# DASATINIB (BMS-354825)

# ONCOLOGIC DRUG ADVISORY COMMITTEE (ODAC) BRIEFING DOCUMENT

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# 1 EXECUTIVE SUMMARY

Chronic myeloid leukemia (CML) is caused by reciprocal translocation between chromosomes 9 and 22 leading to the synthesis of a constitutively activated tyrosine kinase, BCR-ABL. Chronic myeloid leukemia is a continuum of disease, and a patient's characteristics and prognosis are different at each phase. Imatinib mesylate (imatinib, Gleevec®), a selective inhibitor of BCR-ABL, is the current frontline therapy for CML of all phases; however, emerging evidence suggests that molecular resistance to imatinib may limit its long-term success.

Dasatinib was identified as a novel, oral, multi-targeted inhibitor of both BCR-ABL and SRC kinases. Data collected from 5 pivotal Phase 2 studies (CA180005, CA180006, CA180013, CA180015, and CA180017) comprise the safety and efficacy analyses for the current application (Table 1). In addition to the Phase 2 results, data collected in a Phase 1 study (CA180002) from 84 treated patients with all phases of CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) support the dose selection and the overall safety and efficacy of dasatinib (Table 1). Patients in all of the studies had received prior imatinib treatment and were either resistant or intolerant to imatinib.

**Table 1: Number of Treated Patients in the Phase 1 and 2 Clinical Studies**

| | CA180002 | CA180005 | CA180006 | CA180013 | CA180015 | CA180017 | Total |
|---|---|---|---|---|---|---|---|
| **Chronic** | 40 | - | - | 186 | - | 36[a] | **262** |
| **Accelerated** | 11 | 107 | - | - | - | - | **118** |
| **Myeloid Blast** | 23 | - | 74 | - | - | - | **97** |
| **Lymphoid Blast** | 5 | - | - | - | 42 | - | **47** |
| **Ph+ ALL** | 5 | - | - | - | 36 | - | **41** |
| **Total** | **84** | **107** | **74** | **186** | **78** | **36** | **565** |

[a] 22 dasatinib-treated patients and 14 imatinib-treated patients

No established therapy is available for patients with CML or Ph+ ALL who are resistant or intolerant to imatinib. Therefore, 4 out of the 5 pivotal studies had a single-arm design with dasatinib administered as 70 mg twice daily (BID). The fifth study (CA180017) was a 2:1 randomized, non-comparative study of dasatinib (70 mg BID) and high-dose imatinib (400 mg BID) in patients with chronic phase CML who were resistant to lower doses of imatinib. In all 6 trials, most patients had a long history of leukemia and were heavily pretreated, not only with imatinib but also with interferon and other chemotherapeutic agents. Many patients had also undergone a prior stem cell transplant.

Efficacy data, with a minimum of 6 months of follow-up, were reported separately by phase of disease for each of the 4 single-arm, Phase 2 studies. In addition, efficacy data in the Phase 1 study (CA180002) were based on follow-up of up to 19 months. Given that the randomized Phase 2 study (CA180017) was the last study to start and close enrollment, interim efficacy data with a minimum of 3 months of follow-up were reported. Safety data, with a minimum of 7 months of follow-up, were based on the 120-day safety update and pooled across all 6 studies by phase of disease. Not included in the pooled safety analysis were 14 patients treated with imatinib (CA180017) and 40 patients with chronic phase CML who received dasatinib, and had multiple dose escalations and different dosing schedules in the Phase 1 study (CA180002).

A high level of efficacy with considerable durability was reported in the Phase 1 (CA180002) study. This led to a rapid Phase 2 development program, in which patients treated with dasatinib achieved hematologic and cytogenetic responses across all phases of CML or Ph+ ALL (Table 2). Durable hematologic and cytogenetic responses were achieved in both imatinib-intolerant and imatinib-resistant patients. In general, imatinib-intolerant patients remained on therapy with dasatinib longer than imatinib-resistant patients and did not experience Grade 3 to 4 cross-intolerance toxicity while on dasatinib.

Cytogenetic response is associated with a survival benefit. Therefore, based on the cytogenetic responses achieved in these studies, it is reasonable to expect that treatment with dasatinib will result in a survival benefit in patients with CML or Ph+ ALL.

**Table 2: Efficacy in Dasatinib Phase 2 Studies**

| | CA180013 Chronic[a] (N = 186) | CA180017 Chronic[b] (N = 36: 22D/14I) | CA180005 Accelerated[a] (N = 107) | CA180006 Myeloid Blast[a] (N = 74) | CA180015 Lymphoid Blast[a] (N = 42) | CA180015 Ph+ ALL[a] (N = 36) |
|---|---|---|---|---|---|---|
| **Hematologic Response (%)** | | | | | | |
| OHR (95% CI) | NA[c] | NA | 80 (72 - 87) | 53 (41 - 64) | 36 (22 - 52) | 47 (30 - 65) |
| MaHR (95% CI) | NA | NA | 59 (49 - 68) | 32 (22 - 44) | 31 (18 - 47) | 42 (26 - 59) |
| CHR | 90 | 95/93 | 33 | 24 | 26 | 31 |
| NEL | NA | NA | 26 | 8 | 5 | 11 |
| MiHR (95% CI) | NA | NA | 21 (14 - 31) | 20 (12 - 31) | 5 (0.6 - 16) | 6 (0.7 - 19) |
| **Cytogenetic Response (%)** | | | | | | |
| MCyR (95% CI) | 45 (37 - 52) | 45/21 (24-68)/(5-51) | 31 (22 - 41) | 30 (20 - 42) | 50 (34 - 66) | 58 (41 - 75) |
| CCyR | 33 | 32/7 | 21 | 27 | 43 | 58 |

Shaded boxes: primary endpoints; OHR: overall hematologic response; MaHR: major hematologic response; CHR: complete hematologic response; NEL: no evidence of leukemia; MiHR: minor hematologic response; MCyR: major cytogenetic response; CCyR: complete cytogenetic response. [a] ≥ 6-month follow-up. [b] ≥ 3-month follow-up; 22 dasatinib-treated (D); 14 imatinib-treated (I). [c] NA: not applicable

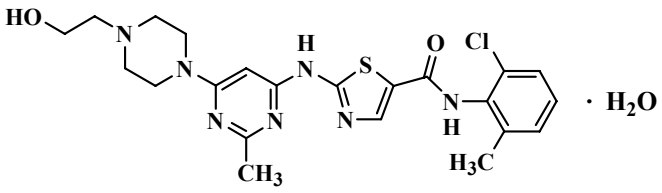
Dasatinib is safe and tolerable in this population of heavily pretreated patients across all phases of CML or Ph+ ALL. Within the pooled safety analysis, the most common adverse events were tolerable, and the majority of serious adverse events were managed by dose interruptions or reductions. Non-hematologic adverse events were generally mild to moderate. Thrombocytopenia, neutropenia, leukopenia, and anemia were frequently reported Grade 3 to 4 laboratory abnormalities. Myelosuppression was the most common reason for dose reductions or interruptions. In addition to myelosuppression, specific analyses were performed for fluid retention, which may represent a mechanism of action related effect. Additional analysis for hemorrhage, which is a safety issue specific to leukemia, was also performed. Recovery from myelosuppression, fluid retention, and hemorrhage was managed in most cases by dose interruptions, dose reductions, or supportive care.

# 2 PRODUCT INFORMATION

- **Dasatinib (BMS-354825)** is a potent oral inhibitor of multiple oncogenic kinases

- **Chemical name:** *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate

- **Chemical structure**:




- **Recommended dose:** 70 mg orally twice a day (BID)

- **Proposed indications:**
  a) Treatment of adults with chronic, accelerated, or blast phase CML with resistance or intolerance to prior therapy including imatinib
  b) Treatment of adults with Ph+ ALL and lymphoid blast CML with resistance or intolerance to prior therapy

# 3 BACKGROUND

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder that is associated with a reciprocal translocation between chromosomes 9 and 22 to produce the Philadelphia (Ph) chromosome. This chromosomal translocation results in a chimeric protein product BCR-ABL, which is a constitutively active form of the ABL tyrosine kinase.[1] Chronic myeloid leukemia represents a disease continuum, evolving through chronic, accelerated, and blast phases.

Prior to the introduction of interferon and imatinib, treatment of CML relied on conventional treatment (eg, radiation therapy and cytotoxic agents such as busulfan and hydroxyurea). With conventional treatment, CML was a fatal disease with a median survival of 4 years for patients with chronic phase CML and 6 months for patients in blast phase. The introduction of interferon in the mid-1980s replaced conventional treatment. As a single agent, interferon prolongs survival compared with conventional treatment, and the combination of interferon and cytosine arabinoside is effective in patients previously refractory to interferon alone. However, the majority of patients develop resistance or intolerance to interferon. The recent introduction of imatinib revolutionized the treatment of CML based on high rates of hematologic and cytogenetic responses (in interferon-refractory patients and as first-line therapy) and improved tolerability over interferon.[2] As with interferon, achievement of a cytogenetic response on therapy with imatinib is associated with a survival benefit.[3] Still, some patients are unable to tolerate imatinib and many develop imatinib-resistant forms of CML.[4,5]

Resistance to imatinib has emerged as an issue of increasing clinical importance. The most common cause of imatinib resistance occurs through the development of point mutations in the ABL kinase domain of BCR-ABL.[5] This leads to amino acid substitutions that preclude the binding of imatinib. The 2-year incidence of resistance is estimated to be 80% in blast phase, 40% to 50% in accelerated phase, and at least 10% in chronic phase.[4] Imatinib-resistant patients have inadequate treatment options, which include imatinib dosage increases (which often cannot be tolerated), interferon, or chemotherapy. There is only 1 published study that evaluated the effect of interferon in treating imatinib resistant CML.[6] In this study, 11 patients who failed first-line treatment with imatinib were treated with a combination of interferon plus cytosine arabinoside.

Only 3 (27%) patients achieved a complete hematologic response (CHR), and none achieved a cytogenetic response.

In addition to the difficulty with imatinib resistance, some patients develop imatinib associated adverse effects and are therefore intolerant of therapy. For imatinib-intolerant patients, there are even more limited options, which include interferon and chemotherapy.

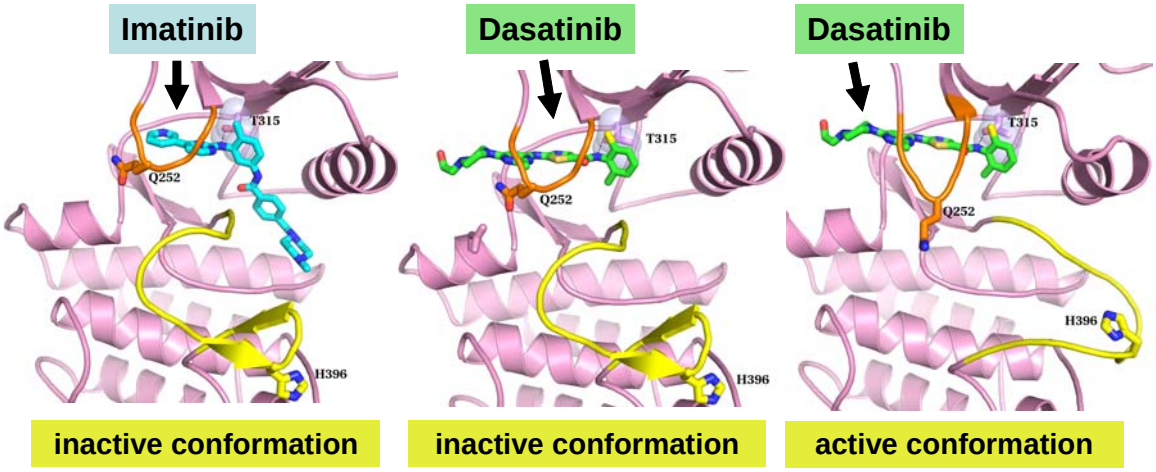
In patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), both interferon and imatinib provide limited benefit.

At the present time, allogeneic hematopoietic stem cell transplantation remains the only known curative treatment in CML. The widespread application of this modality is limited by donor availability and the high toxicity of the procedure in older patients, which limits the age of eligibility at many centers to ≤ 65 years.

# 4 NONCLINICAL PROGRAM

Dasatinib is a potent inhibitor of 5 critical oncogenic kinases (ie, BCR-ABL, SRC, c KIT, platelet-derived growth factor receptor, and ephrin A receptor kinases) that are linked to multiple human malignancies. In contrast to imatinib, which binds only to the inactive conformation,[7] dasatinib is a distinct new chemical entity and binds to both the active or 'opened' conformation and the inactive or 'closed' conformation of the ABL kinase domain of BCR-ABL (Figure 1).[8] This is the basis for the increased binding affinity of dasatinib over imatinib, and the activity of dasatinib against almost all imatinib-resistant kinase domain mutants. Dasatinib has 325-fold greater potency compared with imatinib against cells expressing wild-type BCR-ABL, and is effective against all imatinib-resistant kinase domain mutations tested to date, except T315I.[9] Dasatinib also has the potential to overcome imatinib resistance that results from divergent mechanisms including BCR-ABL overexpression, activation of alternate signaling pathways involving the SRC family kinases (eg, LYN, HCK), and multidrug resistance gene *(MDR1*) overexpression.

**Figure 1: Differential Binding of Imatinib and Dasatinib to the ATP-Binding Site of the ABL Kinase Domain of BCR-ABL**




Dasatinib was extensively tested in nonclinical in vitro and in vivo toxicology studies. In vitro studies showed dose-related inhibition of platelet aggregation and a potential risk for prolongation of the QT interval based on hERG/IKr and Purkinje fiber assays. In the in vivo studies, neither spontaneous bleeding nor drug-related changes in electrocardiogram (ECG) parameters were reported. Reversible gastrointestinal and lymphoid system toxicities occurred in rats and monkeys, and hematopoietic toxicities in rats. Overall, results from the nonclinical toxicology studies supported continuous oral administration to humans.

# 5 CLINICAL DEVELOPMENT PLAN

Overall, data from 229 healthy subjects in 6 Phase 1 studies and 551 patients with leukemia in 1 Phase 1 and 5 Phase 2 studies provided pharmacokinetics (PK), efficacy, and safety results supporting the proposed indications (Table 3) in the new drug application.

**Table 3: Dasatinib Clinical Program**

| Phase | Study | Question or Population | Total Treated |
|---|---|---|---|
| Phase 1 (healthy subjects) | CA180009 | food effect | 54 |
| | CA180016 | formulation comparability | 75 |
| | CA180019 | absorption, distribution, metabolism, and excretion | 8 |
| | CA180020 | pH effect | 24 |
| | CA180022 | simvastatin | 48 |
| | CA180032 | rifampin | 20 |
| Phase 1 (patients with cancer) | CA180002 | Chronic, accelerated, blast phase CML, and Ph+ ALL (imatinib-resistant or imatinib-intolerant) | 84 |
| Phase 2 | CA180013 | Chronic phase CML (imatinib-resistant or imatinib-intolerant) | 186 |
| | CA180017 | Chronic phase CML, randomized, dasatinib vs high dose imatinib (imatinib-resistant only) | 36[a] |
| | CA180005 | Accelerated phase CML (imatinib-resistant or imatinib-intolerant) | 107 |
| | CA180006 | Myeloid blast phase CML (imatinib-resistant or imatinib-intolerant) | 74 |
| | CA180015 | Ph+ ALL or lymphoid phase CML (imatinib-resistant or imatinib-intolerant) | 78 |

[a] 22 dasatinib-treated patients and 14 imatinib-treated patients

## 5.1 Clinical Design and Evaluation

Within the clinical program, there were 6 Phase 1 studies in healthy subjects, all of whom received at least 1 dose of dasatinib (range 1 to 6 doses) of either 50 mg or 100 mg QD. The designs of these studies varied from single dose to multiple doses and periods.

CA180002 is an open-label, Phase 1 dose-escalation study of dasatinib in patients with all phases of CML or Ph+ ALL, who were resistant or intolerant to imatinib. The patients received dasatinib either once a day (QD) or BID, on a 5 days on and 2 days off or continuous daily dosing schedule. In the chronic phase CML BID cohort, the majority of patients on intermittent dosing were escalated to continuous daily dosing, and therefore

the chronic phase data are pooled for analysis. Doses ranged from as low as 15 mg QD to 120 mg BID. Intrapatient dose escalation was allowed to optimize response. The objectives of this study were to establish the maximum tolerated dose (MTD) and to recommend a Phase 2 dose. The MTD was defined by dose limiting toxicities occurring in the first 4 weeks of treatment.

Each of the 4 single-arm Phase 2 studies enrolled imatinib-resistant or imatinib-intolerant patients at a starting dose of 70 mg BID. One dose escalation was allowed for disease progression or lack or response, and dose reductions were allowed for intolerance. The primary endpoint was major cytogenetic response (MCyR) for chronic phase CML (CA180013) and major hematologic response (MaHR) and overall hematologic response (OHR) for the advanced phase studies (CA180005, CA180006, and CA180015).

Each study had similar inclusion criteria and used the following definitions:

- **Chronic phase CML** (patients were to meet all of the following):
  < 15% blasts in peripheral blood (PB) and in bone marrow (BM), < 20% basophils in PB, < 30% blasts + promyelocytes in PB and BM, platelets ≥ 100,000/$mm^3$ unless thrombocytopenia is due to recent therapy, and no extramedullary involvement (other than liver or spleen)
- **Accelerated phase CML** (patients were to meet at least 1 of the following):
  15% to < 30% blasts in PB or BM , ≥ 20% basophils in PB or BM, ≥ 30% blasts + promyelocytes in PB or BM (but < 30% blasts), platelets < 100,000/$mm^3$ unrelated to therapy
- **Blast phase CML or Ph+ ALL** (patients were to meet at least 1 of the following):
  ≥ 30% blasts in PB or BM, extramedullary infiltrates of leukemic cells (other than in spleen or liver)

CA180017 is an open-label, non-comparative, randomized Phase 2 study, with a 2:1 randomization of dasatinib 70 mg BID vs imatinib 800 mg/day in chronic phase CML patients who were resistant to imatinib at a dose of 400 to 600 mg/day (imatinib-intolerant patients or patients treated with > 600 mg/day of imatinib were not eligible for this study). No dose escalations of imatinib were allowed, and dose reductions of imatinib to 600 mg/day were allowed only if patients had not previously received that dose. The primary endpoint is MCyR at 12 weeks. Subsequent cross-over is allowed for insufficient response or intolerance.

All 6 studies are closed to enrollment, and treatment and follow-up are ongoing. The enrollment period includes all patients included in this analysis, as well as additionally enrolled patients not analyzed as of December, 2005 (Table 4).

**Table 4: Enrollment Period for Phase 1 and 2 Studies**

| | Enrollment Start | Enrollment Close |
|---|---|---|
| CA180002 | 04-Nov-2003 | 25-April-2005 |
| CA180005 | 06-Dec-2004 | 12-July-2005 |
| CA180006 | 29-Dec-2004 | 01-July-2005 |
| CA180013 | 04-Feb-2005 | 15-July-2005 |
| CA180015 | 04-Jan-2005 | 01-July-2005 |
| CA180017 | 10-Feb-2005 | 21-Sep-2005 |

The following criteria were used to determine hematologic response; all responses were to be maintained at least 4 weeks:

- **Complete hematologic response (CHR) (chronic):** WBC ≤ institutional ULN, platelets < 450,000/$mm^3$, no blasts or promyelocytes in peripheral blood (PB), < 5% myelocytes plus metamyelocytes in PB, peripheral basophils < 20%, and no extramedullary involvement (patients could not achieve hemorrhage response until 14 days from dose start day)
- **CHR (advanced):** Same as CHR (chronic) except, ANC ≥ 1000/$mm^3$, platelets ≥ 100,000/$mm^3$, and bone marrow (BM) blasts ≤ 5% (no concomitant anagrelide or hydroxyurea)
- **No evidence of leukemia (NEL)**: same criteria as for CHR except 500/$mm^3$ ≤ ANC <1000/$mm^3$, and/or 20,000/$mm^3$ ≤ platelets < 100,000/$mm^3$
- **MaHR = CHR + NEL**

Determination of cytogenetic response was based on the number of Ph+ metaphases in a BM sample. If possible, at least 20 metaphases were evaluated.

- **Complete cytogenetic response (CCyR)** (0% Ph+ metaphases); **Partial cytogenetic response (PCyR)** (1 % to 35%)
- **MCyR = CCyR + PCyR**

## 5.2 Definitions of Imatinib Resistance and Imatinib Intolerance

Imatinib resistance or intolerance status was based upon review of individual patient profiles describing prior imatinib history as well as response to imatinib provided in the Case Report Form.

**Imatinib resistance or intolerance definitions for chronic phase (CA180013):**

1) Imatinib resistance as defined by:
   c) Progressive disease at the maximally tolerated dose of imatinib with either:
      - acquired resistance: prior MCyR or CHR on imatinib with progression defined by 1 of the following: loss of MCyR, loss of CHR, or an increasing WBC
      - primary resistance: defined as 1 of the following: no CHR after 3 months, no cytogenetic response (CyR) after 6 months, no MCyR after 12 months of imatinib, or no prior MCyR or CHR on imatinib with an increasing WBC count on ≥ 2 consecutive evaluations
   d) Resistance to imatinib ≤ 600 mg/day with genetic mutation in the BCR-ABL gene that was associated with a high level of resistance to imatinib
2) Imatinib intolerance defined as either:

   Grade 3 or greater non-hematologic toxicity that is imatinib-related

   Grade 4 hematologic toxicity that is imatinib-related lasting more than 7 days

**Imatinib resistance definitions for chronic phase (CA180017):** Progressive disease while on imatinib of 400-600 mg/day with either acquired or primary resistance.

**Imatinib resistance or intolerance definitions for accelerated phase (CA180005):**

2) Imatinib resistance as defined by:
   a) Initial diagnosis of chronic phase CML that progressed to accelerated phase while on treatment with imatinib ≥ 400 mg/day (primary or acquired resistance)
   b) Initial diagnosis of accelerated phase CML and failure to achieve a hematologic response after ≥ 4 weeks (or ≥ 2 weeks for patients showing rapid disease progression) of imatinib ≥ 600 mg/day (primary resistance)
   c) Initial diagnosis of accelerated or blast phase CML that progressed to accelerated phase CML following an initial hematologic response to imatinib ≥ 600 mg/day (acquired resistance)

3) Imatinib-intolerance defined as either:
   a) toxicity that was considered at least possibly related to imatinib ≤ 400 mg/day that led to a discontinuation of imatinib therapy
   b) ability to tolerate only < 400 mg/day imatinib

The imatinib resistance or intolerance definitions for blast phase disease (CA180006 and CA180015) are similar to those used in accelerated phase CML, with the exception that progression to blast phase had to occur. For Ph+ ALL, patients were previously treated with induction or consolidation chemotherapy and had progression or lack or response to ≥ 600mg/day imatinib after 4 weeks.

## 5.3 Rationale for Phase 2 Dose Selection

Given the high level of clinical activity reported in the Phase 1 study (CA180002) in patients with leukemia, a biologically active and tolerable dose was selected for the Phase 2 studies. In addition, BCR-ABL kinase activity in circulating CML cells relative to serum dasatinib levels provided a rationale for the 70 mg BID dose.

CrkL is a biological substrate of BCR-ABL in CML and phospho-CrkL is a pharmacodynamic biomarker of BCR-ABL used in imatinib studies. The imatinib Phase 1 studies did not identify an MTD, and phospho-CrkL inhibition was used to justify the Phase 2 dose.[2] For dasatinib, the reduction in CrkL phosphorylation was greatest at doses of 50 mg or above; and the level was consistently lower after 24 h in patients treated on the BID schedule. Additionally, the median average dose in chronic phase patients (CA180002) ranged from 35 to 70 mg BID and the majority of CCyR occurred in patients taking 100 to 140 mg/day. There were very few patients who achieved a MCyR at doses < 100 mg/day. These clinical and biomarker data provided the rationale to support the use of dasatinib 70 mg BID for the Phase 2 studies.

# 6 CLINICAL PHARMACOLOGY

The clinical PK of dasatinib was evaluated in 7 studies (6 healthy volunteer studies of 229 treated subjects and 1 leukemia study [CA180002] of 84 treated patients). Although absolute bioavailability was not determined, the oral bioavailability was sufficient to achieve drug levels above preclinical efficacious exposures. Exposure increased in a dose proportional manner and was not affected by intrinsic patient characteristics. Dasatinib was:

- 94% protein bound
- eliminated primarily by hepatic metabolism and excreted in feces
- excreted <1% in the urine
- primarily metabolized by CYP3A4; clearance is likely decreased when given with drugs that inhibit CYP3A4 and increased when given with CYP3A4 inducers

  - Dasatinib is a weak inhibitor of CYP3A4 and may decrease clearance of drugs extensively metabolized by CYP3A4

  - Dasatinib did not induce CYP3A4 and is not likely to increase clearance of drugs extensively metabolized by CYP3A4
- shown to have an overall mean half-life time of approximately 4 to 6 h
- not altered in absorption with coadministration of food

The area under the curve (AUC [TAU]), Cmax, Tmax, and T-HALF values for dasatinib are summarized in Table 5.

**Table 5: Summary of PK Parameters for Dasatinib**

| Study Day (N) | AUC (TAU) (ng x h/ml) Geom. Mean (CV%) | Cmax (ng/mL) Geom. Mean (CV%) | Tmax (h) Median (Min, Max) | T-HALF (h) Mean (SD) |
|---|---|---|---|---|
| 1 (22) | 129.77 (74) | 33.44 (82) | 1.38 (0.50, 6.00) | 3.77 (1.39) |
| 5/8 (20) | 236.14 (52) | 63.21 (60) | 1.42 (0.17, 3.00) | 4.76 (2.74) |
| 26/29 (19) | 162.26 (54) | 45.87 (65) | 1.00 (0.43, 4.17) | 5.44 (3.36) |

Clinical drug-drug interaction studies were conducted with the following:

- **CYP3A4 substrate (simvastatin) (CA180022):** Coadministration led to a modest increase (1 to 9%) in simvastatin AUC. Therefore, CYP3A4 substrates of narrow therapeutic index should be administered with caution.
- **CYP3A4 inducer (rifampin) (CA180032):** Dasatinib administered after 6 days of continuous rifampin decreased the Cmax and AUC of dasatinib by >80%. For this reason, concomitant use of potent CYP3A4 inducers is not recommended.
- **Antacid (eg, Maalox®) and histamine ($H_2$)-blocker (famotidine) (CA180020):** Simultaneous antacid use resulted in a 55% decrease in dasatinib AUC, but no impact was reported when an antacid was given 2 h prior to dasatinib. Famotidine administered 10 h prior to dasatinib decreased dasatinib exposure by >60%. Thus, antacids may be administered with dasatinib if separated by 2 h or more, and $H_2$ blockers should be avoided.

# 7 CLINICAL EFFICACY

Dasatinib is effective in patients with imatinib-resistant or imatinib-intolerant CML or Ph+ ALL in 6 ongoing, open-label studies (Table 1). Efficacy data are reported on patients followed for up to 19 months in the Phase 1 study (CA180002) and for a minimum of 6 months in the 4 single-arm, Phase 2 studies. Given that the randomized Phase 2 study (CA180017) was the last study to start and close enrollment, interim efficacy data with a minimum of 3 months of follow-up are reported.

## 7.1 Chronic Phase CML (CA180002, CA180013, and CA180017)

### Study CA180002

**Baseline Disease-related Characteristics:** The 40 patients with chronic phase CML in this study were heavily pretreated and had a median duration of CML of 90 months prior to entering the study (Table 6). Patients in the BID group had a worse prognosis at baseline than those in the QD group given the lower CHR rate (68% vs 81%) and lower MCyR rate (26% vs 52%) with prior imatinib. The QD patients began enrollment 4 months prior to those in the BID group; the median duration of dasatinib therapy was > 6 months (range 3.2 to 19.3 months) for the majority of patients.

**Table 6: Baseline Characteristics - Chronic Phase CML (CA180002)**

| | QD N = 21 | BID N = 19 | Total N = 40 |
|---|---|---|---|
| Median duration of CML (months) | 79 | 100 | 90 |
| Prior interferon, N (%) | 18 (86) | 19 (100) | 37 (93) |
| Prior imatinib | | | |
| Highest dose: >600 mg/day, N (%) | 15 (71) | 11 (58) | 26 (65) |
| Duration >3 years, N (%) | 11 (52) | 11 (58) | 22 (55) |
| Prior CHR, N (%) | 17 (81) | 13 (68) | 30 (75) |
| Prior MCyR, N (%) | 11 (52) | 5 (26) | 16 (40) |
| Imatinib resistance, N (%) | 17(81) | 15 (79) | 32 (80) |
| BCR-ABL mutations, N (%) | - | - | 33 (83%) |

**Duration of Treatment/Patient Disposition:** The median duration of therapy was 11 months (range 3.0 – 17.1 months) or 6 months (range 1.2 – 12.6 months) for patients in the QD or BID cohorts, respectively. Only 4 patients discontinued: 2 had disease progression, 1 had no response, and 1 had a confirmed CHR and electively went off study to undergo a bone marrow transplant.

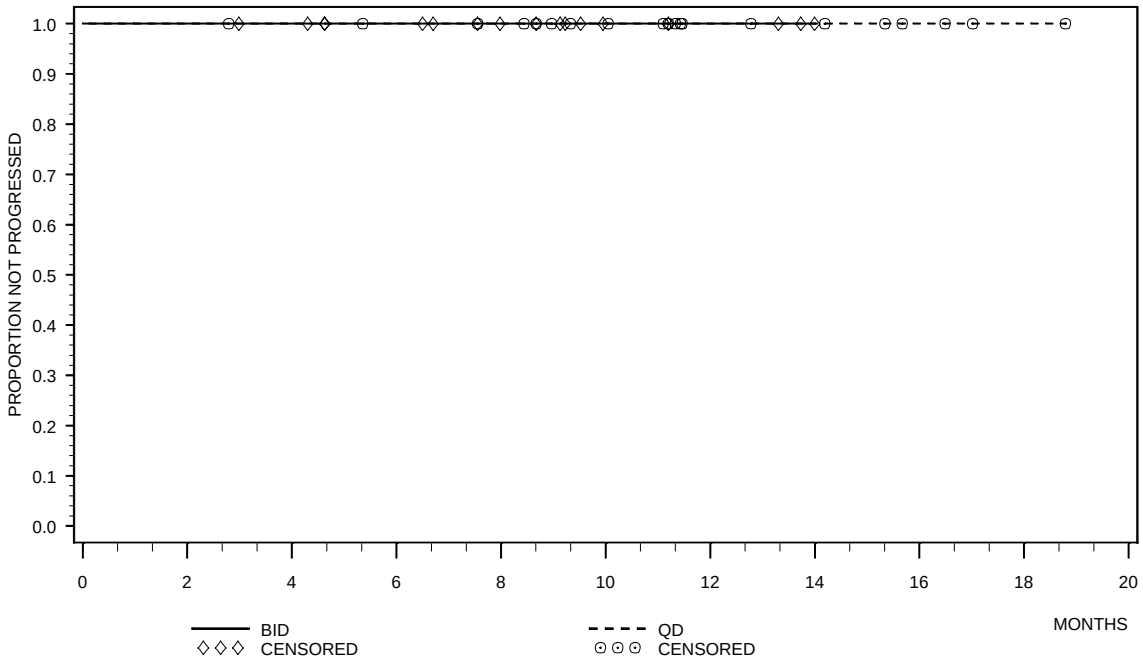
**Complete Hematologic Response:** The CHR rate was 95% for all patients in the QD cohort and 90% in the BID cohort (Table 7). These results are of clinical importance given that only 75% of these patients ever achieved a CHR on prior imatinib (Table 6). Thirty-three (83%) patients had baseline imatinib-resistant mutations (Table 6), and hematologic responses were reported in 31 (94%) patients.

**Table 7: Hematologic Response Rate - Chronic Phase CML (CA180002)**

| | QD | BID |
|---|---|---|
| **All patients: Resistant + Intolerant** | **N = 21** | **N = 19** |
| CHR, % (95% CI) | **95** (76.2 - 99.9) | **90** (66.9 - 98.7) |
| **Imatinib-resistant patients** | **N = 17** | **N = 15** |
| CHR, % (95% CI) | **94** (71.3 - 99.9) | **87** (59.5 - 98.3) |

The duration of CHR ranged from 3+ to 14+ months in imatinib-resistant patients and 4.3+ to 14+ months in imatinib-intolerant patients in the BID group. For the QD group, duration of CHR ranged from 2.8+ to 17+ months in the imatinib-resistant group, and 10+ to 19+ months in the imatinib-intolerant group. Progression was not reported in any of the responding patients (Figure 2).

**Figure 2: Duration of CHR for Chronic Phase CML (CA180002) Patients on BID and QD Dosing**




| Group | # Progressed/# Responded | Median (95% CI) |
|---|---|---|
| **QD** | 0/20 | NA (NA) |
| **BID** | 0/17 | NA (NA) |

**Cytogenetic Response:** A MCyR of 48% (all CCyR) in the QD cohort and 42% (21% CCyR; 21% PCyR) in the BID cohort was achieved in all patients (Table 8). Twelve of the 32 (38%) imatinib-resistant patients achieved a MCyR, and 6/8 (75%) of the imatinib-intolerant patients achieved a MCyR in both the QD and BID cohorts. Given that cytogenetic response is associated with a survival benefit, the MCyR rates with dasatinib in this study are clinically meaningful. In addition, 4 patients with no prior CyR to imatinib had a minimal cytogenetic response to dasatinib. Eight patients with a prior PCyR to imatinib had a CCyR to dasatinib. In the QD cohort, the longest MCyR duration was 14+ months for imatinib-resistant patients and 13+ months for imatinib-intolerant

patients. In the BID cohort, the longest MCyR duration was 5.6+ months for both imatinib-resistant and imatinib-intolerant patients. With nearly 1.5 years of follow-up, none of the patients who achieved a MCyR progressed. The rate and duration of response support the clinical importance of dasatinib in this patient population with limited therapeutic options.

**Table 8: Cytogenetic Response Rates - Chronic Phase CML (CA180002)**

| | QD | BID |
|---|---|---|
| **All patients: Resistant + Intolerant** | **N = 21** | **N = 19** |
| MCyR, % (95% CI) | **48** (25.7 - 70.2) | **42** (20.3 - 66.5) |
| **Imatinib-resistant patients** | **N = 17** | **N = 15** |
| MCyR, % (95% CI) | **41** (18.4 - 67.1) | **33** (11.8 - 61.6) |

Two patients with disease progression had a T315I mutation.[10] As shown in nonclinical studies, this is the only mutation that provides resistance to dasatinib and also resistance to imatinib.

## Study CA180013

**Baseline Disease-related Characteristics:** Patients included in this study had a long history of CML and were extensively pretreated. Most imatinib-resistant patients (91%) achieved a CHR on prior imatinib, while only 30% of patients achieved a MCyR (Table 9). Sixty-six (36%) patients had baseline BCR-ABL mutations.

**Table 9: Baseline Characteristics (CA180013)**

| | Imatinib-intolerant N = 59 | Imatinib-resistant N = 127 | Total N = 186 |
|---|---|---|---|
| Median duration of CML (months) | 26 | 77 | 64 |
| Prior interferon, N (%) | 32 (54) | 98 (77) | 130 (70) |
| Prior imatinib | | | |
| Dose >600 mg, N (%) | 5 (8) | 92 (72) | 97 (52) |
| Duration >3 years, N (%) | 9 (15) | 91 (72) | 100 (54) |
| Prior CHR, N (%) | 45 (76) | 115 (91) | 160 (86) |
| Prior MCyR, N (%) | 24 (41) | 38 (30) | 62 (33) |
| BCR-ABL mutations, N (%) | 6 (10) | 60 (47) | 66 (36) |

Many imatinib-intolerant patients achieved a MCyR (41%) to imatinib, but the duration of prior imatinib therapy was limited by the associated toxicity. The primary reasons for imatinib intolerance included: rash, hepatotoxicity, arthralgias, gastrointestinal symptoms, edema, and hematologic toxicity (see Table 29 below for more details).

**Duration of Treatment/Patient Disposition:** The median duration of therapy was 5.6 months (range 0.03 – 8.3 months). The median average daily dose in all patients was 114 mg/day and was similar for imatinib-resistant and imatinib-intolerant patients. Twenty-six (14%) patients discontinued dasatinib for the following reasons: drug toxicity (11), disease progression (6), adverse event (3), patient request (3), and death (2). One patient went off study electively to undergo a stem cell transplant.

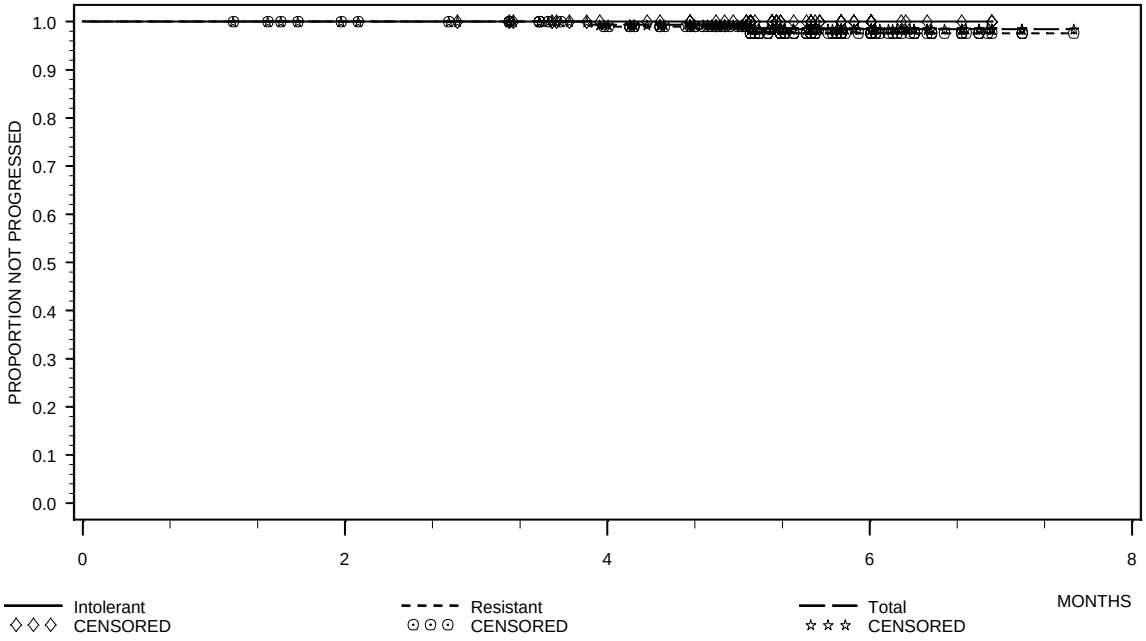
**Complete Hematologic Response:** After 6 months of follow-up, the CHR rate was 90%, which is consistent with the results from the Phase 1 study. The CHR rate was 97% in imatinib-intolerant patients and 87% in imatinib-resistant patients (Table 10). The longest duration of response was 7.6+ months. Only 2 of the 111 imatinib-resistant patients and none of the 57 imatinib-intolerant patients, who achieved a CHR have progressed (Figure 3).

**Table 10: Hematologic and Cytogenetic Response Rates (CA180013)**

| | Imatinib-intolerant N = 59 | Imatinib-resistant N = 127 | Total N = 186 |
|---|---|---|---|
| **Hematologic Response** | | | |
| CHR, N (%) | 57 (97) | 111 (87) | 168 (90) |
| **Cytogenetic Response** | | | |
| 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,[a] N (%) | 42 (71) | 33 (26) | 75 (40) |

[a] MCyR rates based on ≥ 20 metaphases

**Figure 3: Duration of CHR (Study CA180013)**




| Group | # Progressed/# Responded | Median (95% CI) |
|---|---|---|
| **Total** | 2/168 | NA (NA) |
| **Imatinib-resistant** | 2/111 | NA (NA) |
| **Imatinib-intolerant** | 0/57 | NA (NA) |

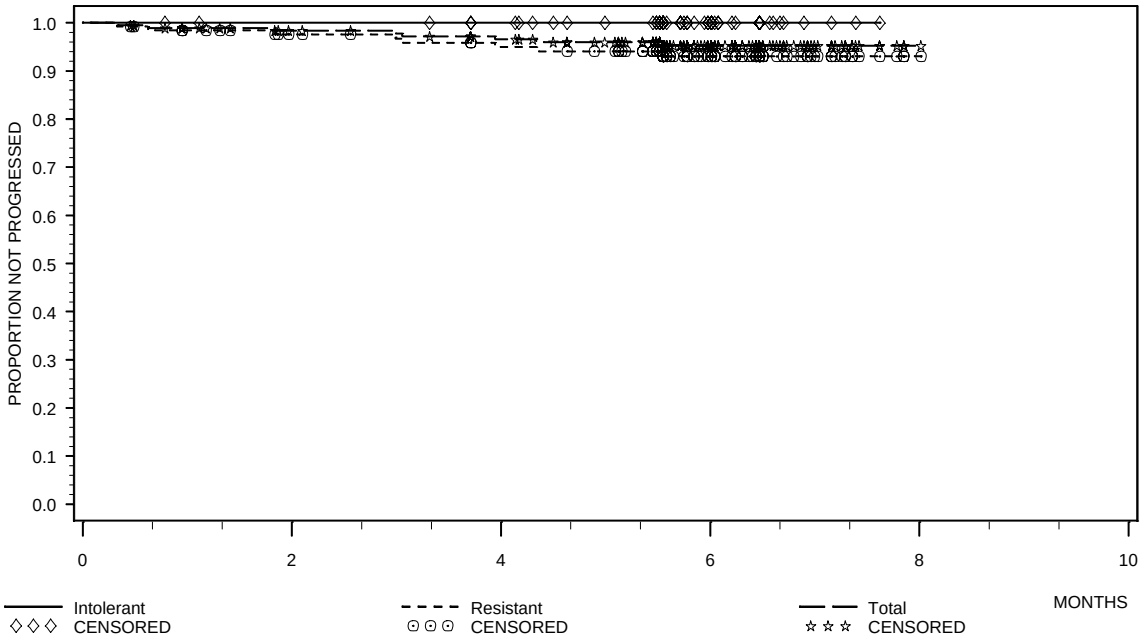
**Cytogenetic Response:** The MCyR was 45% in the total population, 31% in imatinib-resistant patients and 73% in imatinib-intolerant patients. These results were consistent with the MCyR rates based on ≥ 20 metaphases (Table 10). The cytogenetic

responses are consistent with those reported in the Phase 1 study. Given that only 33% of patients achieved a MCyR with prior imatinib, the MCyR rates with dasatinib are clinically valuable. This is especially important for the imatinib-intolerant patients who have limited therapeutic options. Of note, 29 imatinib-intolerant patients never achieved a cytogenetic response on imatinib, and of these, 21 (72%) achieved a MCyR with dasatinib. In addition, none of the 83 patients who had achieved a MCyR on dasatinib progressed or died.

Despite the poor prognosis associated with imatinib-resistant mutations, a CHR was achieved in 59/66 (89%) patients, and a MCyR in 29/66 patients (44%) who had BCR-ABL point mutations identified by central laboratories at study entry. Three patients with baseline mutations, who did not achieve a hematologic response, had a T315I mutation.

In the entire population of 186 patients, only 8 (all imatinib-resistant) patients had progressed (Figure 4).

**Figure 4: Progression-free Survival (CA180013)**




| Group | # Progressed/# Treated | Median (95% CI) |
|---|---|---|
| **Total** | 8/186 | NA (NA) |
| **Imatinib-resistant** | 8/127 | NA (NA) |
| **Imatinib-intolerant** | 0/59 | NA (NA) |

## Study CA180017

**Baseline Disease-related Characteristics:** Similar to CA180013, patients included in this study had a long history of CML and were extensively pretreated. The median duration of CML in both groups was over 5 years (Table 11).

**Table 11: Baseline Characteristics (CA180017)**

| | Dasatinib N = 22 | Imatinib N = 14 |
|---|---|---|
| Median duration of CML (months) | 61 | 61 |
| Prior stem cell transplant, N (%) | 5 (23) | 0 |
| Prior interferon, N (%) | 14 (64) | 11 (79) |
| Prior imatinib | | |
| Highest dose: 600 mg/day (%) | 16 (73) | 12 (86) |
| Duration >3 years (%) | 13 (59) | 7 (50) |
| Prior CHR (%) | 19 (86) | 14 (100) |
| Prior MCyR (%) | 9 (41) | 3 (21) |
| BCR-ABL mutations (%) | 10 (45) | 1 (7) |

**Duration of Treatment/Patient Disposition:** The median duration of treatment was 3.7 months (range 1.4 to 6.5 months) in the dasatinib group and 2.7 months (range 0.2 to 3.7 months) in the imatinib group. At this interim analysis, 20 (91%) dasatinib and 3 (21%) imatinib patients were still on initial treatment. Two (9%) dasatinib patients and 11 (79%) imatinib patients crossed over to the alternative treatment. Reasons for crossover were: 2 dasatinib (1 intolerance and 1 disease progression); 11 imatinib (6 imatinib intolerance, 4 No MCyR on imatinib at 12 weeks, and 1 No MCyR on imatinib at 12 weeks and disease progression).

**Complete Hematologic Response:** All analyses, otherwise noted, were based on results prior to cross-over. No treatment difference was reported in CHR rate at 12 weeks (95% dasatinib, 93% imatinib) between the 2 groups (Table 12).

**Cytogenetic Response:** The primary endpoint of the study, MCyR at 12 weeks, was reported in 45% of patients in the dasatinib cohort and 21% of patients in the imatinib cohort (Table 12). Of the 13 patients with no prior MCyR on imatinib, 6 (46%) in the

dasatinib group achieved a MCyR, compared with 1/11 (9%) in the imatinib group. This finding suggests that in this population of patients treated previously with lower doses of imatinib, dasatinib may be more efficacious than higher dose imatinib.

Of the 11 imatinib patients who crossed over to dasatinib, 3 were evaluable for cytogenetic response. Of these, 1 patient who crossed over due to imatinib intolerance achieved a PCyR on dasatinib.

**Table 12: Complete Hematologic Response and Major Cytogenetic Response Rates at 12 Weeks (CA180017)**

| | Number of Patients (%) | |
|---|---|---|
| | **Dasatinib N = 22** | **Imatinib N = 14** |
| **Hematologic Response** | | |
| CHR, N (%) [95% CI] | **21 (95)** [77.2 - 99.9] | **13 (93)** [66.1 - 99.8] |
| **Cytogenetic Response** | | |
| MCyR, N (%) [95% CI] | **10 (45)** [24.4 - 67.8] | **3 (21)** [4.7 - 50.8] |
| CCyR, N (%) | 7 (32) | 1 (7) |
| PCyR, N (%) | 3 (14) | 2 (14) |

Eleven of the 36 (31%) [10 dasatinib; 1 imatinib] patients had mutations detected at baseline. Of these, a CHR was achieved in 9 (90%) patients, and a MCyR in 4 (40%) of the 10 patients treated with dasatinib. The 1 patient with a mutation, who was treated with imatinib, achieved a CHR and a MCyR.

Based on these interim results, dasatinib produced early and major cytogenetic response rates in patients with chronic phase CML resistant to imatinib at conventional doses of 400 to 600 mg/day. The preliminary results of this study suggest that dasatinib is an effective alternative in imatinib-resistant patients, especially in those patients for whom escalation of imatinib to 800 mg/day would be the sole therapeutic option.

## 7.2 Accelerated Phase CML (CA180002 and CA180005)

## Study CA180002

**Baseline Disease-related Characteristics:** Eleven patients with accelerated phase CML were enrolled in this study with a 67-month median duration of CML. Eight (73%) of the 11 patients had baseline imatinib-resistant mutations, 9 (82%) were heavily pretreated with prior interferon, and 7 (64%) had received > 600 mg/day of prior imatinib.

**Hematologic Response/Cytogenetic Response:** The MaHR was 57% (all CHR) in imatinib-resistant patients (Table 13), and 50% in imatinib-intolerant patients. The duration of MaHR ranged from 1.3+ to 11+ months for imatinib-resistant patients and 2.2+ to 6.7+ months for imatinib-intolerant patients. None of the patients who achieved a MaHR have progressed.

Two (29%) of the 7 imatinib-resistant patients achieved a CCyR, and 1 (25%) of the 4 imatinib-intolerant patients achieved a PCyR on dasatinib. Despite never attaining a CyR on prior imatinib treatment, 2 of the 3 patients achieved a CyR on dasatinib, with a median duration of 5 months (range 1.3 to 12.9 months).

At last follow-up, there were 7 (64%) patients still on study. Of the 4 patients who discontinued treatment, 3 had documented disease progression, and 1 withdrew consent.

**Table 13: Hematologic and Cytogenetic Response Rates - CA180002 Accelerated Phase CML**

| **All Patients: Resistant + Intolerant** | **N = 11** |
|---|---|
| MaHR, % (95% CI) | **55** (23.4 – 83.3) |
| MCyR, % (95% CI) | **27** (6.0 – 61.0) |
| **Imatinib-resistant patients** | **N = 7** |
| MaHR, % (95% CI) | **57** (18.4 – 90.1) |
| MCyR,[a] % (95% CI) | **29** (3.7 – 71.0) |

[a] all were CCyR

## Study CA180005

**Baseline Disease-related Characteristics:** Patients on this study had a long history of CML and were extensively pretreated (Table 14). Despite most patients (83%) achieving a CHR while on prior imatinib, only 32% achieved a MCyR on imatinib. Nineteen (18%) patients had extramedullary involvement at baseline, and some had Grade 3 or 4 hematologic compromise (ie, thrombocytopenia [23%], neutropenia [7%], leukopenia [5%], and anemia [5%]) reported prior to starting dasatinib.

**Table 14: Baseline Characteristics (CA180005)**

| | Imatinib-intolerant N = 8 | Imatinib-resistant N = 99 | Total N = 107 |
|---|---|---|---|
| Median duration of CML (months) | 69 | 91 | 91 |
| Prior stem cell transplant, N (%) | 2 (25) | 17 (17) | 19 (18) |
| Prior interferon, N (%) | 4 (50) | 76 (77) | 80 (75) |
| Prior imatinib | | | |
| Dose >600 mg, N (%) | 3 (38) | 60 (61) | 63 (59) |
| Duration >3 years, N (%) | 2 (25) | 71 (72) | 73 (68) |
| Prior CHR, N (%) | 5 (63) | 84 (85) | 89 (83) |
| Prior MCyR, N (%) | 1 (12) | 33 (33) | 34 (32) |
| BCR-ABL mutations (%) | 1 (13) | 55 (56) | 56 (52) |

The reasons for imatinib intolerance (total 8 patients) included: gastrointestinal symptoms (1 patient), arthralgia/myalgia (2 patients), rash (1 patient), and hematologic toxicity (6 patients).

**Duration of Treatment/Patient Disposition:** The median duration of therapy was 5.5 months (range 0.2 to 10.1 months). The median average daily dose of dasatinib was 116 mg/day. Twenty-five (23%) patients discontinued dasatinib due to the following: 10 disease progression, 4 study drug toxicity, 3 patient requests, 4 deaths, 1 unrelated AE, and 3 classified as "other". One patient classified as "other" had achieved a confirmed CHR before discontinuing dasatinib to electively undergo a stem cell transplant. Among the patients still on study, the median duration of therapy is 25 weeks (range 9.0 to 45.0 weeks).

**Hematologic Response/Cytogenetic Response:** After a follow-up of ≥ 6 months, the MaHR rate was 59% (63/107), with a CHR rate of 33%. The MCyR rate was 31% in the total population (Table 15). Of those with baseline mutations, a MCyR was achieved in 17 (30%) patients.

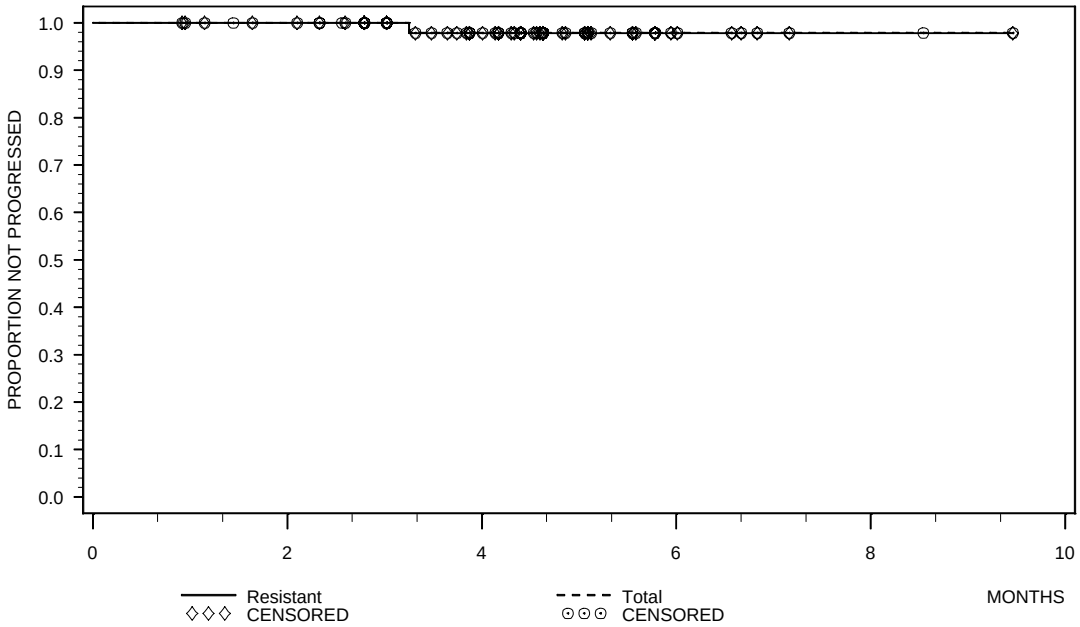
**Table 15: Hematologic and Cytogenetic Response Rates (CA180005)**

| | Imatinib-intolerant N = 8 | Imatinib-resistant N = 99 | Total N = 107 |
|---|---|---|---|
| **Hematologic Response** | | | |
| MaHR, N (%) | 4 (50) | 59 (59) | 63 (59) |
| CHR, N (%) | 1 (13) | 34 (34) | 35 (33) |
| **Cytogenetic Response** | | | |
| MCyR, N (%) | 1 (12) | 32 (32) | 33 (31) |
| CCyR, N (%) | 0 | 23 (23) | 23 (22) |

Among the 63 patients that had achieved MaHR, only 1 imatinib-resistant patient progressed (Figure 5). The longest duration of response was 9.5+ months. In addition, of the 56 (52%) patients with an imatinib-resistant mutation at baseline, a MaHR was achieved in 37 (66%) patients.

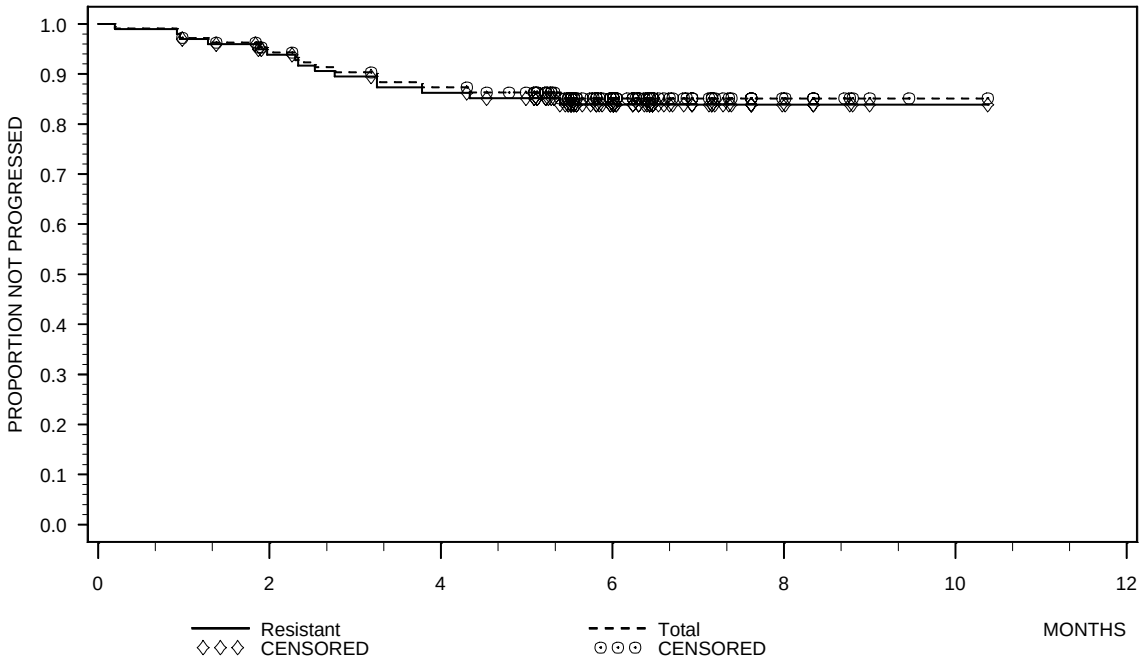
The median progression-free survival (PFS) was not reached (Figure 6).

**Figure 5: Duration of MaHR (CA180005)**




| Group | # Progressed/# Responded | Median (95% CI) |
|---|---|---|
| **Total** | 1/63 | NA (NA) |
| **Imatinib-resistant** | 1/58 | NA (NA) |

**Figure 6: Progression-free Survival (CA180005)**




| Group | # Progressed/# Treated | Median (95% CI) |
|---|---|---|
| **Total** | 15/107 | NA (NA) |
| **Imatinib-resistant** | 15/99 | NA (NA) |

Treatment with dasatinib achieved durable hematologic and cytogenetic responses. This is evidenced by the fact that in highly refractory patients with accelerated phase CML more than two-thirds remain on study following ≥ 6 months of follow-up. The durability of response in these patients with accelerated phase CML are clinically meaningful given the limited therapeutic options available for these patients.

## 7.3 Myeloid Blast Phase CML (CA180002 and CA180006)

## Study CA180002

**Baseline Disease-related Characteristics:** Twenty-three patients with myeloid phase CML were enrolled in this study. The median duration of CML was 44 months. Thirteen patients (57%) had baseline imatinib-resistant mutations, and the majority (>50%) were heavily pretreated with prior interferon and > 600 mg/day of prior imatinib.

**Hematologic Response/Cytogenetic Response:** The MaHR rate in imatinib-resistant patients was 32% (7/22) (Table 16), with a duration ranging from 1.9+ to 10+ months. Only 1 patient who had a MaHR progressed.

Eight (36%) of 22 imatinib-resistant patients achieved a MCyR, with a median duration of dasatinib exposure of 5 months (range 0.2 to 12.0 months). In 10 patients who had no prior CyR to imatinib, 7 achieved a CyR when given dasatinib: 3 CCyR, 2 PCyR, 1 minor CyR, and 1 minimal CyR.

**Table 16: Hematologic and Cytogenetic Response Rates - CA180002 Myeloid Blast Phase CML**

| Imatinib-resistant patients | N = 22 |
|---|---|
| MaHR, % (95% CI) | **32** (13.9 - 54.9) |
| MCyR, % (95% CI) | **36** (17.2 - 59.3) |

Of the 17 patients discontinued, the majority (N = 8) had disease progression, and 1 electively underwent stem cell transplant. Although myeloid blast CML is difficult to treat, cytogenetic responses with dasatinib were still achieved. At last follow-up, there were 6 (26%) patients still on study.

## Study CA180006

**Baseline Disease-related Characteristics:** Patients in CA180006 had approximately a 4-year history of CML and were extensively pretreated (Table 17). Twenty-six (35%) patients had considerable BM disease with ≥ 50% blasts at baseline. In addition, 27 (36%) patients had extramedullary involvement, and at baseline, platelets were < 100,000/mm$^3$ in 53 (72%) patients.

There were 6 patients who were intolerant of imatinib. The reasons for imatinib-intolerance included: hepatotoxicity (2), gastrointestinal (1), rash (1), leucopenia (1), and neutropenia (1).

**Table 17: Baseline Characteristics (CA180006)**

| | Imatinib-intolerant N = 6 | Imatinib-resistant N = 68 | Total N = 74 |
|---|---|---|---|
| Median duration of CML (months) | 73 | 47 | 49 |
| Prior interferon, N (%) | 6 (100) | 35 (51) | 41 (55) |
| Prior stem cell transplant, N (%) | 1 (17) | 8 (12) | 9 (12) |
| Prior chemotherapy, N (%) | 2 (33) | 47 (69) | 49 (66) |
| Prior imatinib | | | |
| Dose > 600 mg, N (%) | 0 | 36 (53) | 36 (49) |
| Duration > 3 years, N (%) | 4 (67) | 31 (46) | 35 (47) |
| Baseline BM blasts ≥ 50%, N (%) | 3 (50) | 23 (34) | 26 (35) |
| BCR-ABL mutations (%) | 2 (33) | 25 (37) | 27 (36) |

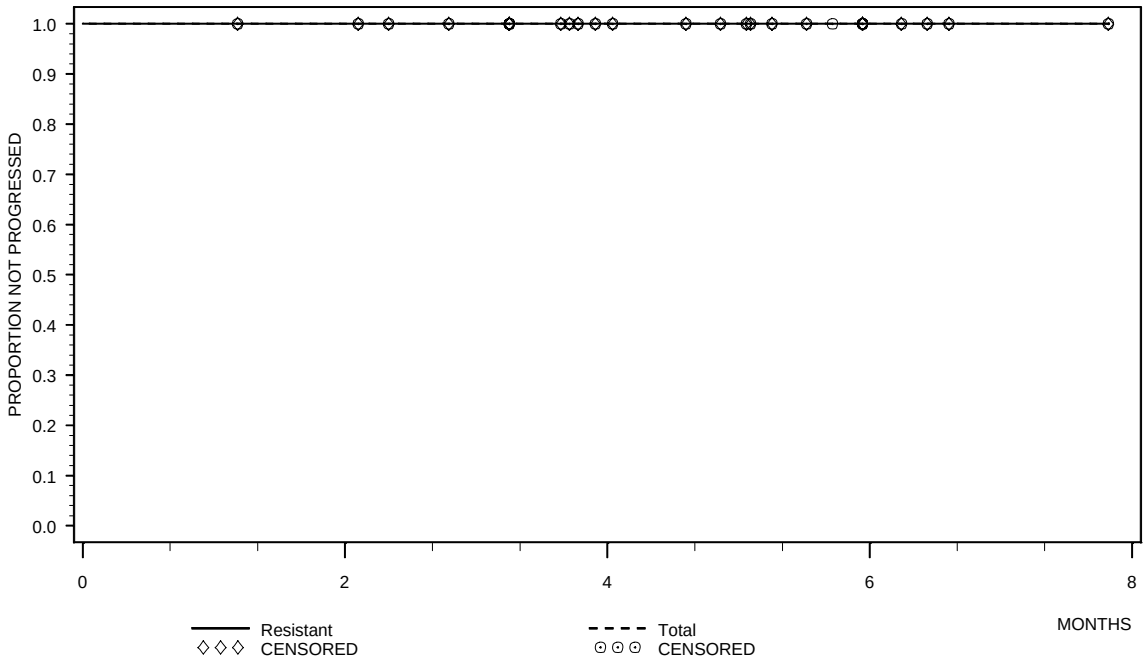
**Duration of Treatment/Patient Disposition:** The median duration of therapy was 3.5 months (range 0.03 to 9.2 months), and the median average daily dose in all patients was 137 mg/day. Forty-two (57%) patients have discontinued dasatinib with the most common reasons being: 22 progressive disease, 7 deaths, 5 with study drug toxicity, and 5 had an elective stem cell transplant.

**Hematologic Response:** With a follow-up of ≥ 6 months, the MaHR rate was 32% (Table 18) with the longest duration being 7.8+ months. None of the patients who achieved a MaHR had progressed (Figure 7).

**Table 18: Hematologic and Cytogenetic Response Rates (CA180006)**

| | Imatinib-intolerant N = 6 | Imatinib-resistant N = 68 | Total N = 74 |
|---|---|---|---|
| **Hematologic Response** | | | |
| MaHR, N (%) | 1 (17) | 23 (34) | 24 (32) |
| CHR, N (%) | 1 (17) | 17 (25) | 18 (24) |
| **Cytogenetic Response** | | | |
| MCyR, N (%) | 2 (33) | 20 (29) | 22 (30) |
| CCyR, N (%) | 2 (33) | 18 (26) | 20 (27) |

**Figure 7: Duration of MaHR (CA180006)**

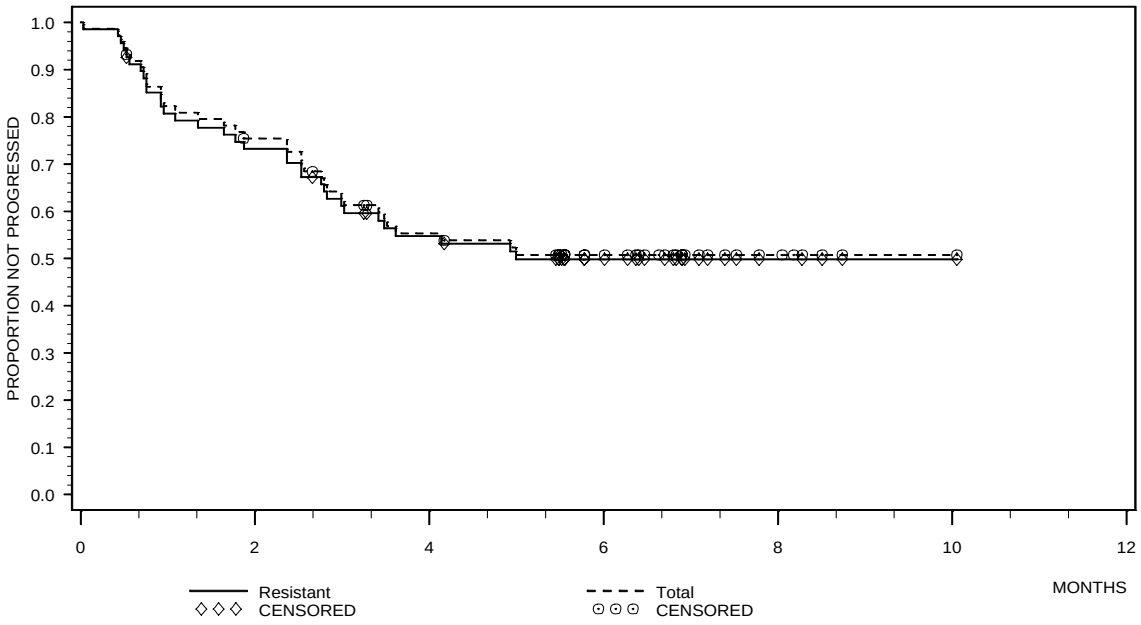



| Group | # Progressed/# Responded | Median (95% CI) |
|---|---|---|
| **Total** | 0/24 | NA (NA) |
| **Imatinib-resistant** | 0/23 | NA (NA) |

**Cytogenetic Response:** The MCyR rate was 30% in the total population (Table 18). In addition, 27 (36%) patients had baseline imatinib-resistant mutations and of those, 6 (22%) achieved a MCyR and 9 (33%) achieved a MaHR.

The median PFS was not reached for the entire patient population, but was 5.0 months (95% CI: 3.0- ) in the imatinib-resistant patients (Figure 8).

**Figure 8: Progression-free Survival (CA180006)**




| Group | # Progressed/# Treated | Median (95% CI) |
|---|---|---|
| **Total** | 35/74 | NA (3.4 - ) |
| **Imatinib-resistant** | 33/68 | 5.0 (3.0 - ) |

Patients with CML in myeloid blast phase historically have had a poor prognosis with survival ranging from 3 to 6 months.[11] Thus, in this poor prognosis population, many of which had imatinib resistance-conferring mutations, a 6-month PFS rate of 51% is clinically meaningful.

## 7.4 Lymphoid Blast Phase CML and Philadelphia Chromosome Positive ALL (CA180002 and CA180015)

## Study CA180002

**Baseline Disease-related Characteristics:** Five patients with lymphoid blast phase CML and 5 patients with Ph+ ALL were included in this study. Five (50%) had received a prior stem cell transplant and 7 (70%) had received > 600 mg/day of prior imatinib. Nine (90%) had achieved a prior MaHR with imatinib and only 3 (30%) achieved a MCyR with imatinib.

**Hematologic Response/Cytogenetic Response:** In this relatively small cohort, the MaHR rate was 50% (Table 19), with a median duration of MaHR in the imatinib-resistant patients of 4.5 months. A MCyR of 80%, with a CCyR rate of 30%, was achieved with dasatinib in these patients with lymphoid blast phase CML or Ph+ ALL. Of the 8 patients with MCyR to dasatinib, 3 had no prior CyR to imatinib.

**Table 19: Hematologic and Cytogenetic Response Rates - CA180002 Lymphoid Blast Phase CML / Ph+ ALL**

| All Treated Patients | N = 10 |
|---|---|
| MaHR, N (%) | 5 (50) |
| MCyR, N (%) | 8 (80) |
| CCyR, N (%) | 3 (30) |

The median duration of dasatinib exposure was 3 months (range 0.5 to 7.7 months). At last follow-up, 9 patients discontinued treatment: 6 due to disease progression, 1 who died, 1 due to resistant mutation, and 1 who underwent an elective stem cell transplant.

## Study CA180015

**Baseline Disease-related Characteristics:** Given the aggressive nature of lymphoid blast phase CML and Ph+ ALL, patients had approximately a median 2-year duration of leukemia prior to starting dasatinib. Fourteen (33%) CML patients and 15 (42%) Ph+ ALL patients had received a prior stem cell transplant, and approximately 50% in both the CML and Ph+ ALL cohorts had a baseline imatinib-resistant mutation (Table 20). Thirty (71%) patients with lymphoid blast CML, and 19 (53%) patients with Ph+ ALL had considerable BM disease with ≥ 50% blasts at baseline. One-third of the patients had extramedullary involvement at baseline, in addition to considerable hematologic compromise: platelets <100,000/$mm^3$ in 33 (79%) patients with lymphoid blast CML, and in 25 (69%) patients with Ph+ ALL.

There were 7 imatinib-intolerant patients on study with the following reasons for intolerance: 3 gastrointestinal and 4 hematologic.

**Table 20: Baseline Characteristics (CA180015)**

| | Lymphoid Blast CML N = 42 | Ph+ ALL N = 36 |
|---|---|---|
| Median duration of CML (months) | 28 | 20 |
| Prior interferon, N (%) | 20 (48) | 3 (8) |
| Prior stem cell transplant, N (%) | 14 (33) | 15 (42) |
| Prior chemotherapy, N (%) | 33 (79) | 33 (92) |
| Prior imatinib, N (%) | | |
| Dose > 600 mg, N (%) | 22 (52) | 17 (47) |
| Prior MCyR, N (%) | 18 (43) | 18 (50) |
| Baseline BM blasts ≥ 50%, N (%) | 30 (71) | 19 (53) |
| Imatinib resistance, N (%) | 37 (88) | 34 (94) |
| BCR-ABL mutations (%) | 20 (48) | 17 (47) |

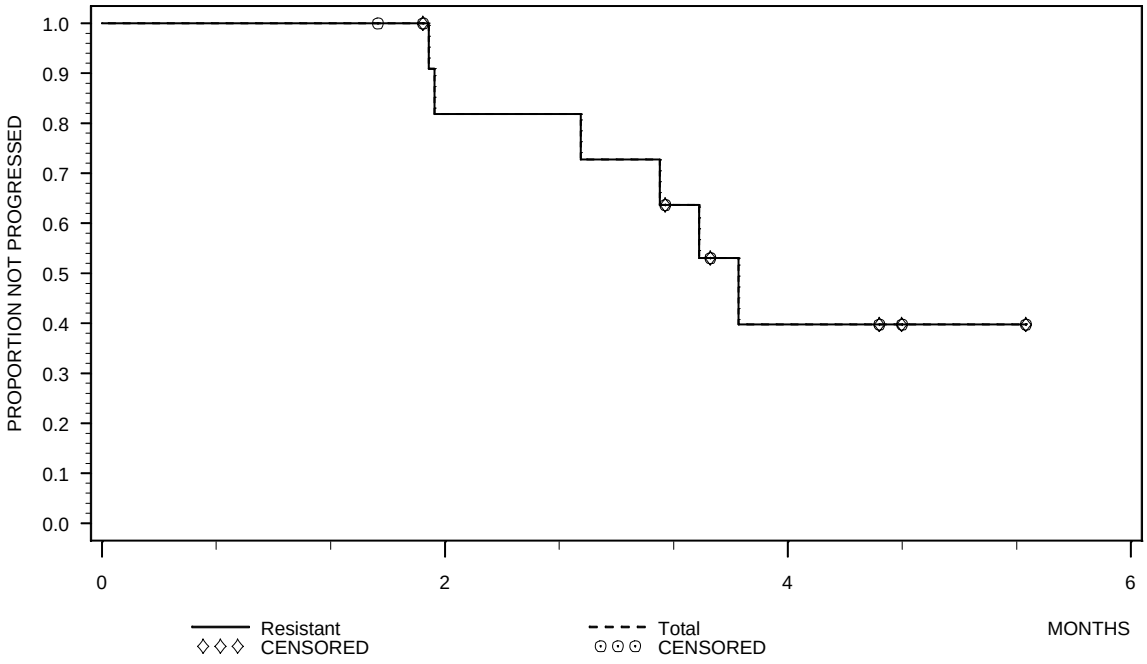
**Duration of Treatment/Patient Disposition:** The median duration of therapy for all treated patients was 3.0 months (range 0.1 to 8.1 months). The median average daily dose was 140 mg/day. Thirty-five (83%) patients with lymphoid blast CML have discontinued dasatinib with the following being the most common reasons: disease progression (21); death in 6 patients, and 4 patients underwent elective stem cell transplant. Twenty-four (67%) Ph+ ALL patients have discontinued dasatinib, with disease progression (16), deaths (3), study drug toxicity (2), and 2 patients underwent elective stem cell transplant. All 12 Ph+ ALL patients still on study have had ≥ 24 weeks of therapy.

**Hematologic Response – Lymphoid Blast Phase:** The MaHR rate was 31% (Table 21). Among the 13 patients who achieved a MaHR, 6 (46%) had progressed. The longest duration of response was 5.4+ months (Figure 9).

**Table 21: Hematologic and Cytogenetic Response Rates - Lymphoid Blast CML/Ph+ ALL (CA180015)**

| | Lymphoid Blast CML N = 42 | Ph+ ALL N = 36 |
|---|---|---|
| **Hematologic Response** | | |
| MaHR, N (%) | 13 (31) | 15 (42) |
| CHR, N (%) | 11 (26) | 11 (31) |
| **Cytogenetic Response** | | |
| MCyR, N (%) | 21 (50) | 21 (58) |
| CCyR, N (%) | 18 (43) | 21 (58) |

**Figure 9: Duration of MaHR – Lymphoid Blast (Study CA180015)**



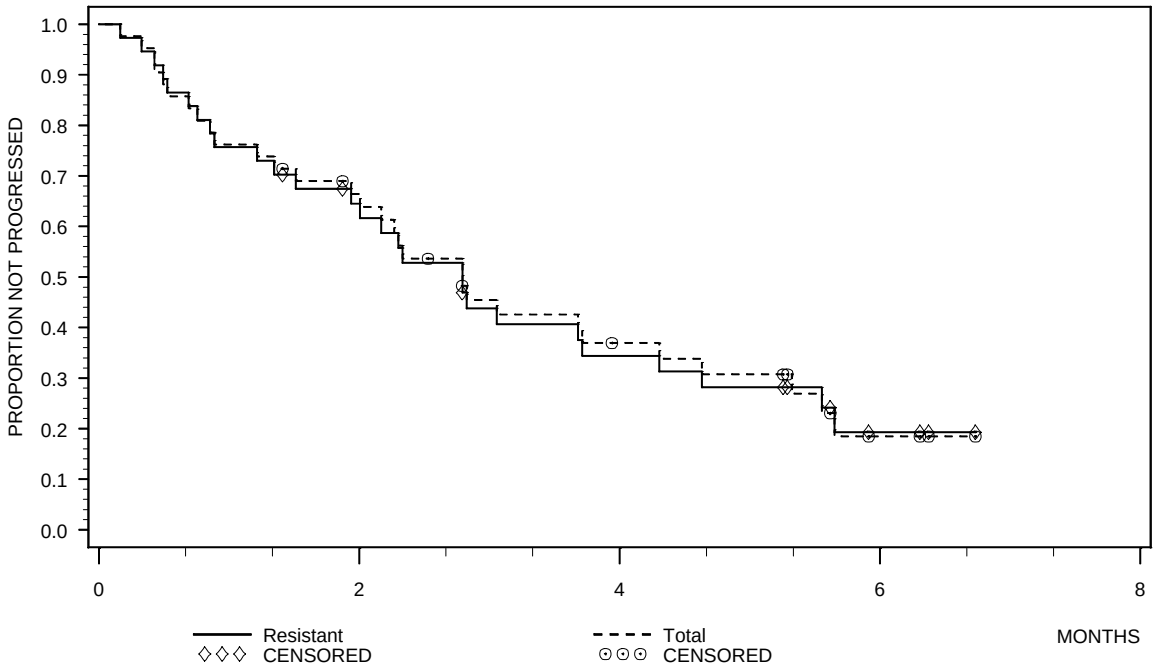

| Group | # Progressed/# Responded | Median (95% CI) |
|---|---|---|
| **Total** | 6/13 | 3.7 (2.8 - ) |
| **Imatinib-resistant** | 6/12 | 3.7 (2.8 - ) |

**Cytogenetic Response – Lymphoid Blast Phase CML:** The MCyR rate was 50% (Table 21). This is of clinical importance in this advanced disease population, especially given that it is an improvement from the 43% MCyR that they had achieved on prior

imatinib. In addition, of the twenty (48%) lymphoid blast patients with baseline imatinib-resistant mutations, a MCyR was achieved in 9 (45%) patients.

In this population, the median PFS was 2.8 months (Figure 10).

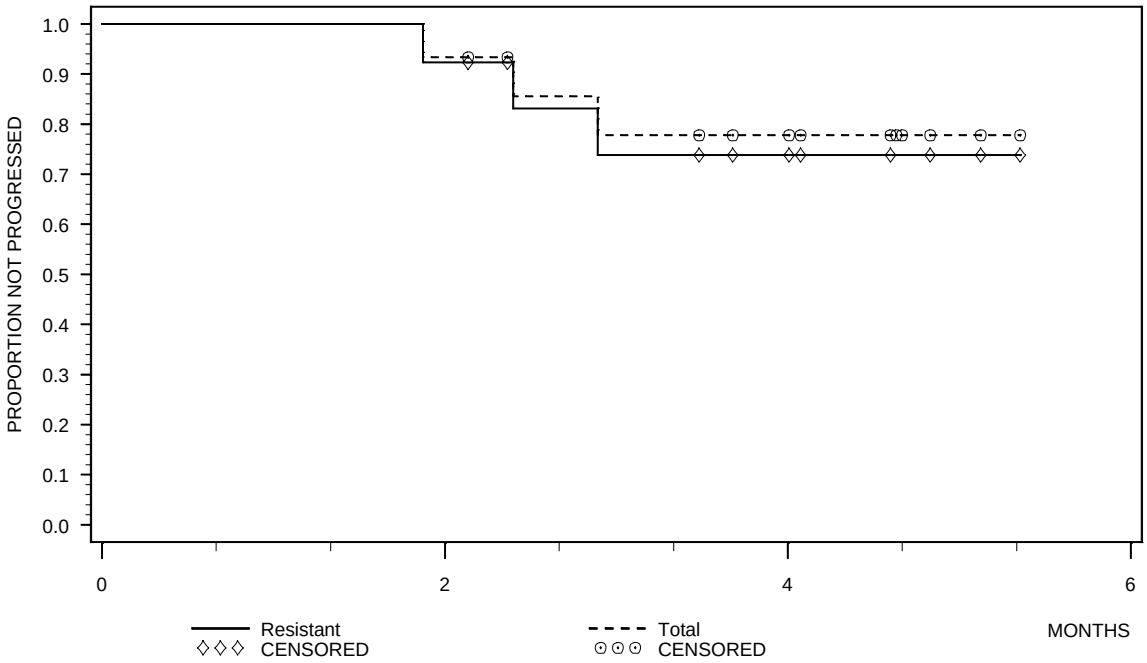
**Figure 10: Progression-free Survival - Lymphoid Blast CML (CA180015)**




| Group | # Progressed/# Treated | Median (95% CI) |
|---|---|---|
| **Total** | 30/42 | 2.8 (2.0 - 4.3) |
| **Imatinib-resistant** | 27/37 | 2.8 (1.9 - 4.3) |

**Hematologic Response - Ph+ ALL:** The MaHR rate was 42% (Table 21). Among the 15 patients who achieved a MaHR, 3 (20%) had progressed. The longest duration of MaHR was 5.4+ months (Figure 11).

**Figure 11: Duration of MaHR in Ph+ ALL (Study CA180015)**

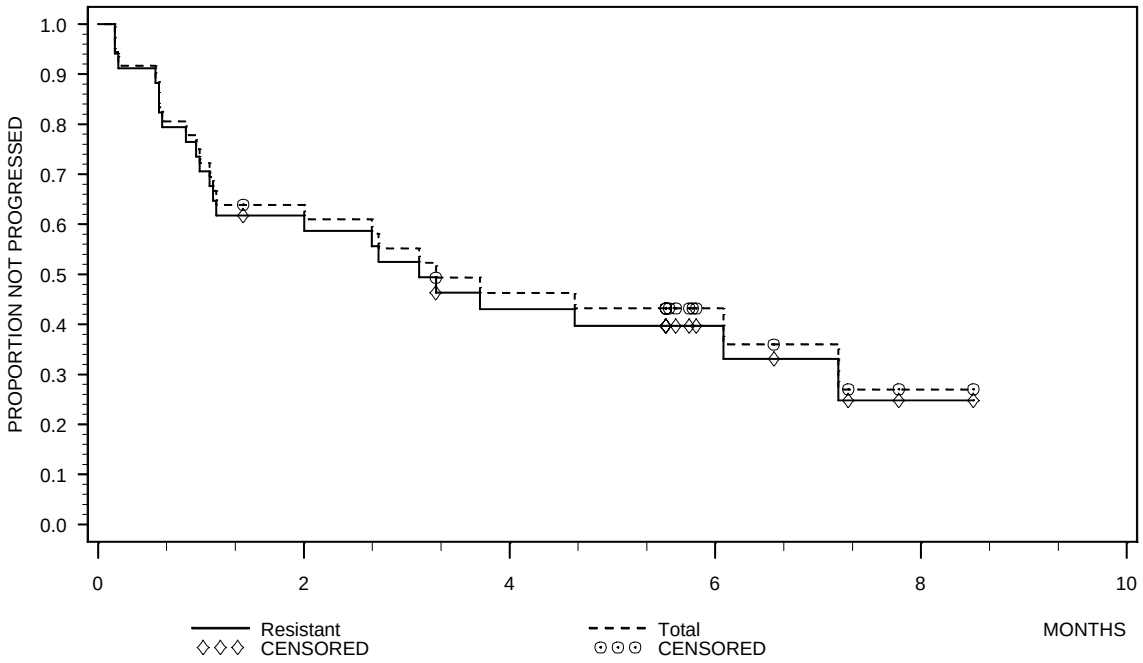



| Group | # Progressed/# Responded | Median (95% CI) |
|---|---|---|
| **Total** | 3/15 | NA (NA) |
| **Imatinib-resistant** | 3/13 | NA (2.9 - ) |

**Cytogenetic Response - Ph+ ALL:** The MCyR rate was 58% (21/36) for the total Ph+ ALL population (Table 21). This is clinically important given the advanced nature of this disease and that with prior imatinib, the MCyR rate was only 50%. Of the 17 (47%) Ph+ ALL patients with imatinib-resistant mutations, a MCyR was achieved in 8 (47%) patients.

In the Ph+ ALL population, the median PFS was 3.3 months (range 1.1 to 7.2 months) (Figure 12).

**Figure 12: Progression-free Survival - Ph+ ALL (CA180015)**




| Group | # Progressed/# Treated | Median (95% CI) |
|---|---|---|
| **Total** | 22/36 | 3.3 (1.1 - 7.2) |
| **Imatinib-resistant** | 22/34 | 3.1 (1.1 - 7.2) |

Lymphoid blast CML and Ph+ ALL patients generally have a rapid disease course and a poor overall prognosis.[2,12] In this study of heavily pretreated patients, many of whom received a prior transplant, 6 patients were able to electively go onto stem cell transplant after receiving dasatinib. Seven (54%) of 13 patients with lymphoid blast CML and 12 (80%) of 15 Ph+ ALL patients who had achieved a MaHR had not progressed.

## 7.5 Overcoming Resistance

Point mutations within the ABL kinase domain are the most common mechanism of resistance to imatinib. The location of the mutation within the kinase domain can include the ATP-binding loop (P-loop), specific imatinib contact residues (C region), and the activation loop (A-loop). Some mutations confer a moderate degree of resistance, whereas mutations within the P-loop distinguish the more difficult-to-treat mutations. Across the Phase 2 program, a total of 197 (41%) patients had baseline BCR-ABL imatinib-resistant mutations. Thirty-four unique imatinib-resistant mutations were

identified in central laboratories, and specifically 9 amino acid substitutions accounted for 68% of all BCR-ABL mutations. Dasatinib therapy resulted in MaHR and MCyR in the presence of all imatinib-resistant mutations, with the exception of the T315I mutation (Table 22).

**Table 22: Overcoming Resistance**

| Mutation | Location | N of Patients | MaHR (N of Patients) | MCyR (N of Patients) |
|---|---|---|---|---|
| M244V | P-loop | 17 | 13 | 9 |
| G250E | | 31 | 19 | 9 |
| Y253H/F | | 20 | 15 | 10 |
| E255K/V | | 19 | 8 | 2 |
| T315I | C region | 19 | 0 | 0 |
| M351T/V | | 15 | 12 | 7 |
| E355G | | 10 | 6 | 2 |
| F359C/I/V | | 16 | 8 | 6 |
| H396P/R | A-loop | 21 | 14 | 7 |

# 8 CLINICAL SAFETY

The clinical safety of dasatinib was assessed in a cohort of 511 patients with imatinib-resistant/intolerant CML or Ph+ ALL treated on the BID schedule in 6 studies (Table 1). Safety data were based on the 120-day safety update and followed for a minimum of 7 months in the 4 single-arm Phase 2 studies. Given that the randomized Phase 2 study (CA180017) was the last study to start and close enrollment, safety data with a minimum of 6 months of follow-up are presented. Safety data were pooled across studies by phase of disease. Not included in the pooled safety analysis were 14 patients treated with imatinib (CA180017) and 40 patients treated with dasatinib with chronic phase CML who had multiple dose escalations and different dosing schedules in the Phase 1 study (CA180002).

Severity of on-study adverse events (AEs) was graded by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 grading system.

Two important safety concerns were identified, ie, myelosuppression and fluid retention. Myelosuppression, especially thrombocytopenia, was common and severe. Although this was expected in advanced disease patients, frequent occurrences of myelosuppression in patients implied that careful monitoring and management are needed. Fluid retention was also reported. Edema events were infrequent and managed with diuretics. Pleural effusion and other fluid retention events were usually manageable with dasatinib interruption and supportive care with diuretics.

Overall, dasatinib was tolerated across all the disease phases. This is supported by the fact that in the heavily pretreated population of patients with advanced CML/Ph+ ALL disease, few patients required discontinuation due to drug-related toxicities. In addition, the majority of the deaths on study were due to disease progression and not to study drug-related events.

## 8.1 Hematologic Toxicity - Myelosuppression

Myelosuppression is part of the natural history of most hematologic malignancies, and thus the level of hematologic toxicity reported may partly be the result of the underlying leukemic diagnosis or the extensive prior therapies.

As expected, myelosuppression was reported in a number of patients at baseline prior to receiving dasatinib. The proportion of patients with Grade 3 to 4 neutropenia at baseline was 3% in chronic phase CML, 7% in accelerated phase CML, 20% in myeloid blast phase, and 31% of patients with lymphoid blast or Ph+ ALL. Similarly, Grade 3 to 4 thrombocytopenia at baseline was documented in only 1% of chronic phase CML patients, 21% of accelerated phase patients, and was the highest in myeloid blast phase CML and lymphoid blast CML/ Ph+ ALL where 45% and 58% of patients had baseline Grade 3 or 4 thrombocytopenia, respectively.

The majority of patients with CML or Ph+ ALL in all 6 studies experienced some degree of hematologic toxicity. It was the most common reason for dose reductions or interruptions in patients with chronic and accelerated phase CML (Section 8.4). Thrombocytopenia, neutropenia, and anemia were the most frequently reported Grade 3 to 4 laboratory abnormalities in all patient populations. The frequency of Grade 3 or 4 thrombocytopenia and neutropenia was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML, whereas Grade 3 or 4 anemia was higher in these

patients with advanced disease phases (Table 23). Few complications of infection and bleeding episodes were reported, which are discussed further in the drug-related adverse events section (Section 8.2).

In chronic phase CML, myelosuppression was reported in 20% to 50% of patients treated with dasatinib (Table 23). This frequency is higher than that reported in chronic phase CML with imatinib (approximately 20%), but the patients treated with dasatinib had a longer disease duration (median 8 years vs 3 years) than those treated in imatinib studies. In addition, the greater potency of dasatinib may contribute to the more profound myelosuppression due to the rapid clearance of BCR-ABL expressing malignant hematopoietic cells. Unlike imatinib,[13] dasatinib is not a substrate of the p-glycoprotein pump, and therefore higher concentrations of dasatinib might be achieved in hematopoietic progenitor cells.

In patients who experienced myelosuppression, recovery occurred following brief (2 to 4 weeks) dose interruptions or reductions, occasionally requiring transfusion or treatment discontinuation. In general, both dasatinib and the underlying disease state, as supported by the high amount of hematologic compromise at baseline, contributed to the degree of myelosuppression.

**Table 23: Grade 3 to 4 Hematologic Laboratory Abnormalities**

| | N (%) of Patients[a] | | | |
|---|---|---|---|---|
| | **Chronic Phase** | **Accelerated Phase** | **Myeloid Blast Phase** | **Lymphoid Blast Phase/Ph+ ALL** |
| Thrombocytopenia | 97/206 (47) | 97/118 (82) | 81/96 (84) | 72/88 (82) |
| Neutropenia | 103/205 (50) | 92/118 (78) | 83/96 (86) | 67/85 (79) |
| Anemia | 41/206 (20) | 83/118 (70) | 69/96 (72) | 45/88 (51) |

[a] For patients with values reported at baseline

## 8.2 Drug-related Adverse Events

The majority (94%) of dasatinib-treated patients experienced drug-related AEs at some time on study, with most of the AEs being mild to moderate (Table 24). Drug-related AEs, excluding hematologic laboratory abnormalities (Section 8.1), at a frequency of ≥ 5%, are shown in Table 24. The incidence of Grade 3 or 4 drug-related AEs was similar

among the different phases of CML and Ph+ ALL, with the exception of Grade 3 or 4 fluid retention/pleural effusion, hemorrhage, and febrile neutropenia. These specific toxicities were reported in greater frequency within the blast phase CML patients (up to 20%) vs those with chronic phase disease (less than 8%). Most of the Grade 3 or 4 drug-related AEs were managed with dose reductions or interruptions.

**Table 24: Drug-related AEs Reported ≥ 5% in Clinical Studies**

| | N (%) of Patients N = 511 | |
|---|---|---|
| **Preferred Term** | **Any Grade** | **Grades 3/4** |
| Patients with any on-treatment AEs | 479 (94) | 265 (52) |
| Fluid Retention | 223 (44) | 42 (8) |
| Superficial edema | 144 (28) | 1 (<1) |
| Pleural effusion | 108 (21) | 25 (5) |
| Other fluid retention | 59 (12) | 23 (5) |
| Diarrhea | 179 (35) | 20 (4) |
| Hemorrhage | 126 (25) | 42 (8) |
| Gastrointestinal bleeding | 52 (10) | 34 (7) |
| CNS bleeding | 3 (1) | 1 (<1) |
| Rash | 132 (26) | 7 (1) |
| Headache | 121 (24) | 5 (1) |
| Dyspnea | 106 (21) | 19 (4) |
| Fatigue | 108 (21) | 9 (2) |
| Nausea | 103 (20) | 5 (1) |
| Asthenia | 82 (16) | 13 (3) |
| Pyrexia | 82 (16) | 12 (2) |
| Musculoskeletal pain | 77 (15) | 4 (1) |
| Vomiting | 68 (13) | 4 (1) |
| Abdominal pain | 53 (10) | 2 (<1) |
| Anorexia | 43 (8) | 2 (<1) |
| Pruritus | 40 (8) | 0 |
| Abdominal distension | 35 (7) | 0 |
| Arthralgia | 38 (7) | 4 (1) |
| Cough | 35 (7) | 3 (1) |
| Infection (including bacterial, viral, fungal, non-specified) | 38 (7) | 12 (2) |
| Pain | 34 (7) | 2 (<1) |

**Table 24: Drug-related AEs Reported ≥ 5% in Clinical Studies**

| | N (%) of Patients N = 511 | |
|---|---|---|
| **Preferred Term** | **Any Grade** | **Grades 3/4** |
| Alopecia | 30 (6) | 0 |
| Mucosal inflammation (including mucositis/stomatitis) | 30 (6) | 0 |
| Myalgia | 33 (6) | 1 (<1) |
| Weight increased | 29 (6) | 0 |
| Acne | 23 (5) | 1 (<1) |
| Febrile neutropenia | 28 (5) | 26 (5) |
| Flushing | 23 (5) | 0 |
| Weight decreased | 26 (5) | 2 (<1) |

**Edema, Pleural Effusion, and Other Fluid Retention:** Fluid retention events were systematically identified in the dasatinib program. In addition to edema and pleural effusion, other events related to fluid retention were also examined (see below).

Edema was classified by MedRA terms and subdivided into superficial edema and generalized edema. Superficial edema was more common than generalized edema. Drug-related edema was reported in 29% of patients and the incidence of edema was similar across all phases of CML and Ph+ ALL (Table 25). The median onset time from the start of dasatinib to an edema event was approximately 24 days. With the exception of 4 events, all events of edema were Grade 1 to 2. The edema rarely led to treatment interruption and never led to treatment discontinuation. The majority of cases of edema were managed with diuretics.

Drug-related pleural effusion occurred in 21% of patients, with the highest incidence (30%) occurring in patients with myeloid blast phase CML (Table 25). The median onset time from the start of dasatinib to a pleural effusion was approximately 3 months. The majority of pleural effusions were Grade 1 to 2, with 5% being classified as Grade 3 or 4. Of the Grade 3 to 4 pleural effusions, the majority were managed with dasatinib interruption, and supportive care with diuretics. In some individuals, oxygen therapy and thoracentesis were necessary to manage recurrent effusions but, in most cases, the

effusion could be managed while continuing dasatinib. Only 4 patients across all studies discontinued dasatinib because of treatment-related pleural effusions.

Other events of fluid retention were uncommon (Table 25) and included:

- **Pulmonary edema**: Of the 10 drug-related pulmonary edema events, only 1 was Grade 3 to 4 and 1 led to discontinuation.
- **Congestive heart failure (CHF)**: Of the 12 drug-related CHF events, 8 were Grade 3 to 4 and only 1 led to discontinuation.
- **Pulmonary hypertension**: Of the 5 drug-related events, 1 was Grade 3, which led to no dose interruption or reduction. None of the patients discontinued because of pulmonary hypertension.
- **Pericardial effusion**: Of the 14 drug-related events, 3 were Grade 3 to 4. All 3 patients had dose interruptions and 2 of them also had dose reductions. None of the patients discontinued because of pericardial effusion.
- **Cardiac dysfunction**: Of the 7 drug-related events, 6 were Grade 3 to 4. Two patients discontinued: 1 due to the cardiac dysfunction and CHF, which was considered by the investigator to be drug-related and the other died ~2 months after the onset of the event and the death was attributed to "global cardiac insufficiency" (Section 8.6).

**Table 25: All Drug-related Edema, Pleural Effusion, and Other Fluid Retention**

| Drug-related terms | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| | Chronic N = 208 | Accelerated N = 118 | Myeloid blast N = 97 | Lymphoid blast/ALL N = 88 | Total N = 511 |
| **Edema** | | | | | |
| All drug-related events | 57 (27) | 39 (33) | 31 (32) | 21 (24) | **148 (29)** |
| Grade 3 to 4 | 1 (<1) | 1 (1) | 1 (1) | 1 (1) | **4 (1)** |
| Discontinuation | 0 | 1 (1) | 0 | 0 | **1 (<1)** |
| **Pleural Effusion** | | | | | |
| All drug-related events | 38 (18) | 26 (22) | 29 (30) | 15 (17) | **108 (21)** |
| Grade 3 to 4 | 7 (3) | 3 (3) | 13 (13) | 2 (2) | **25 (5)** |
| Discontinuation | 2 (1) | 0 | 2 (2) | 0 | **4 (1)** |
| **Pulmonary edema** | | | | | |
| All drug-related events | 3 (1) | 2 (2) | 2 (2) | 3 (3) | **10 (2)** |
| Grade 3 to 4 | 1 (<1) | 0 | 0 | 0 | **1 (<1)** |
| Discontinuation | 1 (<1) | 0 | 0 | 0 | **1 (<1)** |
| **Congestive heart failure** | | | | | |
| All drug-related events | 10 (5) | 0 | 2 (2) | 0 | **12 (2)** |
| Grade 3 to 4 | 6 (3) | 0 | 2 (2) | 0 | **8 (2)** |
| Discontinuation | 0 | 0 | 1 (1) | 0 | **1 (<1)** |
| **Pulmonary hypertension** | | | | | |
| All drug-related events | 2 (1) | 0 | 3 (3) | 0 | **5 (1)** |
| Grade 3 to 4 | 0 | 0 | 1 (1) | 0 | **1 (<1)** |
| Discontinuation | 0 | 0 | 0 | 0 | **0** |
| **Pericardial effusion** | | | | | |
| All drug-related events | 4 (2) | 3 (3) | 6 (6) | 1 (1) | **14 (3)** |
| Grade 3 to 4 | 0 | 1 (1) | 2 (2) | 0 | **3 (1)** |
| Discontinuation | 0 | 0 | 0 | 0 | **0** |
| **Cardiac dysfunction** | | | | | |
| All drug-related events | 3 (1) | 1 (1) | 3 (3) | 0 | **7 (1)** |
| Grade 3 to 4 | 2 (1) | 1 (1) | 3 (3) | 0 | **6 (1)** |
| Discontinuation | 1 (<1) | 0 | 1 (1) | 0 | **2 (<1)** |

**Bleeding-related Events:** One-third of patients had a bleeding event on study and of those, half were considered study drug-related. The majority of these events were Grade 1 to 2 and were classified as "other" (ie, epistaxis, petechiae, gingival bleeding). Severe bleeding events were rare and occurred in 1% of patients on study. Patients rarely interrupted dasatinib and never discontinued treatment due to a drug-related event of hemorrhage.

**Gastrointestinal Hemorrhage:** Gastrointestinal hemorrhage is a known comorbid condition in an acutely ill population of leukemic patients, typically resulting from thrombocytopenia or platelet dysfunction. Drug-related gastrointestinal hemorrhage occurred in 10% of patients and was more common in patients with advanced phase leukemia (Table 26). The majority were reported as lower gastrointestinal tract hemorrhage and were considered related to dasatinib. The majority of patients had drug interruption and received transfusions of packed red blood cells. Three subjects discontinued because of drug-related gastrointestinal hemorrhage.

**Table 26: All Drug-related Gastrointestinal Hemorrhage**

| | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| **Drug-related terms** | **Chronic N = 208** | **Accelerated N = 118** | **Myeloid blast N = 97** | **Lymphoid blast/ALL N = 88** | **Total N = 511** |
| Grade 1 to 4 gastrointestinal hemorrhage events | 8 (4) | 21 (18) | 14 (14) | 8 (9) | **51 (10)** |
| Grade 3 to 4 gastrointestinal hemorrhage events | 3 (1) | 14 (12) | 11 (11) | 6 (7) | **34 (7)** |
| Interruption for any event | 6 (3) | 18 (15) | 11 (11) | 3 (3) | **38 (7)** |
| Discontinuation for event | 0 | 2 (2) | 1 (1) | 0 | **3 (1)** |

**Central Nervous System Hemorrhage:** Central nervous system (CNS) hemorrhage is another known complication of leukemia and, like gastrointestinal hemorrhage, typically results from severe thrombocytopenia or platelet dysfunction.

Three drug-related cases of CNS hemorrhage occurred in the 511 patients evaluated. Two of the 3 cases (1 in lymphoid blast phase CML and 1 in chronic phase CML) were fatal and occurred in the setting of Grade 4 thrombocytopenia. Both cases were diagnosed clinically, without supporting computed tomography or magnetic resonance imaging of

the head. In addition to these subjects, there was another fatality due to CNS bleed in whom the cause of death was listed as "other" (fatal bleed). This occurred in a subject who died more than 30 days from the last dasatinib dose. The investigator listed the bleeding event as being possibly related to dasatinib.

**QT Interval Prolongation:** Dasatinib activity in vitro in hERG/IKr current and Purkinje fiber assays suggested a potential risk for prolongation of cardiac ventricular repolarization (QT interval). Therefore, a thorough analysis across a broad range of doses, with most patients receiving 70 mg BID was performed. In healthy subjects, single doses of dasatinib did not affect the QTc. In 467 patients enrolled in the Phase 2 studies, repeated baseline and on-treatment ECGs were obtained. The QT interval was corrected for heart rate by Fridericia's method (QTcF). The mean changes in QTcF interval with chronic administration of dasatinib were 3 to 6 milliseconds (msec) and the upper 95% confidence interval for the mean changes in QTcF was < 8 msec. Three (0.7%) patients experienced a QTcF > 500 msec and 3% of the patients had a QTcF increase from baseline > 60 msec. No events of torsade de pointes were reported, and treatment with dasatinib was not associated with any clinically-meaningful changes in the electrocardiographic heart rate, PR interval, or QRS interval.

## 8.3 Other Non-hematologic Laboratory Abnormalities

In general, there were few clinically meaningful nonhematologic changes in laboratory parameters reported with dasatinib treatment across all phases of CML and Ph+ ALL. The most common electrolyte abnormality was hypocalcemia; approximately half of the patients with normal (Grade 0) liver function tests (ie, alanine aminotransferase [ALT], aspartate aminotransferase [AST], or total bilirubin) at baseline had some changes during the course of treatment, although they were mostly Grade 1 or 2.

**Liver Function Tests**: Across all studies, most elevations in liver function test values were mild to moderate and few patients (0 to 13%) had Grade 3 to 4 elevations in either ALT, AST, or bilirubin (Table 27). In general, patients experienced their first abnormality within the first month of treatment; these abnormalities usually peaked quickly (≤ 2 weeks) and resolved within the next 2 to 3 weeks. The majority of abnormalities related to hepatic dysfunction were managed with dose modifications as per protocol.

**Table 27: Number of Patients with Grade 3 to 4 Abnormalities Who Had Normal Liver Function Test Values at Baseline**

| | Chronic N = 206 | Accelerated N = 117 | Myeloid Blast N = 95 | Lymphoid Blast/Ph+ ALL N = 88 |
|---|---|---|---|---|
| **ALT** | | | | |
| Grade 3-4, N (%) | 4 (2) | 4 (3) | 7 (7) | 11 (13) |
| **AST** | | | | |
| Grade 3-4, N (%) | 5 (2) | 1 (1) | 3 (3) | 8 (9) |
| **Total bilirubin** | | | | |
| Grade 3-4, N (%) | 0 | 2 (2) | 6 (6) | 8[a] (9) |

[a] N = 86

**Hypocalcemia:** Approximately half to two-thirds of the dasatinib-treated patients who had normal (Grade 0) baseline levels experienced transient hypocalcemia at some time during the course of treatment. The incidence of hypocalcemia generally increased with more advanced disease. Grade 3 to 4 hypocalcemia was reported in 3% to 20% of patients in the various studies (Table 28). However, none of these patients experienced associated clinical symptoms and intervention was not required. The majority of these events were transient and subsided spontaneously during treatment.

**Table 28: Number of Patients with Grade 3 to 4 Abnormalities Who Had Normal Calcium Values at Baseline**

| | Chronic N = 206 | Accelerated N = 118 | Myeloid Blast N = 94 | Lymphoid Blast/Ph+ ALL N = 86 |
|---|---|---|---|---|
| Grade 3-4, N (%) | 6 (3) | 12 (10) | 19 (20) | 13 (15) |

## 8.4 Cross-intolerance with Imatinib

Although imatinib is generally tolerable, 4% of chronic phase CML patients treated with imatinib experience drug-related AEs leading to discontinuation.[14] In CA180013, 59 treated patients were intolerant of previous imatinib. The reasons for imatinib intolerance included: non-hematologic toxicity (Table 29) and severe myelosuppression.

Almost all imatinib-intolerant patients were able to tolerate treatment with dasatinib with only 3 (5%) patients discontinuing therapy. In these 3 cases, the AEs leading to discontinuation were different from the reasons for prior imatinib intolerance.

**Table 29: Grade 3 to 4 Dasatinib Toxicity in Patients with Non-hematologic Intolerance to Imatinib (CA180013)**

| Reason for imatinib intolerance | N of Patients [a] | Grade 3 or 4 on Dasatinib |
|---|---|---|
| Rash/Skin toxicity | 22 | 0 |
| Liver toxicity | 17 | 0 |
| Myalgias/Arthralgias | 13 | 0 |
| Gastrointestinal intolerance | 6 | 2 (nausea, diarrhea) |
| Edema | 5 | 0 |
| Pulmonary toxicity | 3 | 0 |
| Fatigue | 2 | 1 |
| Weight gain | 2 | 0 |
| Renal failure | 1 | 0 |
| Anaphylaxis | 1 | 0 |

[a] Multiple reasons for imatinib intolerance occurred in individual patients

In the advanced phase studies, a total of 27 patients were enrolled who were classified as imatinib-intolerant. Of these, only 1 patient demonstrated the same intolerant non-hematologic toxicity to dasatinib, which led to drug discontinuation. This patient who was intolerant to imatinib due to gastrointestinal symptoms discontinued for multiple reasons (abdominal pain, herpes simplex, herpes zoster, pulmonary hemorrhage, and face swelling).

The overall experience in the imatinib-intolerant patients across all studies implies a lack of cross-intolerance to dasatinib and suggests that the vast majority of these patients can tolerate treatment with dasatinib.

## 8.5 Serious Adverse Events

Drug-related serious adverse events (SAEs) occurring up to 30 days after the last dose of dasatinib were reported in 25% to 43% of patients across all phases of CML and Ph+ ALL. Notable drug-related SAEs (any grade) specific to each disease phase are

displayed (Table 30). Fluid retention, including selected cardiac and pulmonary events, and hemorrhage, were further addressed in Section 8.2.

**Table 30: Selected Drug-related SAEs (Any Grade)**

| Preferred Term | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| | **Chronic Phase N = 208** | **Accelerated Phase N = 118** | **Myeloid Blast Phase N = 97** | **Lymphoid Blast Phase/ Ph+ ALL N = 88** | **Total N = 511** |
| Patients with drug-related SAEs | 51 (25) | 51 (43) | 41 (42) | 34 (39) | **177 (35)** |
| Pleural effusion | 16 (8) | 14 (12) | 9 (9) | 3 (3) | **42 (8)** |
| Pyrexia | 5 (2) | 4 (3) | 4 (4) | 3 (3) | **16 (3)** |
| Gastrointestinal hemorrhage | - | 6 (5) | 6 (6) | 2 (2) | **14 (3)** |
| Pneumonia | 4 (2) | 4 (3) | - | 4 (5) | **12 (2)** |
| Febrile neutropenia | - | - | 5 (5) | 6 (7) | **11 (2)** |
| Congestive heart failure | 5 (2) | - | - | - | **5 (1)** |
| Diarrhea | 1 (<1) | 4 (3) | - | - | **5 (1)** |
| Rash | - | 1 (1) | - | 2 (2) | **3 (<1)** |
| Skin and subcutaneous disorders | 2 (1) | - | - | - | **2 (<1)** |
| Cerebral hemorrhage | - | - | - | 1 (1) | **1 (<1)** |
| Intracranial hemorrhage | 1 (<1) | - | - | - | **1 (<1)** |
| Pericardial effusion | - | - | 1 (1) | - | **1 (<1)** |
| Sepsis | - | - | 1 (1) | - | **1 (<1)** |
| Syncope | - | 1 (1) | - | - | **1 (<1)** |
| Ventricular dysfunction | - | 1 (1) | - | - | **1 (<1)** |
| Urticaria vesiculosa | - | - | 1 (1) | - | **1 (<1)** |
| Dizziness | 1 (<1) | - | - | - | **1 (<1)** |
| Atrial fibrillation | - | - | - | 1 (1) | **1 (<1)** |

## 8.6 Deaths

A total of 109 deaths (21% of 511 patients) were reported across all phases of CML and Ph+ ALL. The primary reason for death was disease progression in 53% of deaths. In

addition, 18% of patients died due to infection, 16% died due to "other" causes, 7% died due to fatal bleeding, 2% died due to cardiovascular disease, 2% died due to study drug toxicity, and 2% died due to "unknown" causes. Deaths occurred more frequently in patients with advanced phases of disease (ie, myeloid and lymphoid blast phases of CML or Ph+ ALL) (Table 31).

**Table 31: Deaths**

| | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| | **Chronic Phase N = 208** | **Accelerated Phase N = 118** | **Myeloid Blast Phase N = 97** | **Lymphoid Blast Phase/Ph+ ALL N = 88** | **Total N = 511** |
| Patients who died | 5 (2) | 15 (13) | 45 (46) | 44 (50) | **109 (21)** |
| Cause of death | | | | | **N = 109** |
| disease progression | 3 (1) | 6 (5) | 29 (30) | 20 (23) | **58 (53)** |
| infection | 0 | 3 (3) | 5 (5) | 12 (14) | **20 (18)** |
| other | 0 | 2 (2) | 6 (6) | 9 (10) | **17 (16)** |
| fatal bleeding | 1 (<1) | 1 (1) | 3 (3) | 3 (3) | **8 (7)** |
| cardiovascular disease | 1 (<1) | 0 | 1 (1) | 0 | **2 (2)** |
| study drug toxicity | 0 | 1 (1) | 1 (1) | 0 | **2 (2)** |
| unknown | 0 | 2 (2) | 0 | 0 | **2 (2)** |

In addition to 2 deaths related to study drug toxicity, 4 Grade 5 AEs and 1 "other" death (fatal bleeding, CNS bleeding) were deemed by the investigator as related to study drug across all studies (Table 32).

**Table 32: Drug-related Deaths**

| Study | Disease Status | Cause of Death |
|---|---|---|
| CA180005 | accelerated phase | pancytopenia |
| CA180005 | accelerated phase | fatal bleeding, CNS bleeding |
| CA180006 | myeloid phase | global cardiac insufficiency |
| CA180006 | myeloid phase | acute respiratory distress syndrome caused by tumor lysis syndrome |
| CA180006 | myeloid phase | sepsis |
| CA180013 | chronic phase | CNS bleeding |
| CA180015 | lymphoid phase | CNS bleeding |

## 8.7 Dose Modifications and Adverse Events Leading to Discontinuation

**Dose Modifications:** Overall, 52% of dasatinib-treated patients had dose reductions and 70% had dose interruptions. Dose reductions were more common in chronic and accelerated phase CML than in blast phase CML or Ph+ ALL. Among chronic phase CML patients, drug interruptions were largely due to hematologic toxicities and were required for both Grade 3 neutropenia and Grade 3 thrombocytopenia. In accelerated and advanced phase CML or Ph+ ALL, the interruptions were the result of both hematologic and nonhematologic toxicities (Table 33).

**Table 33: Dose Modifications**

| | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| | **Chronic Phase N = 208** | **Accelerated Phase N = 118** | **Myeloid Blast Phase N = 97** | **Lymphoid Blast Phase/Ph+ ALL N = 88** | **Total N = 511** |
| **Dose reductions**[a] | 139 (67) | 70 (59) | 37 (38) | 19 (22) | **265 (52)** |
| hematologic toxicity | 84 (40) | 36 (31) | 14 (14) | 5 (6) | **139 (27)** |
| non-hematologic toxicity | 45 (22) | 24 (20) | 13 (13) | 10 (11) | **92 (18)** |
| **Dose interruptions**[a] | 170 (82) | 95 (81) | 60 (62) | 33 (38) | **358 (70)** |
| hematologic toxicity | 89 (43) | 41 (35) | 23 (24) | 10 (11) | **163 (32)** |
| non-hematologic toxicity | 71 (34) | 47 (40) | 33 (34) | 20 (23) | **171 (33)** |

[a] Also including dosing error, rising % of blast, not reported, or other

**Adverse Events Leading to Discontinuation:** Drug-related AEs led to discontinuation in 6% of patients across all phases of CML and Ph+ ALL (Table 34). Most events occurred in 2 or less patients in any category (< 1%). Most AEs leading to discontinuation were Grade 3 or greater.

**Table 34: Drug-related Adverse Events Leading to Discontinuation**

| | N (%) of Patients | | | | |
|---|---|---|---|---|---|
| | **Chronic Phase N = 208** | **Accelerated Phase N = 118** | **Myeloid Blast Phase N = 97** | **Lymphoid Blast Phase/Ph+ ALL N = 88** | **Total N = 511** |
| Drug-related AE leading to discontinuation | 14 (7) | 5 (4) | 5 (5) | 5 (6) | **29 (6)** |

## 8.8 Dasatinib and Imatinib Safety Results (CA180017)

CA180017 is a randomized, non-comparative Phase 2 study of dasatinib and high-dose (800 mg/day) imatinib in patients with chronic phase CML who were resistant to imatinib 400 to 600 mg/day. Since 14 patients treated with imatinib were not included in the pooled safety analysis, safety results from imatinib-treated patients (followed for a minimum of 3 months), as well as those from dasatinib-treated patients in the same treatment period are presented.

No deaths were reported within 30 days of the last dose in both groups. Infrequent incidences of drug-related SAEs were reported, 2 in the dasatinib treatment group and 1 in the imatinib treatment group. Myelosuppression was common in both treatment groups, with higher frequencies of Grade 3 to 4 thrombocytopenia in the dasatinib group and higher incidences of Grade 3 to 4 neutropenia or thrombocytopenia in the imatinib group. Overall, although some degree of cross intolerance was documented, the safety profiles of both drugs appeared to be different, with a higher incidence of nausea, neutropenia, and fluid retention in the imatinib group and of diarrhea, headache, and severe thrombocytopenia in the dasatinib group. There was no evidence of pleural effusion in either group (Table 35).

**Table 35: Dasatinib and Imatinib Safety Results at 12 Weeks (CA180017)**

| | Number of Subjects (%) | |
|---|---|---|
| | **Dasatinib N = 22** | **Imatinib N = 14** |
| **Death within 30 days of the last dose** | 0 | 0 |
| **Drug-related SAEs** | 2 (9) | 1 (7) |
| **Grade 3 to 4 hematologic toxicity** | | |
| Thrombocytopenia | 9 (41) | 2 (14) |
| Neutropenia | 8 (36) | 8 (57) |
| Leukopenia | 3 (14) | 4 (29) |
| **Relevant drug-related non-hematologic AEs** | | |
| Diarrhea | 7 (32) | 1 (7) |
| Nausea | 7 (32) | 7 (50) |
| Headache | 6 (27) | 1 (7) |
| Peripheral edema | 2 (9) | 3 (21) |
| Face or eyelid edema | 2 (9) | 3 (21) |
| Pleural effusion | 0 | 0 |
| Increased weight | 2 (9) | 4 (29) |

# 9 CONCLUSIONS

With the introduction of imatinib, major advances in the treatment of CML were achieved. However, clinical resistance to imatinib has emerged, particularly in the advanced stages of disease. It is estimated that at 4 years of follow-up on imatinib, 16% of chronic phase patients, up to 75% of accelerated phase patients, and 95% of blast phase patients will develop resistance to imatinib and have limited therapeutic options. For chronic phase patients, the potential for resistance is increased to 26% if patients have previously failed interferon as well. Given the degree of imatinib resistance, no accepted standard of treatment, and limited options available for these patients (ie, increasing imatinib dose, interferon, or chemotherapy), CML and Ph+ ALL disease management is an area of unmet medical need.

Dasatinib provided clinical benefit as demonstrated by efficacy in all phases of CML, in Ph+ ALL, and in all subpopulations, including patients who were imatinib-intolerant, imatinib-resistant, previously treated with interferon or other chemotherapeutic agents, and previous stem cell transplant recipients. In addition to being effective on known imatinib-resistant mutations, dasatinib was active in patients who had obtained little or no clinical benefit from imatinib. Patients who could not tolerate imatinib and who had limited therapeutic options also benefited from dasatinib as shown by the fact that none of the imatinib-intolerant patients with chronic phase CML (CA180013) had progressed after 6 months of follow-up.

In CML, MCyR is associated with a survival benefit. In chronic phase CML, patients treated with dasatinib achieved MCyR, with minimal toxicity. In CA180013, the MCyR rate of 73% in the imatinib-intolerant patients is favorable when compared historically with the MCyR rate of 60% achieved with imatinib in a similar population of patients who had failed prior interferon.[15] With nearly 1.5 years of follow-up in CA180002, the median duration of MCyR has not been reached, which supports the durability of the response with dasatinib in chronic phase CML.

In accelerated phase disease, most patients resistant or intolerant to imatinib would have a short period prior to progressing to blast phase disease, yet many (59%) achieved a MaHR on dasatinib, and the median PFS has yet to be reached. Most importantly, in blast phase disease, where the median survival historically is 3 to 6 months, a third of patients achieved a MaHR. None of the patients with myeloid phase disease who achieved a MaHR had progressed, with a maximum response duration of 7.8 months. Of clinical importance, 9 (8%) patients with blast phase disease (CA180006 and CA180015) sufficiently improved to receive a stem cell transplant.

In addition to its efficacy across all phases of CML, dasatinib demonstrated clinical benefit in Ph+ ALL as well. Currently, for this rare disease, there are few therapeutic options, most of which require hospitalization and are quite toxic. Stem cell transplant is often the best option, but is not offered to all patients due to their age, comorbidities, or advanced disease. The ability to stabilize patients for a stem cell transplant is one of the most beneficial responses reported in this population. In a heavily pretreated population with prior chemotherapy, stem cell transplants, and imatinib treatment, patients achieved a higher rate of MCyR after treatment with dasatinib than was achieved on prior therapy with imatinib. In addition, 2 (6%) patients sufficiently improved to be eligible to receive

a stem cell transplant after receiving dasatinib. In those who achieved a MaHR, 12 (80%) had not progressed.

The safety profile of dasatinib is acceptable. Adverse events are frequent, but most are mild to moderate and can be managed with either dose reduction or dose interruption and supportive care. It is difficult to conclude whether all myelosuppressive toxicity is attributable to dasatinib or is also impacted by the underlying leukemia. The baseline disease and hematologic compromise may have a greater contribution in advanced disease. In addition, the greater potency of dasatinib may contribute to more myelosuppression than that reported for imatinib due to the rapid clearance of BCR-ABL expressing hematopoietic cells. Based on the risk profile, careful monitoring for myelosuppression is warranted when administering dasatinib.

Fluid retention is a well-documented AE associated with the use of imatinib and is attributed to the inhibition of platelet-derived growth factor receptors, which regulates interstitial fluid pressure.[16,17,18] Dasatinib-related AEs of fluid retention (ie, edema and pleural effusion) were common. Most events were Grade 1 or 2 and occurred in the first few weeks to 2 months of treatment. These events infrequently led to dose interruptions, and the majority of pleural effusion cases were managed with diuretics. Only 4 patients discontinued treatment as a result of a dasatinib-related pleural effusion.

In summary, dasatinib represents an important therapeutic advance for patients with CML and Ph+ ALL. Based on cytogenetic responses achieved in these studies, it is reasonable to expect that treatment with dasatinib will result in a survival benefit in patients with CML or Ph+ ALL.

# 10 LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| AE | adverse event |
| ALL | acute lymphoblastic leukemia |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC(TAU) | area under the concentration-time curve in 1 dosing interval |
| BCR-ABL | a protein tyrosine kinase |
| BID | twice a day |
| BM | bone marrow |
| BMS | Bristol-Myers Squibb |
| CCyR | complete cytogenetic response |
| CHF | congestive heart failure |
| CHR | complete hematologic response |
| CML | chronic myelogenous leukemia |
| Cmax | maximum concentration |
| CNS | central nervous system |
| CV% | coefficient of variability |
| CYP | cytochrome P450 enzymes |
| CyR | cytogenetic response |
| ECG | electrocardiogram |
| MaHR | major hematologic response |
| MCyR | major cytogenetic response |
| MTD | maximum tolerated dose |
| NEL | no evidence of leukemia |
| OHR | overall hematologic response rate |
| PB | peripheral blood |
| PCyR | partial cytogenetic response |
| Ph+ | Philadelphia chromosome positive |
| PK | pharmacokinetics |
| PR interval | the time in seconds from the beginning of the P wave to the beginning of the QRS complex |

| Term | Definition |
|---|---|
| PFS | progression-free survival |
| QD | once a day |
| QRS | the time it takes for ventricular depolarization to occur |
| QT | the interval between the beginning of the Q-wave and the end of the T-wave on an electrocardiogram |
| $QT_cF$ | QT interval corrected by Fridericia's method |
| SAE | serious adverse event |
| SRC | a protein tyrosine kinase |
| T-HALF | terminal elimination half-life |
| Tmax | time to reach Cmax |

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