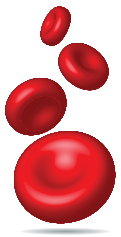
RESEARCH ARTICLE

AJH

Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034



Neil P. Shah,[1]* Philippe Rousselot,[2] Charles Schiffer,[3] Delphine Rea,[4] Jorge E. Cortes,[5] Jorge Milone,[6] Hesham Mohamed,[7] Diane Healey,[7] Hagop Kantarjian,[5] Andreas Hochhaus,[8] and Giuseppe Saglio[9]

Dasatinib was approved at 100 mg once daily for imatinib-resistant or -intolerant patients with chronic myeloid leukemia (CML) in chronic phase, based on results of the phase 3 CA180-034 (NCT00123474) study. Here we present the final 7-year analysis of this pivotal study, the longest follow-up to date of any second-generation BCR–ABL1 tyrosine kinase inhibitor (TKI). Patients (n = 670) with imatinib-resistant or -intolerant CML in chronic phase received dasatinib. Nineteen percent of patients continued on study treatment, with a greater proportion in the 100 mg once daily arm remaining on therapy. Seven-year rates for major molecular response (MMR), progression-free survival (PFS), and overall survival (OS) were similar across doses; MMR, PFS, and OS results were 46, 42, and 65% at 100 mg once daily, respectively. Improved PFS and OS rates were reported in patients who achieved *BCR–ABL1* ≤10% at 3 and 6 months. No new safety signals were identified. The incidence of drug-related pleural effusion was 28% at 100 mg once daily and 35% at the other three dose groups. Incidence of drug-related pulmonary hypertension and pulmonary arterial hypertension remained low (≤3% across all doses). Arterial ischemic events occurred in ≤4% of patients across all doses. These data support the long-term efficacy and well-established safety profile of dasatinib for patients with imatinib-resistant or -intolerant CML in chronic phase.

Am. J. Hematol. 91:869–874, 2016.

Introduction

The introduction of BCR–ABL1 tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML) resulted in improved patient prognosis, including greater survival rates, compared with the two previous standards of care [1–3]. Survival in CML patients is now nearly identical to that of the general population [4]. CML is currently considered a manageable chronic disease, requiring many patients to remain on TKI therapy indefinitely. Given the long-term nature of treatment for CML, monitoring patients as they continue therapy is valuable for understanding the durability of responses, and for recognizing the emergence of new or previously unrecognized adverse events (AEs).

Dasatinib, a second-generation TKI active against ABL, PDGFRβ, KIT, and SRC family kinases, is approved for the treatment of newly diagnosed adults with Ph+ CML in chronic phase (CP); adults with Ph+ CML in chronic phase, accelerated phase (AP), or blast phase (BP) with resistance or intolerance to prior therapy including imatinib; and for adults with Ph+ acute lymphoblastic leukemia who have become resistant to or intolerant of other treatment [5]. Previous analysis from the initial report at 6-month follow-up for the phase 3 CA180-034 dose-optimization study in imatinib-resistant or -intolerant CML-CP patients showed similar dasatinib efficacy with all dosing regimens evaluated; however, the 100 mg once-daily (QD) dosing schedule showed improved tolerability with a reduced incidence of treatment-related AEs of interest (i.e., pleural effusion and cytopenia), leading to a label change as the recommended dasatinib dose regimen in this patient population [5,6]. Longer-term follow-up of patients in this trial at 6 years continued to demonstrate durable efficacy and safety with dasatinib at 100 mg QD [1]. Here, we report

Additional Supporting Information may be found in the online version of this article.

[1]UCSF School of Medicine, San Francisco, California; [2]Hôpital André Mignot and Université Versailles Saint-Quentin-en-Yvelines, Versailles, France; [3]Wayne State University School of Medicine, Detroit, Michigan; [4]Saint Louis Hospital, Paris, France; [5]University of Texas M.D. Anderson Cancer Center, Houston, Texas; [6]Hospital Italiano De La Plata, La Plata, Argentina; [7]Bristol-Myers Squibb, Princeton, New Jersey; [8]Universitätsklinikum Jena, Jena, Germany; [9]University of Turin, Turin, Italy

Clinical trials identifier: NCT00123474

Funding: Bristol-Myers Squibb sponsored this trial.

Disclosure: NPS received research funding from Ariad, BMS, and Pfizer. PR acted as a consultant for and received research funding from BMS. CS received research funding from Ariad, BMS, and Novartis and participates in DSMBs for Teva and Pfizer. DR received honoraria from Ariad, BMS, Novartis, and Pfizer. JEC acted as a consultant for and received research funding from Ariad, BMS, Novartis, and Pfizer, and received research funding from Teva. JM holds membership on the Boards of Directors or advisory committees and Speakers Bureaus for BMS and Roche. HM and DH are employees of BMS. HK received research funding from Amgen, Ariad, and Pfizer. AH received research funding from Ariad, BMS, MSD, Novartis, and Pfizer. GS acted as a consultant for and received speaking fees from BMS, and consulted for and received speaking fees from Ariad, Novartis, and Pfizer.

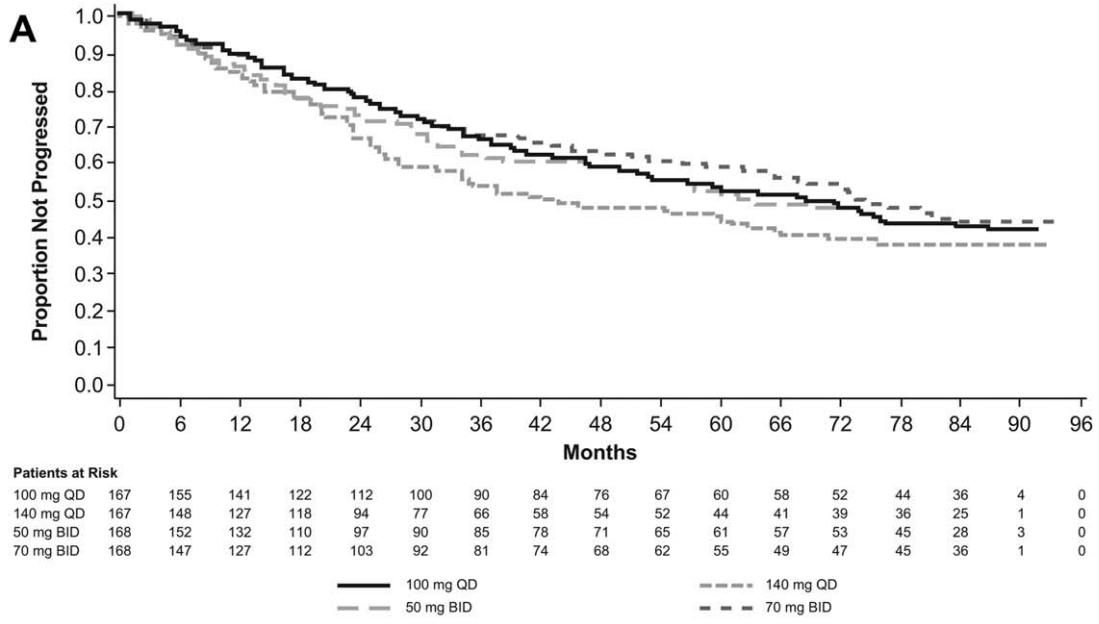
***Correspondence to**: Neil P. Shah; Division of Hematology-Oncology, UCSF, 505 Parnassus Avenue, Suite M1286, Box 1270, San Francisco, CA 94143. E-mail: nshah@medicine.ucsf.edu

Received for publication: 5 May 2016; **Revised:** 10 May 2016; **Accepted:** 16 May 2016

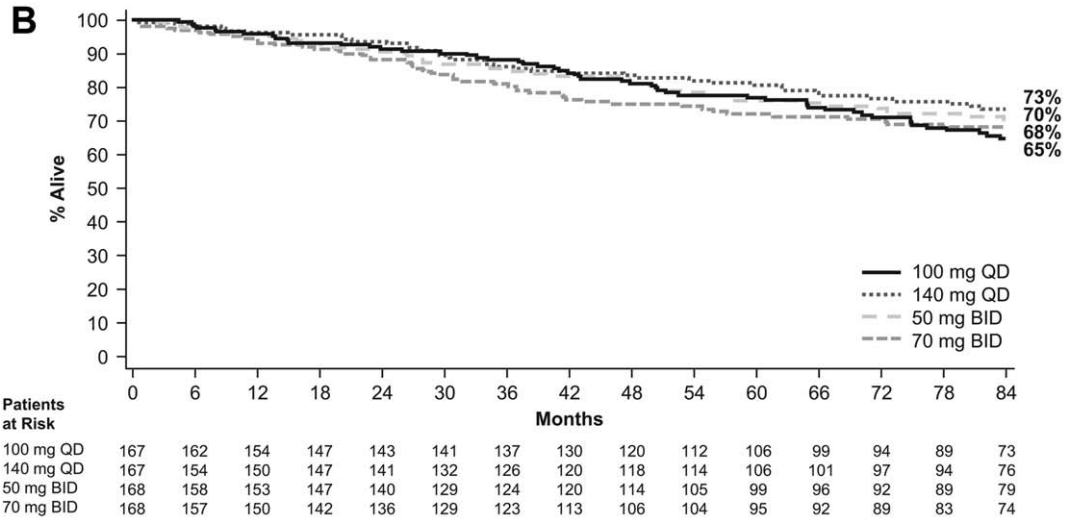
Am. J. Hematol. 91:869–874, 2016.

Published online: 19 May 2016 in Wiley Online Library (wileyonlinelibrary.com).

DOI: 10.1002/ajh.24423



Group	No. Progressed/No. Randomized	Median (95% CI)
100 mg QD	79/167	88.5 (49.8 – .)
140 mg QD	84/167	41.9 (31.5 – 65.4)
50 mg BID	72/168	73.4 (58.2 – .)
70 mg BID	75/168	62.8 (51.0 – 86.2)



	Imatinib-resistant patients	Imatinib-intolerant patients	Overall
OS, % (95% CI)	63 (53–71)	70 (52–82)	65 (56–72)
PFS, % (95% CI)	39 (29–49)	51 (32–67)	42 (33–51)

Figure 1. Kaplan–Meier analyses. All subjects included in these analyses were randomized. Rates for PFS and OS at 7 years from randomization were comparable across treatment arms. Panel A: progression-free survival (PFS), Panel B: overall survival (OS).

the final 7-year analysis of efficacy and safety outcomes of CA180-034, which represents the longest follow-up to date in the second-line of any second-generation BCR–ABL1 TKI.

Methods

Detailed methods have been previously reported and are outlined in Supporting Information Materials. CA180-034 (NCT00123474), a randomized phase 3 study, compared the dose and schedule of dasatinib therapy for optimal benefit/risk ratio among patients with imatinib-resistant or -intolerant CML-CP. The primary objective of this study was to compare the major cytogenetic response (MCyR) rates of dasatinib after a minimum follow-up of 6 months when administered QD with dasatinib administered twice daily (BID). Secondary end points included other efficacy and safety assessments.

Patient eligibility criteria were previously described [6]. Patients were stratified by imatinib resistance or intolerance. The study was conducted in accordance with the Declaration of Helsinki and was approved by local ethics committees. Written informed consent was obtained from each patient before participation.

Eligible patients were randomized 1:1:1:1 to receive dasatinib 100 mg QD, 50 mg BID, 140 mg QD, or 70 mg BID. To manage inadequate responses or AEs, dose escalation (up to a total daily dose [TDD] of 180 mg) and dose interruption or reduction (down to a TDD of 20 mg) were allowed. After 2 years, the protocol was amended to allow switching from a BID to a QD regimen, at the same TDD, if the patient experienced a recurrence of anemia, thrombocytopenia, neutropenia, pleural effusion, or any other fluid retention during study progress following at least one dose reduction, at the investigator's discretion [1]. Treatment was administered until protocol-defined disease progression or death, unacceptable toxicity, or patient/investigator request.

 doi:10.1002/ajh.24423

TABLE I. Subgroup Analyses for Efficacy: MMR, PFS, and OS

	Dasatinib treatment arms							
	100 mg QD (n = 167)		50 mg BID (n = 168)		140 mg QD (n = 167)		70 mg BID (n = 168)	
Imatinib status	Resistant (n = 124)	Intolerant (n = 43)	Resistant (n = 124)	Intolerant (n = 44)	Resistant (n = 123)	Intolerant (n = 44)	Resistant (n = 126)	Intolerant (n = 42)
MMR in assessed treated patients, n (%)	51 (43)	22 (55)	46 (39)	24 (59)	38 (34)	30 (75)	48 (42)	21 (57)
PFS, % (95% CI)	39 (29–49)	51 (32–67)	42 (32–52)	48 (27–65)	30 (21–40)	67 (46–81)	41 (31–51)	50 (30–67)
OS, % (95% CI)	63 (53–71)	70 (52–82)	68 (58–76)	77 (60–87)	68 (58–76)	88 (72–95)	65 (55–73)	78 (60–88)

BID, twice daily; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; QD, once daily.

Efficacy and safety assessments were collected for the intent-to-treat population as described in earlier reports [1,6]; they were assessed and are reported by randomized arm, with the exception of landmark analyses.

Major molecular response (MMR) was defined as *BCR–ABL1* transcript level ≤0.1% on the International Scale (IS), molecular response (MR^4) was defined as *BCR–ABL1* transcript level (IS) ≤0.01%; $MR^{4.5}$ was defined as a *BCR–ABL1* (IS) transcript level ≤0.0032%.

For this study, progression was defined as increasing white blood cell (WBC) count, loss of complete hematologic response (CHR) or MCyR, ≥30% increase in Ph+ metaphases, or transformation to AP or BP disease [6]. OS was defined as time from randomization until death. Survival data for all patients was collected for up to 7 years, including those who discontinued dasatinib treatment earlier. Reason for progression was captured for patients who progressed during treatment, but only the date of progression was captured for events occurring after treatment ended. Patients who survived or who were lost to follow-up were censored on the last date the patient was known to be alive. Mutational analyses were conducted as described previously [6,7]. *BCR–ABL1* mutations were assessed in patients prior to the start of dasatinib and at time of progression or end of treatment. Safety analyses included all patients who received at least one dose of dasatinib. AEs are reported as cumulative incidence, unless otherwise noted. AEs during the 7-year follow-up were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 [8].

No formal statistical comparisons were conducted for the 7-year analysis. PFS, OS, and the landmark analyses were estimated using Kaplan–Meier product-limit methodology [1]. *P* values were not adjusted for multiple comparisons; secondary analyses are thus descriptive.

Results

Patient disposition

Of 670 randomized patients, 662 were treated across 138 sites globally (Supporting Information Fig. 1) [1,6,7]. Patient demographics and baseline characteristics were well balanced among treatment arms (Supporting Information Table I). Across dose groups, the majority of patients (74%) had imatinib resistance. Approximately 41% of patients received prior imatinib therapy for >3 years. Other prior therapies included interferon-α (52%), chemotherapy (26%), and allogeneic stem cell transplantation (5%). The following data are reported according to a database lock at approximately 84 months.

With 7 years of follow-up, the overall median duration of therapy was the longest in the 100 mg QD arm at 37 months (50 mg BID: 28 months, 140 mg QD: 27 months, and 70 mg BID: 29 months). Thirty-eight percent of patients in the 100 mg QD arm maintained their assigned dose, compared with those in the other arms (50 mg BID: 19%, 140 mg QD: 24%, and 70 mg BID: 9%). After 2 years, the protocol was amended to allow switching from BID to QD dosing; 54.8% of those in the 50 mg BID arm and 50.5% of those in the 70 mg BID arm still on treatment switched to the QD dosing schedule. All data included are reported by randomized arm. Twenty-two percent of patients in the 100 mg QD arm remained on dasatinib treatment for at least 7 years, compared with 19% in the 50 mg BID arm, 15% in the 140 mg QD arm, and 19% in the 70 mg BID arm. The most common reason for discontinuation was "other," as a majority of these patients moved off-study and on to commercial supply of dasatinib. Other reasons for discontinuation were drug-related AEs (100 mg QD: 24%, 50 mg BID: 27%, 140 mg QD: 28%, and 70 mg BID: 31%; all percentages given are out of total patients treated; Supporting Information Table II) or protocol-defined progression (100 mg QD: 21%, 50 mg BID: 17%, 140 mg QD: 26%, and 70 mg BID: 16%; all percentages given are out of total patients treated; Supporting Information Table II).

Efficacy: molecular responses, PFS, and OS

During the 7-year follow-up, 94% of patients (n = 624) were evaluable for the achievement of MMR. Best on-study rates for MMR (reported as a percentage of number of responders divided by assessed treated patients) were similar across dose groups at 46, 44, 44, and 46%, in the 100 mg QD, 50 mg BID, 140 mg QD, and 70 mg BID arms, respectively. MMR rates at 7 years among all randomized patients were comparable at 13, 10, 11, and 14%, respectively, in the four treatment arms. Rates for MR^4 and $MR^{4.5}$ at any time, which were evaluated in all randomized patients, were greatest in the 100 mg QD arm at 29 and 20%, respectively, compared with each of the other arms (50 mg BID: 21 and 13%; 140 mg QD: 23 and 11%; 70 mg BID: 22 and 14%, respectively). Rates for PFS and OS at 7 years from randomization were comparable across treatment arms (Fig. 1).

Subgroup analyses showed that MMR rates were comparable in imatinib-resistant patients across dose groups (Table I). For imatinib-intolerant patients, MMR was 75% in the 140 mg QD arm, 55% in the 100 mg QD arm, 59% in the 50 mg BID arm, and 57% in the 70 mg QD arm. For imatinib-resistant patients, OS and PFS rates were similar across the dose groups with overlapping 95% CIs, which was also a trend in the imatinib-intolerant subgroup and in the overall population.

A landmark analysis conducted in patients in the dasatinib 100 mg QD arm who achieved *BCR–ABL1* (IS) ≤10% at 3 and 6 months demonstrated improved PFS and OS compared with patients with *BCR–ABL1* (IS) >10% (Supporting Information Table III; Fig. 2). Seven-year OS rates for patients with *BCR–ABL1* (IS) ≤10% at 3 and 6 months were 72 and 74%, respectively; for patients with *BCR–ABL1* (IS) >10% at 3 and 6 months they were 56 and 50%, respectively (Supporting Information Table III). Seven-year PFS rates for patients with *BCR–ABL1* (IS) ≤10% at 3 and 6 months were 56 and 57%, respectively; for patients with *BCR–ABL1* (IS) >10% at 3 and 6 months they were 21 and 4%, respectively (Supporting Information Table III).

Mutational analysis

BCR–ABL1 kinase domain mutations were assessed in all patients at baseline and at the end of treatment. The majority of patients who discontinued because of loss of response did not have a *BCR–ABL1* mutation at baseline (n = 72) or at end of treatment (n = 71), as shown in Supporting Information Table IV. Of those with mutations, the three most common that emerged while on dasatinib were V299L (n = 10), T315I (n = 19), and F317L (n = 12), each a known dasatinib-resistant mutation. Furthermore, two of these mutations were detected both at baseline and at the end of study (T315I [n = 9], F317L [n = 3]); selected mutations characterized as dasatinib-sensitive were lost during the

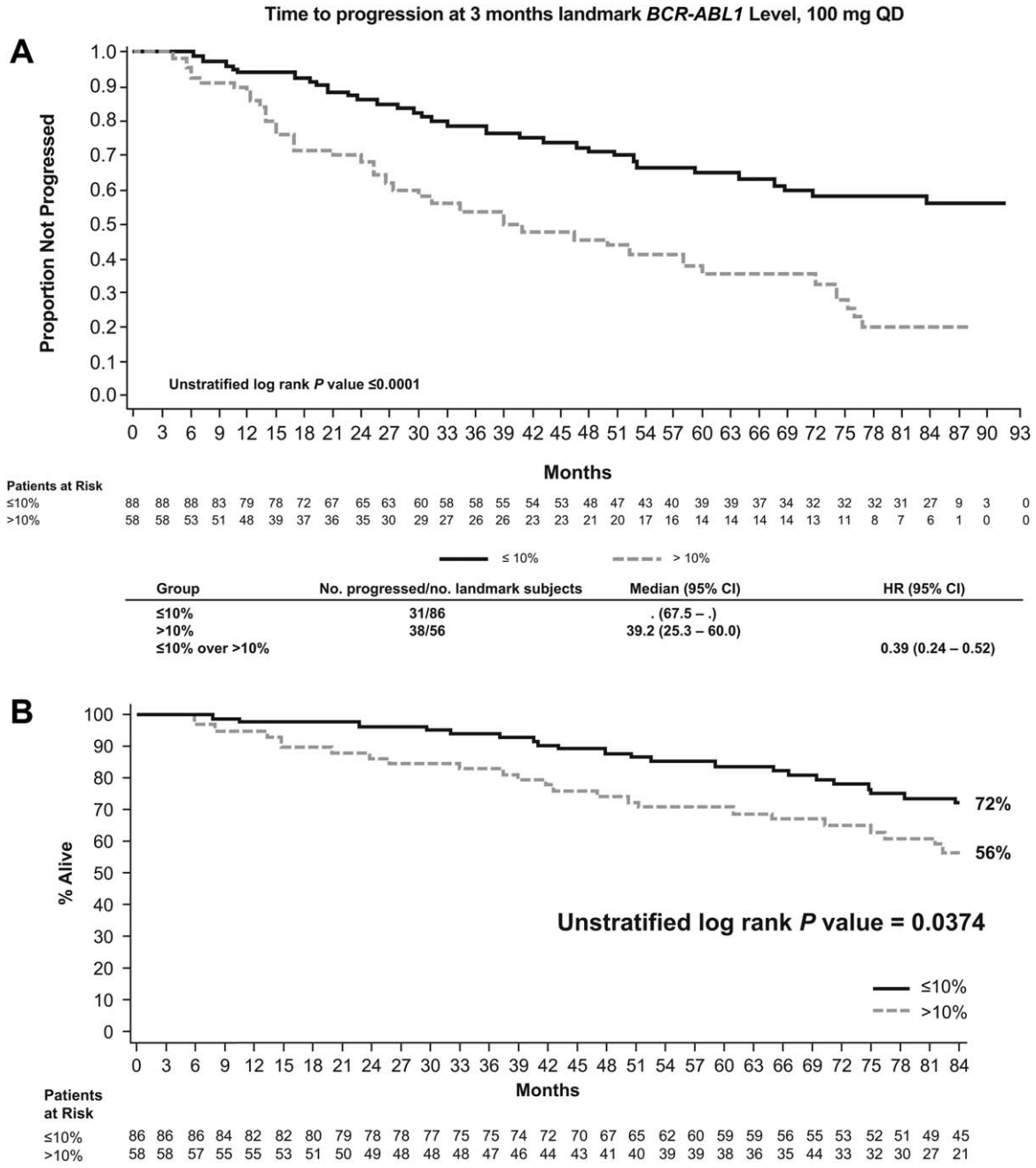


Figure 2. Kaplan–Meier landmark analyses at 3 months for 100 mg QD. All subjects included in these analyses were randomized. The analyses show improved PFS and OS compared with patients with *BCR–ABL1* >10%. Panel A: progression-free survival (PFS), Panel B: overall survival (OS).

course of treatment (total number in brackets = retained + emerged; T315I [n = 28], and F317L [n = 15]; Supporting Information Table IV).

Safety

Most patients (99%) participating in this study experienced at least one AE, with the majority considered drug-related AEs (94%) by the investigators. Severe (grade ≥3) drug-related AEs were reported in 53% of treated patients, and in a lower proportion of patients in the 100 mg QD arm than the other treatment arms (45 vs. 56%, respectively).

A total of 184 deaths (28%) were reported, with similar percentages in the 100 mg QD arm (31%) and the other arms (27%). The most common cause of death was disease related (17% in the 100 mg QD arm and 11% in the other arms). There were three deaths (<1%) attributed to study-drug toxicity across all arms (one due to sepsis; one due to necrosis of the colon; and one in a patient with pulmonary edema, congestive heart failure, neck pain, and pleural effusion). Across all study arms, 22 (3%) patients died due to infection; the most common types leading to death were sepsis (9) and pneumonia (8); 19 of the 22 patients who died due to infection had discontinued dasatinib more than 30 days before death. There were no new deaths due to study drug toxicity reported since the 6-year follow-up report [1].

Most AEs (all grades) first occurred within 24 months of treatment and were primarily mild to moderate (grade 1/2). At 7 years, cumulative rates of AEs of special interest (regardless of relationship to study drug; all grades) for the 100 mg QD arm compared with the other treatment arms were: hemorrhage (26 vs. 28%), pleural effusion (27 vs. 36%), diarrhea (42 vs. 47%), nausea/vomiting (27 vs. 43%), fatigue (37 vs. 34%), myalgias/arthralgias (38 vs. 33%), and rash (33 vs. 36%; Supporting Information Table V).

First occurrences of pleural effusion (regardless of relationship to study therapy; any grade) were reported in 34%, with a minority (8%) experiencing severe pleural effusion (100 mg QD: any grade

 doi:10.1002/ajh.24423

TABLE II. Drug-Related Adverse Events of Interest Over Time

	Treated patients, *n*/at risk (%)					
	100 mg QD (n = 165)			Other dose groups (n = 497)		
	2-year	5-year	7-year	2-year	5-year	7-year
Pleural effusion	23/121 (14)	40/55 (24)	46/42 (28)	118/309 (24)	158/127 (32)	174/91 (35)
Pulmonary hypertension	0 (0)	0 (0)	3 (2)	5 (1)	8 (2)	13 (3)
Pulmonary arterial hypertension	–	0 (0)	1 (<1)	–	0 (0)	0 (0)

Number of patients at risk = number of patients treated within a given year not having that adverse event.
QD, once daily.

[grades 3/4], 28% [5%] vs. other treatment arms: any grade [grades 3/4], 36% [9%]). No deaths due to pleural effusion events were reported. In year 7 of the study, new cases of pleural effusion (regardless of relationship to study therapy) occurred in 5% (2/42) of patients at risk treated in the 100 mg QD arm compared with 8% (7/88) in the other treatment arms. Half the pleural effusion events (23/46 cases; Table II) occurred within the first 2 years of treatment among patients in the 100 mg QD arm. Drug-related pleural effusion was reported at a rate of 28% in the 100 mg QD arm vs. 35% in the other dose groups (Table II). Pleural effusion cases leading to treatment discontinuation were all considered drug-related; 7% of patients with pleural effusion in the 100 mg QD arm discontinued therapy (2% grade 3/4) vs. 11% (3% grade 3/4) in the other dose groups.

Pulmonary hypertension (PH), or pulmonary arterial hypertension (PAH), were reported on the basis of diagnostic evaluations including echocardiogram, chest X-ray, cardiac catheterization, and blood tests. PH of any grade was reported in 16 patients (2.4%) with seven (1.1%) experiencing a grade 3/4 event (100 mg QD: any grade [grades 3/4], three patients (1.8%) [two patients (1.2%)] vs. other treatment arms: any grade [grades 3/4], 3% [1%]). PAH confirmed by right-heart catheterization was reported in one patient in the 100 mg QD group (at 75 months). Cumulative rates of PH and PAH over time are shown in Table II.

Incidence of arterial ischemic events (all grades) was low overall in the study. Cardiovascular ischemic events (defined as myocardial infarction, angina pectoris, or coronary artery disease) were reported in 4% of patients in the 100 mg QD arm and 4% in the other dose groups. The specific cardiac ischemic events reported in the 100 mg QD arm and the other dose groups were myocardial infarction (2 vs. 1%, respectively), angina pectoris (1 vs. 2%, respectively), and coronary artery disease (1 vs. <1%, respectively). The majority of cardiac ischemic events were grades 3/4 (2 vs. 2%, respectively); additionally, one patient (<1%) in the other dose groups experienced a fatal grade 5 myocardial infarction. Peripheral vascular events (all grades) were reported in 1% of patients in the other dose groups (no events in the 100 mg QD arm), with <1% reported as grades 3/4. Cerebrovascular events (all grades) were reported in 3 and 1% of patients in the 100 mg QD and other dose groups, respectively. In the 100 mg QD arm, 1% of cerebrovascular events were grades 3/4; all events in the other dose groups were grades 3/4. There were no reports of stroke.

Over the 7-year course of the study, 66% of all treated patients experienced infections (any cause, all grades); 67% of patients in the 100 mg QD arm and 65% of patients in the other dose arms experienced infections (Supporting Information Table VI). In the 100 mg QD arm, 53% of patients had on-study worst grade 1/2 infections, and 13% had worst grade events of 3 or 4; across the other arms, 49% of patients had on-study worst grade 1/2 infections and 15% had a worst grade 3/4 infection. Among the two patients in the 100 mg QD arm who had an on-study worst grade infection of 5, one was a lung infection and one was due to septic shock. In the other arms, three patients had an on-study worst grade 5 infection, one from pneumonia, and two from skin infections. The majority of infectious deaths occurred after dasatinib treatment was discontinued (range, 1 day–16 months). Neutropenia was not associated with infections among patients who received dasatinib. The majority of infections resolved.

Discussion

At 7 years of follow-up, this analysis of dasatinib treatment from the CA180-034 dose optimization trial represents the longest follow-up of a second-generation BCR–ABL1 TKI in the second line. Consistent with previous reports, dasatinib treatment at a dose of 100 mg QD demonstrated durable efficacy and a tolerable long-term safety profile in imatinib-resistant and -intolerant CML-CP patients.

With the advent of BCR–ABL1 TKIs, CML is currently considered a chronic condition, in which most patients are able to achieve long-term survival [1–3]. Initial and continuing monitoring of responses is critical to ensure optimal management of CML, since early responses are predictive of long-term outcomes [9–13]. Furthermore, prompt identification of patients who are resistant or intolerant to their first-line therapy is imperative, so that they may be switched early to a second-line TKI and potentially improve long-term outcomes [12–14].

In this analysis, we report that 19% of extensively pretreated patients continued dasatinib on study for at least 7 years, with a greater proportion of patients in the 100 mg QD arm remaining on treatment (median duration, 37 months). Dasatinib at 100 mg QD was better tolerated than other dosing regimens: more patients in this group maintained their assigned dose (38%) compared with the other treatment groups (50 mg BID: 19%, 140 mg QD: 24%, and 70 mg BID: 9%). With a minimum follow-up of 7 years, treatment with dasatinib at 100 mg QD continues to provide efficacy similar to the initially approved dose of 70 mg BID, as evidenced by comparable rates of MMR (46 and 46%, respectively), PFS (42 and 44%, respectively), and OS (65 and 68%, respectively). Deaths were most commonly disease-related.

According to current European LeukemiaNet (ELN) recommendations, achievement of *BCR–ABL1* (IS) ≤10% at 3 months defines treatment response, predictive of long-term benefit and outcomes for first-line therapy [9,15]. At 7 years, landmark analyses continue to demonstrate that achieving early responses at 3 and 6 months translates to long-term clinical benefit with superior PFS and OS, consistent with our previous study findings [1]. Seven-year OS rates for patients with *BCR–ABL1* (IS) ≤10% at 3 and 6 months were 72 and 74%, respectively, and the 7-year PFS rates for patients with *BCR–ABL1* (IS) ≤10% were 56 and 57% at 3 and 6 months, respectively.

Dasatinib was well tolerated, and no new safety signals were detected in this analysis. The majority of AEs, both nonhematologic and hematologic, occurred early in the course of treatment. Cumulative rates of pleural effusion increased gradually over time in the study population, including the 100 mg QD arm; however, with a minimum follow-up of 7 years, incidence of drug-related pleural effusion was less common in the 100 mg QD arm relative to other

treatment arms. Cumulative rates of PAH (and PH) remained low throughout the duration of this study, at 0 to <1% (pH: 0–3%). We recognize that PAH may not have been fully investigated, as to do so would have required catheterizing patients, a procedure which was performed in only a small number of patients.

As cardiac AEs have been identified with use of some BCR–ABL1 TKIs in CML [16–18], we evaluated their incidence with dasatinib. Across all doses, arterial ischemic events occurred at low frequencies (≤4%). Most cardiovascular ischemic events occurred during the first year of treatment. Moreover, no increase in cardiovascular ischemic events over time was observed. Likewise, peripheral vascular events occurred in <1% across all dose groups, and no peripheral vascular event occurred in the 100 mg QD dose group. Cerebrovascular events were observed in ≤3% of patients, and there were no reports of stroke.

During this 7-year period, infections due to any cause occurred in 66% of patients. The most common types of infection were upper respiratory infections, nasopharyngitis, and pneumonia. Most infections were grades 1/2. All infections were captured during the treatment period, regardless of relationship to study treatment. Only a minority of infections (17%) was deemed drug-related, and the majority of infections resolved.

In this study, progression was defined as increasing WBC, loss of CHR or MCyR, ≥30% increase in Ph+ metaphases, or transformation to AP or BP disease. This definition differs from the current ELN and National Comprehensive Cancer Network definitions of progression [9,18,19]. Although patients were followed for OS on study discontinuation, they were not followed for study-defined disease progression after discontinuation. Additionally, in patients for whom progression was reported, the reason of progression in the follow-up period was not captured. Thus, we were not able to analyze PFS according to intent-to-treat principles as per the ELN definition of progression [9,19]. The differences between this study design and definitions set forth by consensus guidelines underscores the challenges in making cross-study comparisons. It was not possible to assess the incidences of AP and BP, because of termination of follow-up, according to study protocol. Also, the availability of commercial dasatinib substantially reduced the number of patients who continued the study.

It should be noted that many of the patients included in this trial received early lines of treatment that were not TKIs, such as interferon, chemotherapy, and even allogeneic stem cell transplants. Therefore, the study population may not be representative of CML-CP patients who received imatinib as frontline therapy, and then switched to dasatinib once they became resistant or intolerant to imatinib. It is then possible that data for dasatinib in CML-CP patients pretreated with imatinib only are better than those reported here.

With a minimum follow-up of 7 years, study CA180-034 provides the longest follow-up for safety and efficacy of any second-line second-generation BCR–ABL1 TKI. Overall OS was 65%. Long-term follow-up data presented here confirm the 6-month, 2-year, and 6-year results [1,6,7] of a positive benefit/risk associated with long-term dasatinib use at its approved dose of 100 mg QD in CML-CP patients with resistance or intolerance to imatinib. Arterial ischemic events occurred at low frequencies. As pleural effusion may occur for the first time in dasatinib-treated patients even after years of treatment, monitoring for these symptoms should continue.

Acknowledgments

The authors would like to thank all participating study sites for this Bristol-Myers Squibb (BMS)–sponsored trial. Professional medical writing and editorial assistance were provided by Ami P. Modi, PhD; Beverly E. Barton, PhD; and Artur Romanchuk, PhD, of StemScientific, an Ashfield Company, part of UDG Healthcare plc, funded by BMS. The authors did not receive financial compensation from BMS for authoring this manuscript.

Author Contributions

All authors provided feedback and guidance on the analysis and interpretation of the results, critically reviewed and provided revisions to the manuscript, and approved the final draft for submission.

References

1. Shah NP, Guilhot F, Cortes JE, et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: Follow-up of a phase 3 study. Blood 2014;123:2317–2324.
2. Baccarani M, Efficace F, Rosti G. Moving towards patient-centered decision-making in chronic myeloid leukemia: Assessment of quality of life and symptom burden. Haematologica 2014;99:205–208.
3. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs sti571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib clinically [Abstract]. Blood 2009;114:1126.
4. Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: Analysis of patient data from six prospective clinical trials. Lancet Haematol 2015;2:e186–e193.
5. Sprycel (dasatinib) [prescribing Information]. Princeton, NJ: Bristol-Myers Squibb; 2015.
6. Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 2008;26:3204–3212.
7. Shah NP, Kim DW, Kantarjian H, et al. 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. Haematologica 2010;95:232–240.
8. National Cancer Institute: Common Terminology Criteria for Adverse Events v3.0. 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.
9. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013;122:872–884.
10. Goldberg SL, Chen L, Guerin A. Association between molecular monitoring and long-term outcomes in chronic myelogenous leukemia patients treated with first line imatinib. Curr Med Res Opin 2013;29:1075–1082.
11. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR–ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. J Clin Oncol 2012;30:232–238.
12. Hochhaus A, Kantarjian H. The development of dasatinib as a treatment for chronic myeloid leukemia (CML): From initial studies to application in newly diagnosed patients. J Cancer Res Clin Oncol 2013;139:1971–1984.
13. Hochhaus A, Muller MC, Radich J, et al. Dasatinib-associated major molecular responses in patients with chronic myeloid leukemia in chronic phase following imatinib failure: Response dynamics and predictive value. Leukemia 2009;23:1628–1633.
14. Quintas-Cardama A, Cortes JE, O'Brien S, et al. Dasatinib early intervention after cytogenetic or hematologic resistance to imatinib in patients with chronic myeloid leukemia. Cancer 2009;115:2912–2921.
15. Hanfstein B, Muller MC, Hehlmann R, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). Leukemia 2012;26:2096–2102.
16. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor–associated cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol 2015;33:4210–4218.
17. Aichberger KJ, Herndlhofer S, Schernthaner G-H, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am J Hematol 2011;86:533–539.
18. Quintás-Cardama A, Kantarjian H, Cortes JE. Nilotinib-associated vascular events. Clin Lymphoma Myeloma Leuk 2012;12:337–340.
19. Guilhot J, Baccarani M, Clark RE, et al. Definitions, methodological and statistical issues for phase 3 clinical trials in chronic myeloid leukemia: A proposal by the European LeukemiaNet. Blood 2012;119:5963–5971.