toxicity; dose increase to 100mg PO BID was permitted for disease progression; dose reduction x 2 (50mg BID, then 40mg BID) was permitted for toxicity</p> <p>Primary endpoint: major hematologic response (MaHR) and overall hematologic response (OHR) rates</p> <p>Secondary endpoints: durability and time to hematologic response; assess hematologic, cytogenetic and molecular responses in the imatinib-intolerant group; measure health-related QOL; assess safety and tolerability of dasatinib</p>																						
Criteria	<p>Inclusion criteria: men/women; age \geq 18 yrs of age; ECOG PS 0-2; Ph+ (or BCR-ABL) accelerated phase CML; primary or acquired hematologic resistance to imatinib; imatinib intolerance; adequate hepatic/renal function; serum potassium/magnesium/calcium within normal limits</p> <p>Exclusion criteria: eligible/willing to undergo transplantation; women of childbearing potential unwilling/unable to use contraceptive methods; men whose partners are women of childbearing potential unwilling/unable to use contraceptive methods; pregnancy or breastfeeding; accelerated or blast phase CML; intolerance to imatinib; significant cardiovascular disease or bleeding disorder; concurrent incurable malignancy; BCR-ABL mutation; received imatinib within 7 days, interferon or cytarabine within 14 days; targeted therapy within 14 days; investigational agent within 28 days</p> <p>A total of 107 patients with a long history of chronic phase CML, and extensive pretreatment, were included. The median duration of CML was > 91 months (7.5 years). Prior therapies included stem cell transplant, interferon and imatinib.</p> <p>Baseline demographics: male/females equally represented; majority were Caucasians</p>																						
Results	<p>Hematologic and Cytogenetic Response Rates After Follow-up of \geq 6 months</p> <table border="1" data-bbox="431 1402 1421 1686"> <thead> <tr> <th></th> <th>Imatinib-intolerant N = 8</th> <th>Imatinib-resistant N=99</th> <th>Total N = 107</th> </tr> </thead> <tbody> <tr> <td>MaHR, N(%)</td> <td>4 (50)</td> <td>59 (59)</td> <td>63 (59)</td> </tr> <tr> <td>CHR, N(%)</td> <td>1 (13)</td> <td>34 (34)</td> <td>35 (33)</td> </tr> <tr> <td>MCyR, N(%)</td> <td>1 (12)</td> <td>32 (32)</td> <td>33 (31)</td> </tr> <tr> <td>CCyR, N (%)</td> <td>0</td> <td>23 (23)</td> <td>23 (22)</td> </tr> </tbody> </table> <p>MaHR (major hematologic response); CHR (complete hematologic response); MCyR (major cytogenetic response); CCyR (complete cytogenetic response); MiHR (minor hematologic response)</p> <p>OHR (overall hematologic response) rate defined as CHR + MiHR + NEL was 80%</p> <p>CyR based on \geq 20 metaphases, the MCyR rate was 37% (16 of 43 subjects)</p>				Imatinib-intolerant N = 8	Imatinib-resistant N=99	Total N = 107	MaHR, N(%)	4 (50)	59 (59)	63 (59)	CHR, N(%)	1 (13)	34 (34)	35 (33)	MCyR, N(%)	1 (12)	32 (32)	33 (31)	CCyR, N (%)	0	23 (23)	23 (22)
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	<p>Duration of therapy 5.5 months (range, 0.2-10.1)</p> <p>Most responses occurred during the first 3 months of dasatinib therapy. Median time to MaHR was 57 days; median time to OHR was 30 days.</p>
Conclusions	<p>The authors note that dasatinib achieved durable hematologic and cytogenetic responses as evidenced by the majority of patients still on study at ≥ 6 months of follow-up.</p>

Citation	Study CA180006																							
Study Goals	Determine the efficacy of dasatinib in myeloid blast phase CML among patients who were resistant or intolerant to imatinib.																							
Methods	<p>Study Design: Phase II, open-label, multicenter trial Patients in myeloid blast phase CML with imatinib-resistance or intolerance.</p> <p>Treatment: dasatinib 70mg PO BID until disease progression or toxicity; dose increase to 100mg PO BID was permitted for disease progression; dose-reduction x 2 (50mg BID, then 40mg BID) was permitted for toxicity</p> <p>Primary endpoint: major hematologic response (MaHR) and overall hematologic response (OHR) rates</p> <p>Secondary endpoints: durability and time to hematologic response; assess hematologic, cytogenetic and molecular responses in the imatinib-intolerant group; assess cytogenetic and molecular responses in the imatinib-resistant group; measure health-related QOL; assess safety and tolerability of dasatinib</p>																							
Criteria	<p>Inclusion criteria: men/women; age ≥ 18 yrs of age; ECOG PS 0-2; Ph+ (or BCR-ABL) myeloid blast phase CML; primary or acquired hematologic resistance to imatinib; imatinib intolerance; adequate hepatic/renal function; serum potassium/magnesium/calcium within normal limits</p> <p>Exclusion criteria: eligible/willing to undergo transplantation; women of childbearing potential unwilling/unable to use contraceptive methods; men whose partners are women of childbearing potential unwilling/unable to use contraceptive methods; pregnancy or breastfeeding; intolerance to imatinib; BCR-ABL mutation</p> <p>A total of 74 patients with a 4-year history of CML, and extensive pretreatment, were included. Prior therapies included stem cell transplant, chemotherapy, interferon and imatinib. Patients had baseline bone marrow blast cell count ≥ 50%</p> <p>Baseline demographics: males/females equally represented; majority (78%) were younger than 66 years; 58% had ECOG PS 0/1; 38% PS 2.</p>																							
Results	<p>Hematologic and Cytogenetic Response Rates at follow-up ≥ 6 months</p> <table border="1" data-bbox="431 1430 1344 1713"> <thead> <tr> <th></th> <th>Imatinib-intolerant N = 6</th> <th>Imatinib -resistant N=68</th> <th>Total N = 74</th> </tr> </thead> <tbody> <tr> <td>MaHR, N(%)</td> <td>1 (17)</td> <td>23 (34)</td> <td>24 (32)</td> </tr> <tr> <td>CHR, N(%)</td> <td>1 (17)</td> <td>17 (25)</td> <td>18 (24)</td> </tr> <tr> <td>MCyR, N(%)</td> <td>2 (33)</td> <td>20 (29)</td> <td>22 (30)</td> </tr> <tr> <td>CCyR, N (%)</td> <td>2 (33)</td> <td>18 (26)</td> <td>20 (27)</td> </tr> </tbody> </table> <p>MaHR (major hematologic response); CHR (complete hematologic response); MCyR (major cytogenetic response); CCyR (complete cytogenetic response)</p> <p>OHR (overall hematologic response) rate defined as CHR + MiHR + NEL was 53%. MCyR based on ≥ 20 metaphases, the MCyR rate was 37% (16 of 43 subjects)</p>					Imatinib-intolerant N = 6	Imatinib -resistant N=68	Total N = 74	MaHR, N(%)	1 (17)	23 (34)	24 (32)	CHR, N(%)	1 (17)	17 (25)	18 (24)	MCyR, N(%)	2 (33)	20 (29)	22 (30)	CCyR, N (%)	2 (33)	18 (26)	20 (27)
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	<p>Median duration of therapy was 3.5 months (range, 0.03 – 9.2)</p> <p>Most responses occurred during the first 3 months of dasatinib therapy.</p>
Conclusions	<p>The authors conclude that in this poor prognosis population of patients with imatinib-resistance, a 6-month progression-free survival rate of 51% is clinically meaningful.</p>
Critique	<p>Although the authors were unable to comment on health-related QOL assessment at this time, will await this information as it will be important to evaluate the impact that dasatinib has on QOL at this stage of disease.</p>

Citation	Study CA180015
Study Goals	Estimate the major and overall hematologic response rates to dasatinib in Ph+ ALL or lymphoid phase CML among patients who were resistant or intolerant to imatinib.
Methods	<p>Study Design: Phase II, open-label, single-arm trial. Patients in lymphoid blast phase CML and Ph+ALL with primary or acquired resistance to imatinib.</p> <p>Treatment: dasatinib 70mg PO BID until disease progression or toxicity; dose increase to 100mg PO BID was permitted for disease progression; dose-reduction x 2 (50mg BID, then 40mg BID) was permitted for toxicity</p> <p>Primary endpoint: major hematologic response (MaHR) and overall hematologic response (OHR) rates</p> <p>Secondary endpoint: durability and time to hematologic response in imatinib-resistant group; assess minor hematologic, cytogenetic and molecular responses in the imatinib-resistant group; assess hematologic, cytogenetic and molecular responses in the imatinib-intolerant group; durability and time to hematologic response in the imatinib-intolerant group; measure health-related QOL; assess safety and tolerability of dasatinib; explore role of gene expression and point mutations as surrogates of response</p>
Criteria	<p>Inclusion criteria: men/women; age \geq 18 yrs of age; ECOG PS 0-2; Ph+ (or BCR-ABL) lymphoid blast phase CML and primary or acquired hematologic resistance to imatinib or intolerance to imatinib; Ph+ ALL previously treated with standard induction or consolidation chemotherapy and progression or lack of response to imatinib \geq 600mg/day after 4 weeks; adequate hepatic/renal function; serum potassium/magnesium/calcium within normal limits</p> <p>Exclusion criteria: eligible/willing to undergo transplantation; women of childbearing potential unwilling/unable to use contraceptive methods; men whose partners are women of childbearing potential unwilling/unable to use contraceptive methods; pregnancy or breastfeeding; serious uncontrolled medical disorder/active infection; uncontrolled/significant cardiovascular disease; altered mental status; history of bleeding disorder unrelated to CML; disorder that prevents administration of study therapy; use of imatinib within 7 days, interferon, cytarabine or other targeted therapy within 14 days, other investigational drug or antineoplastic within 28 days; drugs with known risk of torsades de pointes, or irreversible platelet inhibitors</p> <p>A total of 78 patients with extensive pretreatment and baseline blast count in bone marrow \geq 50% were included. The median duration of CML was 24 months. Prior therapies included stem cell transplant, chemotherapy, interferon and imatinib.</p> <p>Baseline demographics: male/female equally represented in lymphoid blast population; majority (33%) male population in ALL population; majority of both groups < 65 years; majority with ECOG PS 0-1; imatinib-intolerant population was small (~10%)</p>

Results	Hematologic and Cytogenetic Response Rates After Follow-up of \geq 6 months		
		Lymphoid Blast CML N=42	Ph+ ALL N=36
	MaHR, N(%)	13 (31)	15 (42)
	CHR, N(%)	11 (26)	11 (31)
	MCyR, N(%)	21 (50)	21 (58)
	CCyR, N (%)	18 (43)	21 (58)
	<p>MaHR (major hematologic response); CHR (complete hematologic response); MCyR (major cytogenetic response); CCyR (complete cytogenetic response)</p> <p>Median duration of response in lymphoid blast population was 3.71 months. Median duration of response in ALL population was 4.83 months.</p>		
Conclusions	The authors note in this population of heavily pretreated patients, some were able to undergo stem cell transplant. In addition, a significant percentage of patients who had achieved a hematologic response had not progressed at the time of this report.		
Critique	Although the authors were unable to comment on health-related QOL assessment at this time, will await this information as it will be important to evaluate the impact that dasatinib has on QOL at this stage of disease.		