Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib

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ABSTRACT

Background
Dasatinib 100 mg once daily achieves intermittent BCR-ABL kinase inhibition and is approved for chronic-phase chronic myeloid leukemia patients resistant or intolerant to imatinib. To better assess durability of response to and tolerability of dasatinib, data from a 2-year minimum follow-up for a dose-optimization study in chronic-phase chronic myeloid leukemia are reported here.

Design and Methods
In a phase 3 study, 670 chronic-phase chronic myeloid leukemia patients with resistance, intolerance, or suboptimal response to imatinib were randomized to dasatinib 100 mg once-daily, 50 mg twice-daily, 140 mg once-daily, or 70 mg twice-daily.

Results
Data from a 2-year minimum follow-up demonstrate that dasatinib 100 mg once daily achieves major cytogenetic response and complete cytogenetic response rates comparable to those in the other treatment arms, and reduces the frequency of key side effects. Comparable 2-year progression-free survival and overall survival rates were observed (80% and 91%, respectively, for 100 mg once daily, and 75%-76% and 88%-94%, respectively, in other arms). Complete cytogenetic responses were achieved rapidly, typically by 6 months. In patients treated with dasatinib 100 mg once daily for 6 months without complete cytogenetic response, the likelihood of achieving such a response by 2 years was 50% for patients who had achieved a partial cytogenetic response, and only 8% or less for patients with minor, minimal, or no cytogenetic response. Less than 3% of patients suffered disease transformation to accelerated or blast phase.

Conclusions
Intermittent kinase inhibition can achieve rapid and durable responses, indistinguishable from those achieved with more continuous inhibition.
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Key words: chronic myeloid leukemia, chronic phase, dasatinib, cytogenetic response, inhibition.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the presence of the BCR-ABL tyrosine kinase,[1] and the first disease to be successfully treated by a small molecule tyrosine kinase inhibitor, imatinib mesylate (Gleevec/Glivec ®, Novartis, Basel, Switzerland).[2] Imatinib and its active metabolite, the N-desmethyl derivative,[3] have prolonged half-lives that provide clinically continuous BCR-ABL kinase inhibition.[2,4,5] Since the approval of imatinib, several tyrosine kinase inhibitors with long half-lives have also become available for other malignancies.[6-9]

Dasatinib (Sprycel ®; Bristol-Myers Squibb, New York, NY, USA) is approved for the treatment of imatinib-resistant and -intolerant CML and Philadelphia chromosome positive (Ph^+) acute lymphoblastic leukemia,[10] and is unique amongst approved tyrosine kinase inhibitors in that its half-life is 3-5 hours.[10] Surprisingly, short-term exposure of CML cell lines to clinically-achieved concentrations of dasatinib triggers an irreversible commitment of cells to apoptosis.[11] Additionally, despite achieving only transient inhibition of BCR-ABL when administered once daily in CML patients, dasatinib has substantial clinical activity.[11,12] Although the original dasatinib dosing regimen investigated in phase 2 studies and subsequently approved was 70 mg twice daily,[13-16] a randomized phase 3 dose-optimization study[12] led to the revision of the recommended dose to 100 mg once daily in chronic-phase CML (CP-CML) patients, based upon non-inferior cytogenetic response rates and improved tolerability. However, because the 100 mg once-daily treatment regimen employs a lower total daily dasatinib dose, and because treatment exposure is predicted to be less than that with 70 mg twice daily, an important unresolved issue concerns the potential for compromise of response duration and progression-free survival with the 100 mg once-daily regimen.

A primary goal in the management of CP-CML is to maintain patients in hematologic remission and prevent progression to blast transformation. However, it has become evident that patients who achieve a complete cytogenetic response (CCyR) on imatinib have improved outcomes.[17] Studies of outcomes on a large cohort of patients treated with imatinib have led to new definitions of imatinib treatment failure, which now notably include failure to achieve CCyR by 18 months after initiation of therapy.[17,18] Significantly, CCyR has also been shown to be an effective surrogate marker for survival in CML patients treated with interferon-α,[19-21] and is likely to represent an equally important therapeutic milestone in patients treated with second-line tyrosine kinase inhibitors.

Currently, some patients with imatinib resistance or intolerance may have, in addition to second-line tyrosine kinase inhibitors,[10,22] the option of allogeneic stem cell transplantation. However, due to the toxicity associated with transplantation, it is generally believed that an initial trial of second-line tyrosine kinase inhibitors is reasonable in nearly all patients in whom imatinib treatment fails before proceeding to transplantation. An important unresolved issue regarding the second-line tyrosine kinase inhibitors is how long one should wait for achievement of a CCyR before exploring other therapeutic options. Recently, data from a single institution experience with second-line tyrosine kinase inhibitors in 113 patients were presented.[23] In this analysis, patients who did not have a major cytogenetic response (MCyR) after 1 year of therapy had inferior survival, and the authors, therefore, concluded that MCyR by 12 months was an acceptable therapeutic milestone with these agents. Although informative, this analysis was limited due to the relatively small number of patients analyzed and the heterogeneity of drugs and dosing regimens studied, which in the case of dasatinib largely included patients treated with 70 mg twice daily. Here we present a minimum of 2 years of follow-up of the study (CA180034) which includes the largest cohort (n = 167) of CP-CML patients to date treated with the currently recommended dasatinib regimen (100 mg once daily). Additionally, we determined the likelihood of achieving CCyR, and of the patients' disease transforming to accelerated or blast phase, based upon cytogenetic response at 6 and 12 months, information which should be of particular use to clinicians using dasatinib to manage imatinib-resistant or -intolerant patients who are candidates for allogeneic stem cell transplantation.

Design and Methods

The study design has been previously published,[12] and is also described briefly in the *Online Supplementary Material*.

Statistical analyses

As intent-to-treat analyses, the efficacy results included all randomized patients. Mutation and molecular analyses included patients for whom mutation data were available. Safety analyses included treated patients.

Non-inferiority of the primary endpoint was determined based on whether the lower bound of the 95% confidence interval (CI) for the difference in MCyR rates between the regimens was -15% or greater. A minimum of either 174 imatinib-resistant patients on a twice daily and once daily schedule, or 87 imatinib-resistant patients per treatment group, was required to provide at least 80% power. As the primary endpoint of non-inferiority of MCyR for once daily versus twice daily regimens after a minimum of 6 months follow-up was met and previously published,[12] this report focuses on results after a minimum of 2 years of follow-up.

Two-sided 95% CI were calculated for best responses of a MCyR (CCyR and/or partial cytogenetic response [PCyR]) or confirmed complete hematologic response, and estimated by treatment arm, total daily dose, and dosing schedule. The Kaplan-Meier product-limit method was used to estimate time to and duration of response, progression-free survival, and overall survival. The CCyR analysis and rates at 2 years (with 95% CI) were specified subsequently as post-hoc analyses. In the time to CCyR analysis, non-responders were censored at the maximum time between the maximum time to CCyR among responders and maximum time to last cytogenetic assessment for non-responders. The resulting curve reaches a maximal value corresponding to the overall observed CCyR rate.

An additional analysis on the probability of CCyR by 2 years

by cytogenetic response at 6 or 12 months was defined as the proportion of patients who achieved a CCyR within 2 years among patients with a cytogenetic assessment available at 6 or 12 months. Similarly, the probability of progression due to transformation to accelerated/blast phase by 2 years by cytogenetic response at 6 or 12 months was defined as the proportion of patients who progressed due to development of accelerated/blast phase before 2 years among patients with a cytogenetic assessment available at 6 or 12 months.

Progression-free survival was defined as the time from randomization until progression or death. Duration of response (MCyR or CCyR) was the time from the date of response until progression or death. For analyses of duration of response and progression-free survival, patients who had not died or progressed were censored on the last assessment date. Patients were not followed for progression-free survival or duration of response after they had discontinued dasatinib. Overall survival was defined as the time from randomization until death and patients who had not died or were lost to follow-up were censored on the last date they were known to be alive. After discontinuation of dasatinib, patients continued to be followed for overall survival.

Incidences of selected adverse events were compared between the four arms using Fisher's exact test. On-study adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Results

There were 724 patients enrolled from 139 centers between July 2005 and March 2006, of whom 670 were randomized and 662 treated (Figure 1). Fourteen eligible Ph-negative, BCR-ABL-positive patients were randomized but retrospectively excluded from the MCyR and CCyR analysis. The current results are based on analyses of data from 2 years of study follow-up from the last patient's initial visit. Baseline demographics and disease characteristics were well balanced.[12] Key baseline characteristics and reasons for primary imatinib resistance/suboptimal response and acquired imatinib resistance are presented (*Online Supplementary Table S1*).

Hematologic, cytogenetic, and molecular responses

Hematologic, cytogenetic, and molecular response, all patients

Dasatinib provided similar complete hematologic response (87% to 92%), MCyR (61% to 63%), and CCyR (50% to 54%) rates across the four treatment arms (Table 1). These MCyR and CCyR rates were similar to the response rates reported when the 14 patients with Ph-negative BCR-ABL-positive disease were excluded (Table 1). Among patients with a MCyR on dasatinib, the MCyR was maintained at 2 years in 87% on 100 mg once daily, 88% on 70 mg twice daily, 68% on 140 mg once daily, and 88% on 50 mg twice daily. The MCyR rates were also comparable regardless of a once daily or twice daily regimen (63% and 61%), or a total daily dose of 100 mg or 140 mg (62% and 62%).

The CCyR rates were also similar across treatment groups (Table 1). Among patients who experienced a CCyR during treatment, 89% on 100 mg once daily, 85% on 70 mg twice daily, 78% on 140 mg once daily, and 93% of patients on 50 mg twice daily had not lost the CCyR at 2 years (Figure 2A). Only 83 of 341 patients lost a CCyR (18 in the 100 mg once daily, 22 in the 140 mg once daily, 20 in the 50 mg twice daily and 23 in the 70 mg twice daily groups). Among these 83 patients, 31 lost a MCyR, but 36 subsequently regained their CCyR. Only 2 of the 83 patients progressed to accelerated or blast phase. In patients treated with dasatinib 100 mg once daily, CCyR was achieved within 3, 6, 9, and 12 months of treatment in 25%, 40%, 41%, and 45%, respectively. A similar proportion of patients achieved CCyR within these time points in the other three arms (Figure 2B). CCyR tended to occur rapidly, typically within 6 months of dasatinib initiation, although a small proportion of patients achieved CCyR at later time points.

The likelihood of achieving a response to dasatinib appeared to be greater for imatinib-intolerant patients than for patients with resistance or suboptimal response to imatinib (Table 1). Median times to MCyR (2.8 to 2.9 months) and complete hematologic response (0.5 to 0.7 months) were similar between the treatment groups among imatinib-resistant/suboptimal response patients. In imatinib-intolerant patients the median times to MCyR and CHR were 2.8 months and 0.5 months, respectively, across treatment arms. In the imatinib-resistant/suboptimal response population, the once daily regimen yielded a MCyR rate that was non-inferior to the twice daily regimen (1.9% treatment difference; 95% CI, -6.8 to 10.6) and the 100 mg total daily dose MCyR rate was also non-inferior to the MCyR rate in response to a 140 mg total daily dose (-0.2% treatment difference; 95% CI, -8.9 to 8.5). In the imatinib-intolerant population, the MCyR rate was also non-inferior between patients treated with once daily (n = 87) and twice daily regimens (n = 86; 1.4% difference, 95% CI, -11.2 to 14.2) and between those receiving total daily doses of 100 mg (n = 87) and 140 mg (n = 86) (1.4% difference; 95% CI, -11.2 to 14.1).

Forty-four percent of patients (125 of 283) with primary imatinib resistance/suboptimal response and 53% (82 of 155) of patients with acquired imatinib resistance had baseline mutations. Overall, 42 different baseline mutations were identified among 212 patients with mutations across all four treatment arms (Table 1). The 2-year MCyR and CCyR rates for patients on the 100 mg once daily were 55% and 41%, respectively, for those with any mutation; 75% and 50%, respectively, for those with a P-loop mutation; and 66% and 54%, respectively, for those with no mutation. Of 15 patients with the BCR-ABL/T315I mutation, none achieved a CCyR. One of six patients with the F317L mutation, which has a relatively high *in vitro* IC_{50} to dasatinib,[26] achieved a CCyR; this patient had 5/30 Ph^+ metaphases prior to treatment with dasatinib (*data not shown*). Response rates among patients with any or no mutations were comparable across all four treatment arms (Table 1).

There were 600 patients assessed for molecular response with at least one quantitative polymerase chain reaction (PCR) assessment during treatment. The major molecular response rates among assessed patients were 37% to 38% across treatment arms. Among assessed patients with a CCyR, the major molecular response rate

was 69% with 100 mg once daily, 66% with 70 mg twice daily, 72% with 140 mg once daily, and 70% with 50 mg twice daily (Table 1).

Cytogenetic response excluding Philadelphia chromosome-negative, BCR-ABL-positive patients

Fourteen patients who were Ph-negative and BCR-ABL-positive were enrolled in the study and, by definition, these patients were not evaluable for cytogenetic response as assessed by the study protocol. When these 14 patients were excluded from the analysis, MCyR and CCyR rates were comparable across all four dasatinib regimens. The MCyR rates were 63% for dasatinib 100 mg once daily, 61% for 70 mg twice daily, 63% for 140 mg once daily, and 61% for 50 mg twice daily (Table 1). For dasatinib 100 mg once daily, the CCyR rate was 49%, and for the other three treatment arms the CCyR rate was 53% for dasatinib 70 mg twice daily and 50% for

Table 1. Molecular response and best hematologic and cytogenetic responses.

	Dasatinib							
	100 mg QD (n=167)		70 mg BID (n=168)		140 mg QD (n=167)		50 mg BID (n=168)	
	n/N*	%	n/N*	%	n/N*	%	n/N*	%
Complete hematologic response (95% CI)	153/167	92 (86.3-95.3)	148/168	88 (82.2-92.6)	145/167	87 (80.7-91.6)	155/168	92 (87.1-95.8)
Without CHR at baseline	67/81	83	87/102	85	77/98	79	86/97	89
By Status								
Imatinib resistant/suboptimal response	110/124	89	112/126	89	106/123	86	114/124	92
Imatinib intolerant	43/43	100	36/42	86	39/44	89	41/44	93
Major cytogenetic response (95% CI)	106/167	63 (55.7-70.8)	103/168	61 (53.5-68.7)	105/167	63 (55.1-70.2)	103/168	61 (53.5-68.7)
Without MCyR at baseline	76/133	57	77/137	56	80/139	58	83/145	57
Excludes Ph-negative patients†	104/164	63	100/163	61	103/163	63	102/166	61
By Status								
Imatinib resistant/suboptimal response	73/124	59	72/126	57	71/123	58	69/124	56
Imatinib intolerant	33/43	77	31/42	74	34/44	77	34/44	77
Complete cytogenetic response	83/167	50	90/168	54	84/167	50	84/168	50
Without CCyR at baseline	76/158	48	82/157	52	72/153	47	78/161	48
Excludes Ph-negative patients†	81/164	49	87/163	53	82/163	50	83/166	50
By Status								
Imatinib resistant/suboptimal response	54/124	44	61/126	48	52/123	42	52/124	42
Imatinib intolerant	29/43	67	29/42	69	32/44	73	32/44	73
Major molecular response‡	57/154	37	56/146	38	55/144	38	59/156	38
With CCyR	54/78	69	52/79	66	54/75	72	56/80	70
By Status								
Imatinib resistant/suboptimal response	41/117	35	38/111	34	33/111	30	38/117	32
With CCyR	38/53	72	35/55	64	32/51	63	35/51	69
Imatinib intolerant	16/37	43	18/35	51	22/33	67	21/39	54
With CCyR	16/25	64	17/24	71	22/24	92	21/29	72
Baseline Mutations§								
MCyR								
Any mutation	27/49	55	27/50	54	28/50	56	30/63	48
No mutation	65/98	66	64/96	67	62/89	70	58/86	67
P-loop mutation‖	6/8	75	10/17	59	6/17	35	5/17	29
T315I	0/5	0	0/1	0	1/4¶	25	0/5	0
F317L	0/2	0	1/2#	50	0/1	0	0/1	0
CCyR								
Any mutation	20/49	41	23/50	46	17/50	34	23/63	37
No mutation	53/98	54	56/96	58	52/89	58	49/86	57
P-loop mutation‖	4/8	50	10/17	59	1/17	6	3/17	18

*QD: once daily; BID: indicates twice daily; Ph-negative: Philadelphia-chromosome negative. *Number of patients over total patients. †Excludes 14 Ph-negative, BCR-ABL-positive CP-CML patients. ‡Among patients who had at least one molecular assessment while on treatment. §581 patients who were randomized and treated had data available on baseline mutations. ‖P-loop: amino acids 248-256. ¶One patient had a partial cytogenetic response. #One patient had a complete cytogenetic response.*

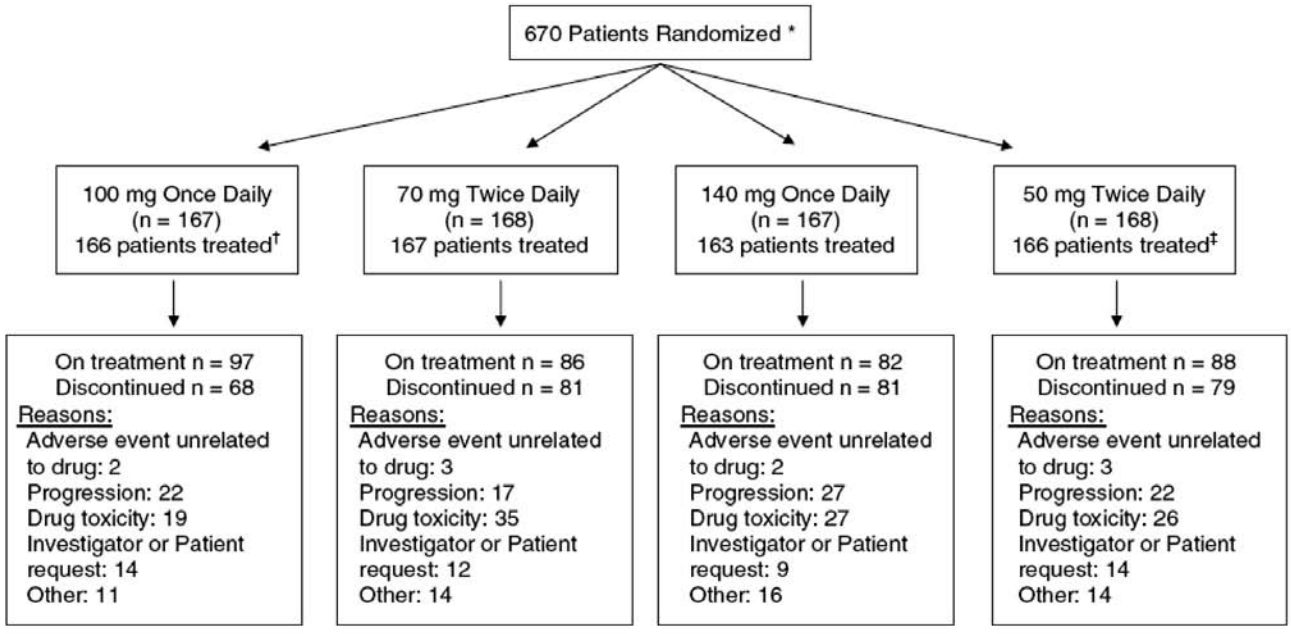

Figure 1. Study CONSORT diagram (adapted from Shah, *et al.*[12]). *The reasons 54 of 724 enrolled patients were not randomized or treated were previously reported.[12] †165 patients received 100 mg once daily and 1 received 50 mg twice daily. ‡166 patients were randomized to 50 mg twice daily and 1 was randomized to 100 mg once daily.

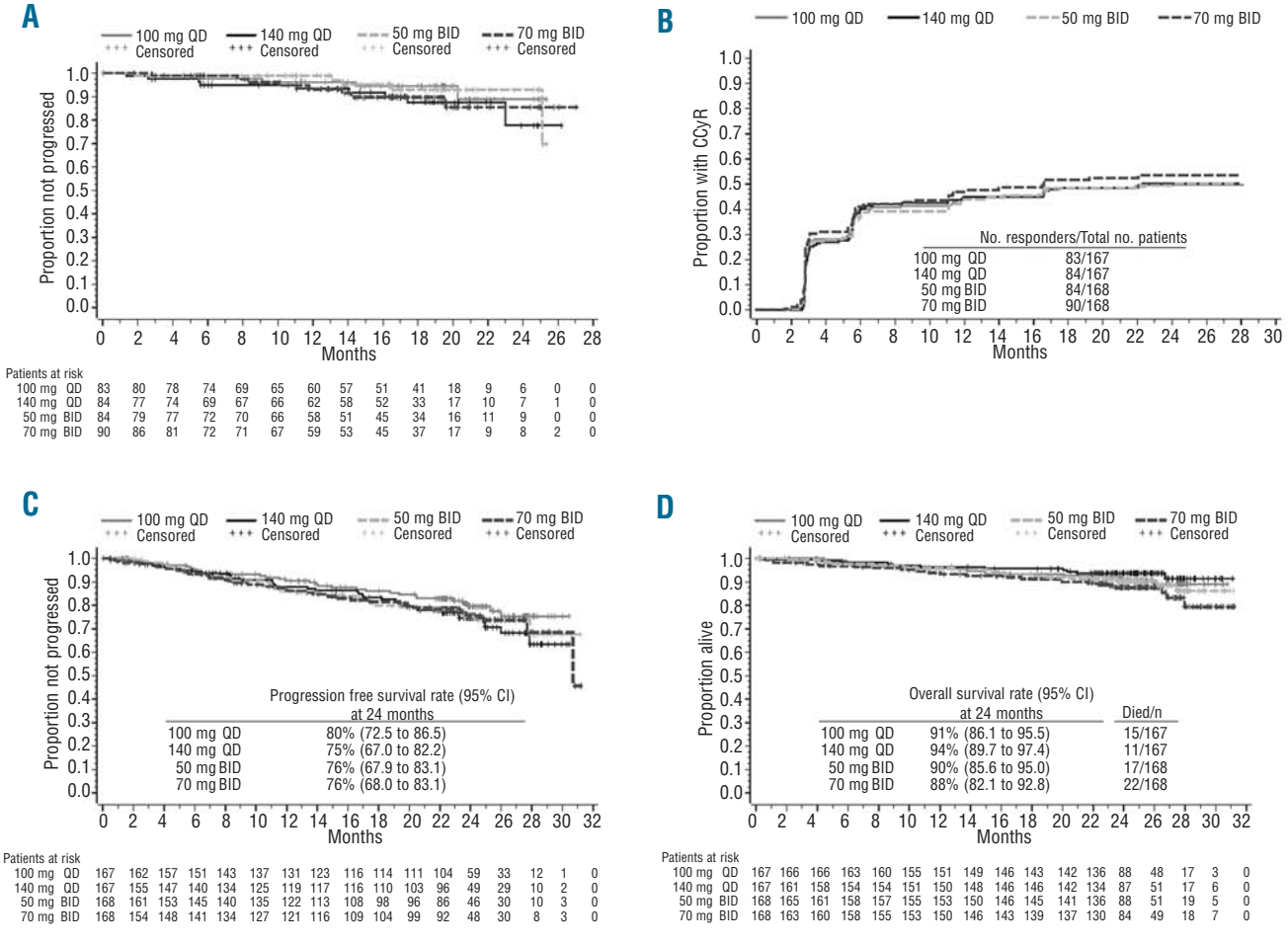

Figure 2. Kaplan-Meier analyses. (A) Duration of complete cytogenetic response. (B) Time to complete cytogenetic response. QD, once daily; BID, twice daily. (C) Progression-free survival (patients who had not died or progressed were censored on the last assessment date). (D) Overall survival (patients lost to follow-up or who had not died were censored on the last date they were known to be alive).

both the 140 mg once daily and 50 mg twice daily arms.

For patients treated with dasatinib 100 mg daily who had not achieved CCyR by 6 months, the probability of obtaining a CCyR by 2 years with dasatinib 100 mg once daily was 50% for patients who had achieved a PCyR at 6 months whereas the probability of developing accelerated/blast phase disease transformation by 2 years was 4%. In contrast, patients with a minor and minimal/no cytogenetic response at 6 months had a small probability of achieving CCyR by 24 months (8% and 5%, respectively). On the other hand, these patients had a relatively low likelihood of developing disease transformation by 24 months (Table 2). By 12 months, patients with a PCyR, minor, or minimal/no cytogenetic response while receiving dasatinib 100 mg once daily had a probability of achieving CCyR by 2 years of 35%, 20%, and 0%, respectively. None of these patients experienced disease transformation by 2 years. These results were comparable among the imatinib-resistant/suboptimal response and -intolerant patients (Table 2).

Overall and progression-free survival

The estimated progression-free survival rates at 24 months were 80% for 100 mg once daily, 76% for 70 mg twice daily, 75% for 140 mg once daily, and 76% for 50 mg twice daily (Figure 2C). The estimated overall survival rates were 91% for 100 mg once daily, 88% for 70 mg twice daily, 94% for 140 mg once daily, and 90% for 50 mg twice daily (Figure 2D). A total of 65 deaths (9.7%; 65 of 670 patients) were reported (Figure 2D). Of two deaths thought to be related to drug toxicity, one patient had pulmonary edema, congestive heart failure, neck pain, and pleural effusion while the other had necrosis of the colon.

Safety

Rates of cytopenias and treatment-related pleural effusions were lower among patients receiving 100 mg once daily relative to the patients in the other three treatment arms (*Online Supplementary Table S2*). The difference in the lower rate of treatment-related pleural effusions (any grade) for the 100 mg once daily regimen (14%) compared with the other three regimens (23-25%) was statistically significant (P=0.049). Grade 3/4 pleural effusions were reported in 2% of patients receiving 100 mg once daily and in 4% to 5% of patients on the other three treatment arms. For cytopenias the difference between the lower incidence on the 100 mg once daily arm and the other arms was also statistically significant for neutropenia (P=0.034), leukocytopenia (P=0.017), and grade 3/4 thrombocytopenia (P=0.003).

Treatment-related adverse events, of which patients could have had more than one, were less frequent in the 100 mg once daily arm, occurring in 85% of patients (141 of 165) relative to 93% (156 of 167) in the 70 mg twice daily arm, 94% (153 of 163) in the 140 mg once daily arm, and 92% (153 of 167) in the 50 mg twice daily arm. The most common (≥ 20% in at least one group) treatment-related non-hematologic adverse events that occurred across treatment groups were fluid retention, headache, diarrhea, nausea, fatigue, rash, and dyspnea (*Online Supplementary Table S2*).

The median duration of dasatinib treatment was 22 months (range, <1-31) with a median average daily dose of 99 mg/day (range, 10 -173). Among patients receiving 100 mg once daily, there were fewer dose reductions and interruptions, with a higher frequency of dose escalations (*Online Supplementary Table S3*). After 2 years of follow-up, there were fewer discontinuations on the 100

Table 2. Probability analyses for patients randomized to 100 mg once daily.*

	All patients n=164			Imatinib-resistant/suboptimal response patients n=123			Imatinib-intolerant patients n=41		
Cytogenetic response level	n (%)	Probability of CCyR by 2 years	Probability of progression due to tranformation to accelerated/blast phase† by 2 years	n (%)	Probability of CCyR by 2 years	Probability of progression due to tranformation to accelerated/blast phase† by 2 years	n (%)	Probability of CCyR by 2 years to	Probability of progression due to tranformation to accelerated/blast phase† by 2 years
6 months									
Complete	59 (36)	NA	0%	37 (30)	NA	0%	22 (54)	NA	0%
Partial	26 (16)	50%	4%	22 (18)	50%	5%	4 (10)	50%	0%
Minor	12 (7)	8%	8%	10 (8)	10%	0%	2 (5)	0%	50%
Minimal/none	41 (25)	5%	5%	33 (27)	3%	6%	8 (20)	13%	0%
Not assessed	26 (16)	NA	NA	21 (17)	NA	NA	5 (12)	NA	NA
12 months									
Complete	55 (34)	NA	2%	35 (28)	NA	3%	20 (49)	NA	0%
Partial	23 (14)	35%	0%	17 (14)	29%	0%	6 (15)	50%	0%
Minor	10 (6)	20%	0%	10 (8)	20%	0%	0 (0)	NA	NA
Minimal/none	24 (15)	0%	0%	21 (17)	0%	0%	3 (7)	0%	0%
Not assessed	52 (32)	NA	NA	40 (33)	NA	NA	12 (29)	NA	NA

*NA: not applicable;*excludes patients who were Ph-negative and BCR-ABL-positive; †proportion of patients who progressed due to development of accelerated/blast phase before 2 years.*

mg once daily arm than in the other three treatment arms (Figure 1). Fifteen patients on 100 mg once daily, 22 patients on 70 mg twice daily, 11 patients on 140 mg once daily and 17 patients on 50 mg twice daily died; of these deaths 3, 5, 2, and 6, respectively, were within 30 days of the last dose. Cause of death as reported by the investigator was disease progression in 26 patients, infection in 14 patients, complications of stem cell transplantation (n=7), cardiovascular disease (n = 5), bleeding related events (n = 2), drug toxicity (n = 2), "idiopathic pneumonia syndrome" (n=1), overdose of narcotics (n=1), suicide (n=1), motor vehicle accident (n=1), intestinal ischemic necrosis (n=1), other malignancy (n=1), and unknown (n = 3).

Discussion

After a minimum of 2 years of follow-up, these results demonstrate that intermittent BCR-ABL inhibition with dasatinib 100 mg once daily provides response rates that are similar to rates observed with dasatinib regimens that achieve more continuous target inhibition. Importantly, MCyR durability, estimated progression-free survival, and estimated overall survival were not compromised with the 100 mg once daily dosing regimen despite the lower intended total daily dose. Moreover, this regimen reduces the incidence of key toxicities (pleural effusion, neutropenia, leukocytopenia, and thrombocytopenia), and is also associated with less frequent treatment-related adverse events overall, implying that certain toxicities may be related to more prolonged target or off-target inhibition. Encouragingly, grade 3/4 pleural effusion (2%) in patients treated with dasatinib 100mg once daily remained uncommon with longer follow-up.

The MCyR and CCyR rates for 100 mg once daily (63% and 49%, respectively) and 70 mg twice daily (61% and 53%, respectively) are comparable to those reported after 2 years of follow-up in two phase 2 studies that employed the previously approved dasatinib dose of 70 mg twice daily, which reported MCyR rates of 53% and 62% and CCyR rates of 44% and 53%.[27,28] The MCyR and CCyR rates were consistent whether or not the Ph-negative, BCR-ABL-positive patients were included in the analysis. In this phase 3 study, the inclusion criteria encompassed imatinib-resistant and -intolerant patients, as well as suboptimal responders as defined by the European LeukemiaNet criteria.[18] Those patients who had less than a complete hematologic response at 3 months, less than a PCyR at 6 months, and less than a CCyR at 12 months[18] could be enrolled as the study definition of primary resistance included less than a MCyR (CCyR and/or PCyR) at 6 months or beyond or less than a CCyR at 12 months or beyond.

In this study, cytogenetic responses were typically achieved rapidly with dasatinib 100 mg once daily in patients with imatinib resistance, intolerance, or suboptimal response. Failure to achieve at least a PCyR by 6 months of therapy was associated with a low likelihood of eventual achievement of CCyR. The relative likelihood of these outcomes should be weighed in clinical decision-making involving patients who do not have a PCyR at 6 months of treatment with dasatinib 100 mg once daily. Encouragingly, only four of the total 138 (3%) patients with bone marrow assessments at 6 months experienced transformation to accelerated/blast phase disease by 2 years, and of 59 patients who had achieved a CCyR at 6 months, none had suffered disease transformation at their last follow-up. Although the true prognostic impact of achieving CCyR on dasatinib 100 mg once daily will require longer follow-up, a goal of achieving at least a PCyR, and preferably a CCyR, with a 6-month trial of dasatinib in patients who fail to benefit from imatinib and have the option of pursuing allogeneic stem cell transplantation is supported by these data.

The preserved efficacy and reduced toxicity observed with dasatinib 100 mg once daily are supported by recent pharmacokinetic data.[29] Results of the exposure-response analyses of patients treated on this study demonstrated that higher dasatinib trough levels (C_{min}) correlated with dose reductions and interruptions; increasing trough levels were also associated with a greater risk of pleural effusion.[29] The lowest dasatinib C_{min} levels were achieved in the 100 mg once daily cohort. Importantly, achievement of cytogenetic response in patients did not correlate with trough levels,[29] and it can, therefore, be postulated that response to dasatinib is driven by achieving effective dasatinib peak plasma levels, which are presumably obtained with any of the four dosing regimens tested. Furthermore, an *in vitro* analysis of CML cell lines exposed for 20 min to a clinically achievable concentration of dasatinib found that most cells had died after 48 h, whereas a supra-therapeutic concentration of imatinib was required to achieve the same degree of cytotoxicity.[11] While the mechanism of action of pleural effusion associated with dasatinib remains to be elucidated, one hypothesis involves dasatinib's ability to inhibit platelet-derived growth factor receptor beta (PDGFRβ).[10,30,31] A potential rationale for the reduction in pleural effusions with dasatinib 100 mg once daily is that the lower trough levels associated with this regimen,[29] coupled with the short half-life of the drug,[10] may reduce off-target exposure of PDGFRβ to dasatinib. Theoretically, the short terminal half-life of dasatinib could make this drug less vulnerable to certain resistance-conferring mechanisms, such as genomic amplification of *BCR-ABL*, which have been documented both in imatinib-treated patients as well as in experimental systems employing continuous exposure to imatinib.[32-34] Interestingly, although *BCR-ABL* genomic amplification has been well-described in a proportion of imatinib-resistant cases, to date, no evidence for this mechanism of resistance has been found in patients with loss of response to dasatinib, but this issue requires future study.

The estimated overall survival at 2 years (91%) in patients treated with dasatinib 100 mg once daily, coupled with the very low likelihood of disease transformation (< 3% at 24 months) observed in the present study, supports the use of dasatinib for 6 months at a minimum dose in nearly all CP-CML patients with resistance, intolerance, or suboptimal response to imatinib. Moreover, the results provided herein represent the first mature clinical data to support the longer-term therapeutic

promise of potent, intermittent kinase inhibition for the treatment of CML and other human malignancies.

Appendix

The following principal investigators (study site specific), in addition to the authors, also participated in this trial: Argentina: I Otero, J Milone, E Bullorsky, JJ Garcia; Australia: T Hughes, C Arthur, J Gibson, J Seymour, K Taylor, R Herrmann; Austria: P Valent; Belgium: A Bosly, D Bron, GEG Verhoef, J Van Droogenbroeck, M Andre, W Schroyens; Brazil: A Moellmann-Coelho, CA De Souza, N Hamerschlak, R Pasquini; Canada: P Laneuville, AR Turner, BF Leber, C Gambacorti-Passerini; Czech Republic: H Klamova, J Mayer; Denmark: C Marcher, I Dufva, J Nielsen; Finland: K Porkka; France: R Herbrecht, A Charbonnier, F Guilhot-Gaudeffroy, F Huguet, J Harrousseau, J Cahn, M Michalet, M Leporrier, M Tulliez, T Facon; Germany: C Bokemeyer, D Niederwieser, G Ehninger, OG Ottmann, T Fischer; Hungary: T Masszi; Ireland: E Conneally, M O'Dwyer; Israel: A Nagler; Italy: B Rotoli, E Abruzzese, E Pogliani, F Ferrara, G Alimena, G Saglio, V Liso; Netherlands: A Schattenberg, J Cornelissen; Norway: H Hjorth-Hansen; Peru: J Navarro, L Casanova; Philippines: P Caguioa; Poland: A Skotnicki, A Hellmann, A Dmoszynska, J Holowiecki, T Robak, W Jedrzejczak; Republic of Korea: HJ Kim, K-H Lee, S-S Yoon; Russian Federation: N Khoroshko, A Zaritsky; Singapore: C Chuah; South Africa: G Cohen, M Patel, N Novitzky, P Ruff, V Louw; Spain: F Prosper, J Odriozola, J Steegmann; Sweden: B Simonsson, M Ekblom; Switzerland: A Gratwohl; Taiwan: J Tang, L Shih; UK: A Green, C Craddock, J Apperley, R Clark, S O'Brien, T Holyoake; USA: E Asatiani, R Collins, K Harris, J Cortes, R. Paquette, M. Deininger, A Rapoport, A Maniam, A Liem, B Wong, C Schiffer, C Hagenstad, D Bodensteiner, E Hu, E Asatiani, FA Greco, J Schwartz, JG Berdeja, JF Dipersio, J Lister, J Catlett, J Hajdenberg, K Jamieson, K Mcdonagh, L Fehrenbacher, M Saleh, M Devetten, M Goodman, M Tallman, M Kalaycio, P Emanuel, R Larson, RM Stone, R Strair, R Mcintyre, S Thomas, S Tarantolo, S Petersdorf, S Goldberg, T Shea. J Zamparo served as the protocol manager for this trial.

Authorship and Disclosures

NPS, HMK and AH designed and performed research, collected, analyzed and interpreted data and wrote the manuscript; DWK, RTS, HJK and JV-O performed research, collected, analyzed and interpreted the data; PDL and PR performed research; AE and MCM collected, analyzed and interpreted the data; AL performed statistical analysis; JM collected, analyzed and interpreted data. All authors provided final approval of the manuscript.

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