

## Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial

Jorge E. Cortes, Giuseppe Saglio, Hagop M. Kantarjian, Michele Baccarani, Jiří Mayer, Concepción Boqué, Neil P. Shah, Charles Chuah, Luis Casanova, Brigid Bradley-Garelik, George Manos, and Andreas Hochhaus

Jorge E. Cortes and Hagop M. Kantarjian  
The University of Texas MD Anderson Cancer Center, Houston, TX; Neil P. Shah, University of California San Francisco School of Medicine, San Francisco, CA; Brigid Bradley-Garelik and George Manos, Bristol-Myers Squibb, Princeton, NJ; Giuseppe Saglio, University of Turin, Turin; Michele Baccarani, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; Jiří Mayer, University Hospital Brno and Central European Institute of Technology, Masaryk University, Brno, Czech Republic; Concepción Boqué, Institut Català d'Oncologia, Hospital Duran i Reynals, L'Hospitalet, Barcelona, Spain; Charles Chuah, Singapore General Hospital, Duke-National University of Singapore Medical School, Singapore; Luis Casanova, Instituto Nacional de Enfermedades Neoplásicas, Lima, Perú; and Andreas Hochhaus, Universitätsklinikum Jena, Jena, Germany.

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Corresponding author: Jorge E. Cortes, MD, Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 0428, Houston, TX 77030; e-mail: [jcortes@mdanderson.org](mailto:jcortes@mdanderson.org).

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### ABSTRACT

#### Purpose

We report the 5-year analysis from the phase III Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients (DASISION) trial, evaluating long-term efficacy and safety outcomes of patients with chronic myeloid leukemia (CML) in chronic phase (CP) treated with dasatinib or imatinib.

#### Patients and Methods

Patients with newly diagnosed CML-CP were randomly assigned to receive dasatinib 100 mg once daily (n = 259) or imatinib 400 mg once daily (n = 260).

#### Results

At the time of study closure, 61% and 63% of dasatinib- and imatinib-treated patients remained on initial therapy, respectively. Cumulative rates of major molecular response and molecular responses with a 4.0- or 4.5-log reduction in *BCR-ABL1* transcripts from baseline by 5 years remained statistically significantly higher for dasatinib compared with imatinib. Rates for progression-free and overall survival at 5 years remained high and similar across treatment arms. In patients who achieved *BCR-ABL1*  $\leq 10\%$  at 3 months (dasatinib, 84%; imatinib, 64%), improvements in progression-free and overall survival and lower rates of transformation to accelerated/blast phase were reported compared with patients with *BCR-ABL1* greater than 10% at 3 months. Transformation to accelerated/blast phase occurred in 5% and 7% of patients in the dasatinib and imatinib arms, respectively. Fifteen dasatinib-treated and 19 imatinib-treated patients had *BCR-ABL1* mutations identified at discontinuation. There were no new or unexpected adverse events identified in either treatment arm, and pleural effusion was the only drug-related, nonhematologic adverse event reported more frequently with dasatinib (28% v 0.8% with imatinib). First occurrences of pleural effusion were reported with dasatinib, with the highest incidence in year 1. Arterial ischemic events were uncommon in both treatment arms.

#### Conclusion

These final results from the DASISION trial continue to support dasatinib 100 mg once daily as a safe and effective first-line therapy for the long-term treatment of CML-CP.

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### INTRODUCTION

The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients (DASISION) study was a randomized phase III trial comparing the efficacy and safety of dasatinib with imatinib in patients with newly diagnosed chronic myeloid leukemia (CML) in chronic phase (CP). Initial results showed that dasatinib had met its primary end point of superior efficacy compared with imatinib and had an acceptable safety profile, leading to its approval for first-line use.<sup>1,2</sup>

In subsequent analyses,<sup>3-6</sup> dasatinib continued to demonstrate deep and fast responses. Progression-free survival (PFS) and overall survival (OS) remained high and comparable between dasatinib and imatinib. Furthermore, the safety profile of dasatinib was consistent through each update.

Several studies with *BCR-ABL1* tyrosine kinase inhibitors (TKIs) have reported that a deep, early response predicts improved outcomes in patients with CML-CP.<sup>5,7-18</sup> The achievement of *BCR-ABL1* transcript levels of  $\leq 10\%$  according to the International Scale (IS) at 3 months has

been associated with significantly improved PFS, event-free survival, and OS and a reduced risk of transformation.<sup>5,8,9,14</sup>

Here, we present the final, planned, 5-year analysis from DASISION. Long-term efficacy and safety outcomes, CML-related and -unrelated deaths, and *BCR-ABL1* mutation status are reported. Expected survival by age at diagnosis and response by Euro (Hasford) risk score are described.

## PATIENTS AND METHODS

### Study Design and Treatment

DASISION was a multinational, open-label, phase III trial (CA180-056; [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT00481247). Patients were stratified by Euro risk score<sup>19</sup> and randomly assigned 1:1 to receive either oral dasatinib (100 mg once daily) or imatinib (400 mg once daily). Adverse events (AEs) were managed through treatment interruptions and dose reductions. Dose escalations to dasatinib 140 mg once daily or imatinib 600 to 800 mg once daily were permitted for suboptimal response at 3 to 18 months.<sup>20</sup> The primary end point was confirmed complete cytogenetic response (cCCyR) rate by 12 months. Secondary end points were overall time to cCCyR and its duration, major molecular response (MMR) rate at any time, time to MMR overall, PFS, and OS.

### Patients

Eligibility criteria and patient characteristics have been described,<sup>1</sup> and key exclusion criteria are available in the Appendix (online only). Patients with uncontrolled or serious cardiovascular disease were not eligible, but those with common cardiovascular risk factors (uncontrolled hypertension or angina, congestive heart failure > 3 months before enrollment, and myocardial infarction > 6 months before enrollment) were eligible. The trial was approved by all institutional review boards and ethics committees. All patients gave written informed consent before random assignment in accordance with the Declaration of Helsinki.

### Evaluations

Analyses after a minimum follow-up of 5 years are presented (database lock: March 24, 2014). Complete cytogenetic response (CCyR) was defined as 0% Philadelphia chromosome-positive cells in  $\geq 20$  bone marrow metaphases. MMR and molecular responses MR<sup>4</sup> and MR<sup>4.5</sup> represent *BCR-ABL1* transcript levels of  $\leq 0.1\%$ ,  $\leq 0.01\%$ , and  $\leq 0.0032\%$  (IS), corresponding to a 3-log, 4-log, and 4.5-log reduction from a standardized baseline, respectively.<sup>10,20,21</sup> Missing samples and patients with atypical *BCR-ABL1* transcripts (not b2a2 or b3a2) were considered nonresponders. A central laboratory (MolecularMD, Portland, OR) performed molecular assessments. Treatment failure was defined as no hematologic response at 3 months, no complete hematologic response or no cytogenetic response at 6 months, no partial cytogenetic response at 12 months, no CCyR at 18 months, or progression at any time.<sup>20</sup> Protocol-defined disease progression, on the basis of guidelines available during protocol design,<sup>20</sup> included doubling of WBC count to greater than  $20 \times 10^9/L$ , loss of complete hematologic response, increase in Philadelphia chromosome-positive bone marrow metaphases to  $\geq 30\%$  from nadir, transformation to accelerated/blast phase (AP/BP), or death from any cause. Transformation to CML-AP/BP did not include clonal evolution.<sup>20</sup> Patients who agreed to follow-up (> 98% in each arm) continued to be observed for transformation and survival for up to 5 years. Expected patient life spans by treatment were calculated by applying the OS rate as a percentage of the life span of the general population without CML.<sup>22</sup> Poststudy CML treatment was to be captured for all patients. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.<sup>23</sup> Mutations were assessed at

discontinuation of study treatment in patients with sufficient *BCR-ABL1* cDNA for amplification using Sanger direct sequencing (MolecularMD).

### Statistical Considerations

Cumulative response rates were calculated using the cumulative incidence approach and Kaplan-Meier method. Comparisons of MR rates were performed using Cochran-Mantel-Haenszel testing methodology and stratified by Euro score. Unstratified comparison of rates by Euro score was performed using an exact test. Post hoc analyses compared response rates at various time points; therefore, *P* values are descriptive and unadjusted for multiple comparisons. PFS and OS were estimated using Kaplan-Meier analysis. For PFS, patients who discontinued the study without progression were censored at the date of their last on-study hematologic or cytogenetic evaluation. Progression and transformation data after study discontinuation were obtained for patients who agreed to follow-up. For OS, patients were censored on the date they were last known to be alive. Hazard ratios (HRs) were based on the Cox model.

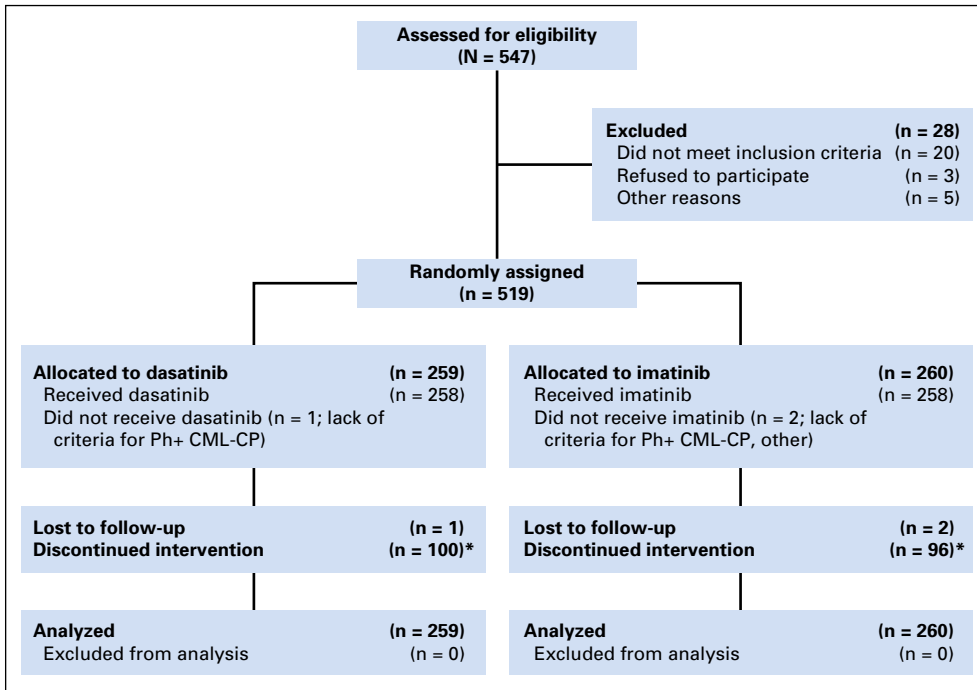
## RESULTS

### Patient Disposition

Of 519 patients enrolled onto DASISION, 259 were randomly assigned to receive dasatinib, and 260 were randomly assigned to receive imatinib (Fig 1), with well-balanced baseline characteristics in each arm.<sup>1</sup> After 5 years, 61% of dasatinib-treated patients and 63% of imatinib-treated patients were still on initial therapy (Table 1 and Appendix Table A1, online only). The median average daily dose for treated patients was 99 mg (range, 21 to 139 mg) for dasatinib and 400 mg (range, 125 to 741 mg) for imatinib. Patients who discontinued the study as a result of study closure received 99 mg (range, 56 to 139 mg) of dasatinib and 400 mg (range, 287 to 741 mg) of imatinib, and patients who discontinued the study as a result of all other reasons received 95 mg (range, 21 to 127 mg) of dasatinib and 400 mg (range, 125 to 740 mg) of imatinib. After discontinuation, the most common subsequent treatments were imatinib (19%), nilotinib (9%), dasatinib (3%), and hydroxyurea (2%) for the dasatinib arm, and dasatinib (16%), imatinib (11%), nilotinib (9%), and hydroxyurea (3%) for the imatinib arm. All other poststudy CML treatments were reported for less than 2% of patients. Some patients continued the treatment received in DASISION after discontinuation from study drug.

### Efficacy

Cumulative, 5-year MMR and MR<sup>4.5</sup> rates were 76% and 42% for dasatinib and 64% and 33% for imatinib, respectively (*P* = .0022 and *P* = .0251, respectively; Fig 2). Proportions of randomly assigned patients with responses at 5 years in the dasatinib and imatinib arms were 28% and 26% for cCCyR, 52% and 49% for MMR, 39% and 28% for MR<sup>4</sup>, and 25% and 18% for MR<sup>4.5</sup>, respectively. At study end, patients were not required to provide samples for bone marrow cytogenetics, possibly leading to lower values for cCCyR in both arms. The achievement of MMR and MR<sup>4.5</sup> at any time by Euro score was also investigated (Appendix Fig A1, online only). Significant differences between dasatinib- and imatinib-treated patients were observed for MMR in the low-risk group (*P* < .001) and for MR<sup>4.5</sup> in the intermediate-risk group (*P* = .0218).



**Fig 1.** CONSORT diagram for the DASISION trial after a minimum follow-up of 5 years. CML-CP, chronic myeloid leukemia in chronic phase; Ph+, Philadelphia chromosome positive. (\*) Reasons for discontinuation are listed in Table 1.

Estimated 5-year OS was 91% for dasatinib and 90% for imatinib (HR, 1.01; 95% CI, 0.58 to 1.73; Appendix Fig A2, online only). In the analysis of expected life span by age at diagnosis, the age-adjusted life expectancy for patients with CML-CP in both arms of DASISION approached that for patients from an external, non-CML population<sup>22</sup> (Appendix Fig A3, online only). More imatinib-treated patients died as a result of CML-related causes (n = 17) compared with dasatinib-treated patients (n = 9); however, the related 5-year OS was not statistically significantly different (P = .1192; HR, 0.53; 95% CI, 0.24 to 1.19).

Estimated 5-year PFS was 85% for dasatinib and 86% for imatinib (HR, 1.06; 95% CI, 0.68 to 1.66; Appendix Fig A2).

Including follow-up beyond on-study treatment discontinuation (intent to treat), 4.6% and 7.3% of patients on dasatinib and imatinib, respectively, transformed to AP/BP by 5 years. Two patients in the imatinib group and none in the dasatinib group transformed between 3 and 5 years.

As reported previously, a higher percentage of dasatinib-treated patients achieved *BCR-ABL1* ≤ 10% (IS) at 3 months compared with imatinib-treated patients (84% and 64%, respectively).<sup>5</sup> The proportions of dasatinib-treated patients age 65 and younger and older than 65 years who achieved *BCR-ABL1* ≤ 10% (IS) at 3 months were similar, as were the proportions of

**Table 1.** Patient Status at 5 Years

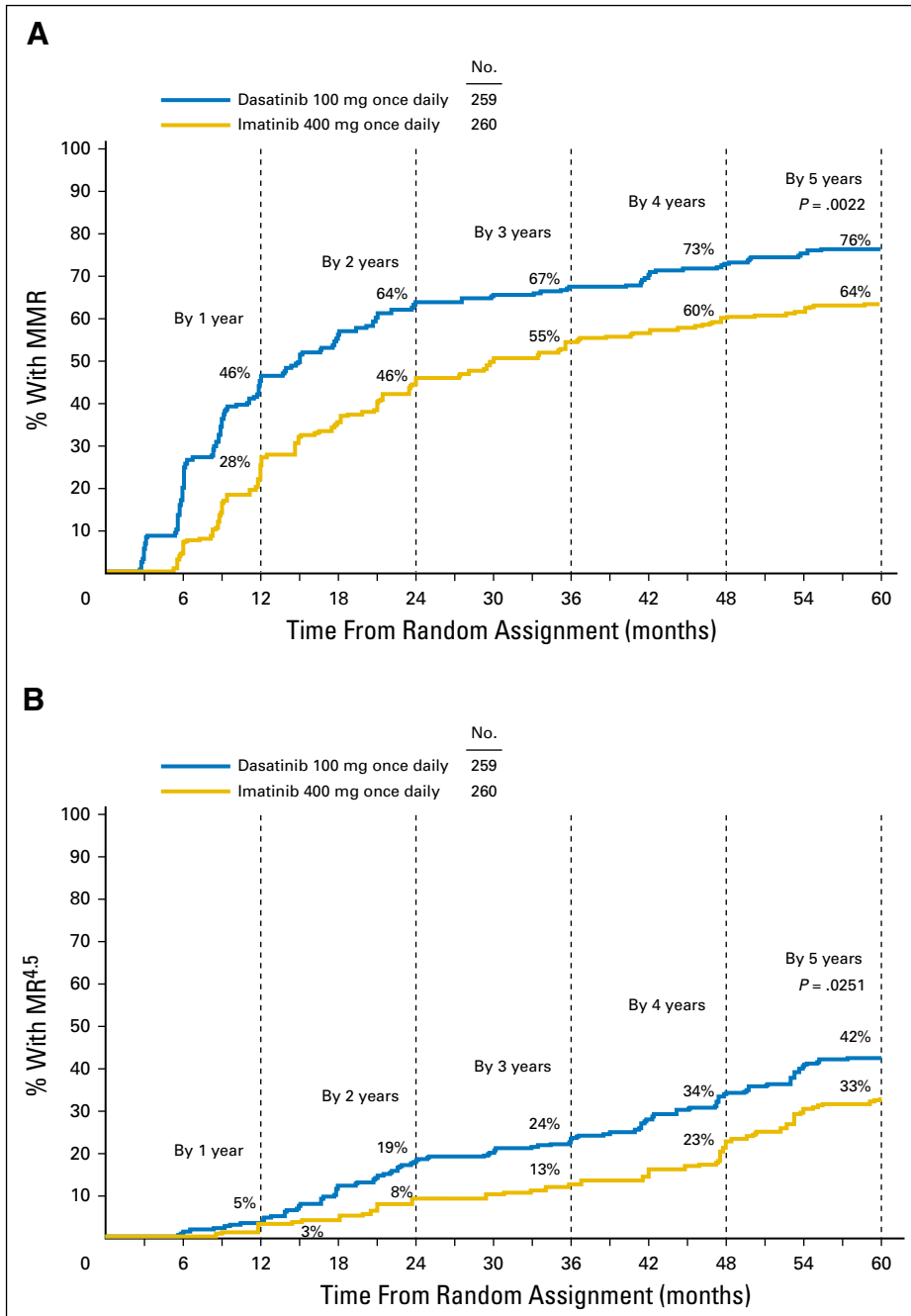
Status	No. of Patients (%)	
	Dasatinib 100 mg Once Daily (n = 258)	Imatinib 400 mg Once Daily (n = 258)
On initial therapy at study end	158 (61)	162 (63)
Discontinued		
Progression or treatment failure	28 (11)	36 (14)
Intolerance*	42 (16)	17 (7)
AE unrelated to study treatment	12 (5)	4 (2)
Poor compliance/nonadherence	1 (< 1)	7 (3)
Patient request	4 (2)	10 (4)
Withdrawal of consent	4 (2)	3 (1)
Lost to follow-up	1 (< 1)	2 (1)
Other	8 (3)†	16 (6)‡

Abbreviation: AE, adverse event.

\*As decided by investigator. Intolerance is defined as recurrent grade ≥ 3 hematologic toxicity or grade ≥ 2 nonhematologic toxicity requiring discontinuation despite dose reduction.

†Includes insufficient molecular response (n = 3), pregnancy (n = 2), loss of complete cytogenetic response (n = 1), increased *BCR-ABL1* (n = 1), and relocation to the United States (n = 1).

‡Includes no molecular response/loss of molecular response (n = 4), suboptimal response (n = 3), insufficient cytogenetic response (n = 2), investigator request (n = 2), pregnancy (n = 1), recurrence of blasts in bone marrow (n = 1), no complete molecular response (n = 1), no major molecular response (n = 1), and appearance of mutation (n = 1).



**Fig 2.** Cumulative response rates over time. The percentages of patients with (A) major molecular response (MMR) and (B) molecular response with a 4.5-log reduction in *BCR-ABL1* transcripts from baseline ( $MR^{4.5}$ ; *BCR-ABL1* transcript level  $\leq 0.0032\%$  [International Scale]) by 1, 2, 3, 4, and 5 years are shown.

imatinib-treated patients age 65 and younger and older than 65 years. In both arms, patients who achieved *BCR-ABL1*  $\leq 10\%$  (IS) at 3 months more often reached CCyR, MMR, and  $MR^{4.5}$  by 5 years (Table 2), had higher rates of OS and PFS (Fig 3), and had a lower transformation rate (3% v 14% to 15% in patients who did not achieve *BCR-ABL1*  $\leq 10\%$  at 3 months).

### Mutational Analysis

Testing for *BCR-ABL1* mutations was planned in all patients at treatment or study discontinuation (Appendix Table A2, online only). Of the available samples, 200 patients (81%) in the dasatinib arm and 214 patients (83%) in the imatinib arm had mutation

analysis performed. Mutations were identified in 15 (8%) of 200 patients and 19 (9%) of 214 patients in the dasatinib and imatinib arms, respectively. T315I mutations were identified in eight dasatinib-treated patients and no imatinib-treated patients. Most patients who had mutations discontinued treatment as a result of progression or treatment failure (dasatinib, n = 13 of 15 patients; imatinib, n = 14 of 19 patients).

### Safety

No new AEs were observed with dasatinib or imatinib by 5 years. Overall, most AEs reported with both drugs were grade 1 or 2; 15% of AEs reported with dasatinib and 11% of AEs reported

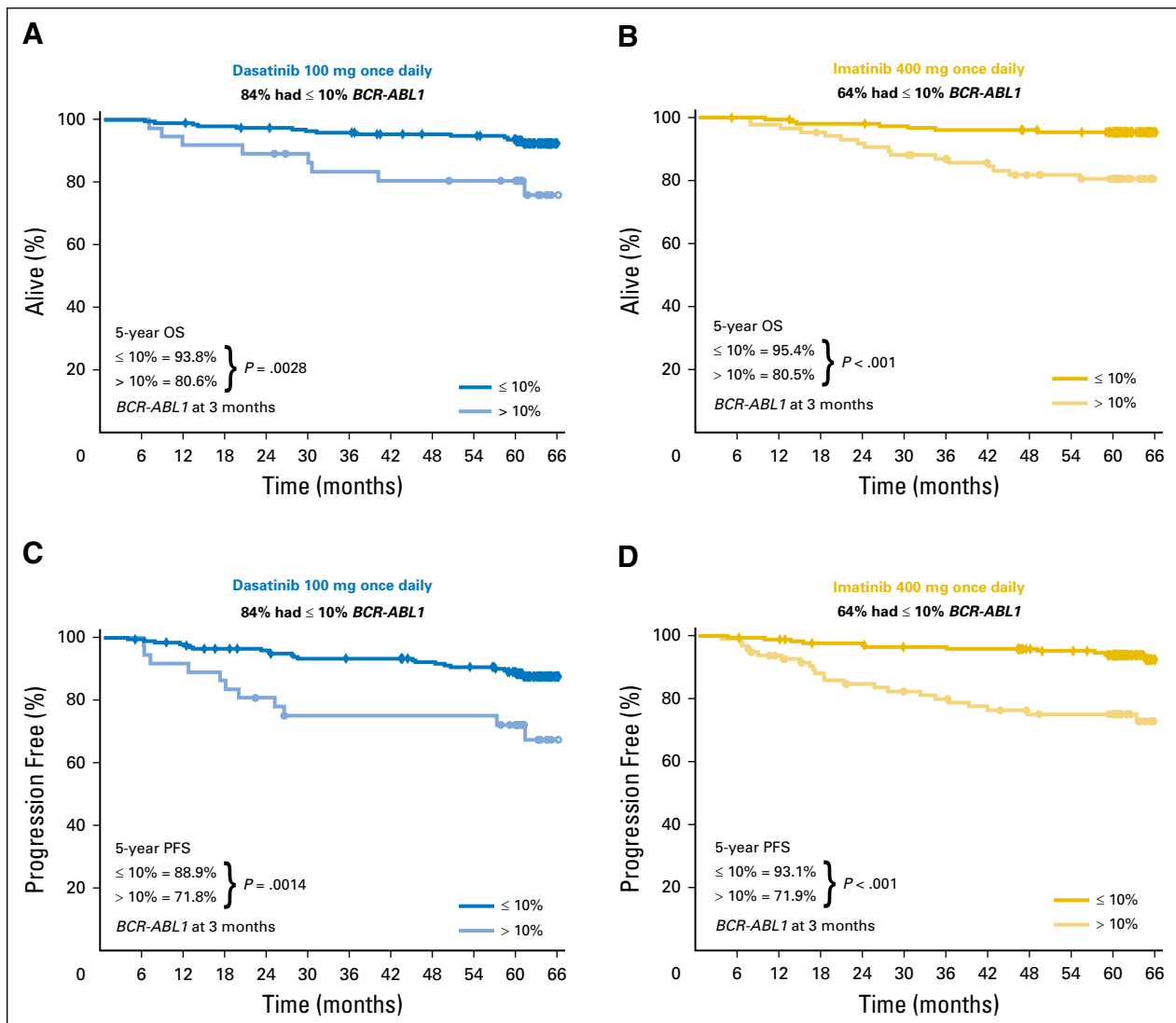
**Table 2.** Five-Year Responses by *BCR-ABL1* (IS) Transcript Levels at 3 Months

Response	% of Patients			
	Dasatinib 100 mg Once Daily (n = 259)		Imatinib 400 mg Once Daily (n = 260)	
	3-Month <i>BCR-ABL1</i> Transcript Level ≤ 10% (n = 198; 84%)	3-Month <i>BCR-ABL1</i> Transcript Level > 10% (n = 37; 16%)	3-Month <i>BCR-ABL1</i> Transcript Level ≤ 10% (n = 154; 64%)	3-Month <i>BCR-ABL1</i> Transcript Level > 10% (n = 85; 36%)
Complete cytogenetic response	94	41	92	59
Major molecular response	87	38	81	41
MR <sup>4.5</sup>	54	5	48	12

Abbreviations: IS, International Scale; MR<sup>4.5</sup>, molecular response with a 4.5-log reduction in *BCR-ABL1* transcripts from baseline (*BCR-ABL1* transcript level ≤ 0.0032% [IS]).

with imatinib were grade 3 or 4. Rates of grade 3 or 4 hematologic AEs were higher for dasatinib versus imatinib (neutropenia, 29% v 24%; anemia, 13% v 9%; and thrombocytopenia, 22% v 14%,

respectively). Except for pleural effusion, drug-related, non-hematologic AEs were reported less frequently with dasatinib than imatinib or were comparable (Fig 4). Drug-related AEs were



**Fig 3.** Estimated 5-year (A, B) overall survival (OS) and (C, D) progression-free survival (PFS) by molecular response at 3 months for both treatment arms. OS and PFS were calculated using patients on study treatment and in follow-up after discontinuation of randomly assigned treatment.

manageable, leading to discontinuation in 16% and 7% of patients in the dasatinib and imatinib arms, respectively.

Drug-related pleural effusion was more common with dasatinib (28%) than with imatinib (0.8%). Sixty-six patients (26%) experienced grade 1 or 2, seven patients (3%) experienced grade 3 or 4, and no patients experienced grade 5 pleural effusion on dasatinib. Pleural effusion developed in approximately 8% of at-risk dasatinib-treated patients in year 1 of therapy and was comparable each subsequent year (Appendix Table A3, online only). The percentage of patients who developed pleural effusions was higher in patients age  $\geq 65$  years (15 of 25 patients; 60%) compared with patients younger than age 65 years (58 of 233 patients; 25%). Drug-related pleural effusion was managed with dose interruption (62%) and/or dose reduction (41%), diuretics (47%), corticosteroids (32%), or therapeutic thoracentesis (12%). Only 15 patients (6%) discontinued dasatinib and only one patient discontinued imatinib as a result of pleural effusion. Pleural effusion did not impair the ability of patients to obtain a response; 71 patients (96%) achieved a cCCyR, 61 (82%) achieved an MMR, and 37 (50%) achieved an MR<sup>4,5</sup>.

Pulmonary hypertension (PH), which was diagnosed with two-dimensional echocardiography, was reported in 14 dasatinib-treated patients (5%) and one imatinib-treated patient (0.4%). Of the 14 PH diagnoses in dasatinib-treated patients, nine patients had pleural effusion. Right heart catheterization is recommended by the WHO to confirm moderate to severe precapillary PH and establish a diagnosis of pulmonary arterial hypertension (PAH).<sup>24</sup> However, only one dasatinib-treated patient with PH had this procedure performed, and it did not support a diagnosis of PAH. The remaining 13 patients with a PH diagnosis were not evaluated according to these criteria. Of the 14 PH diagnoses, 12 were drug related.

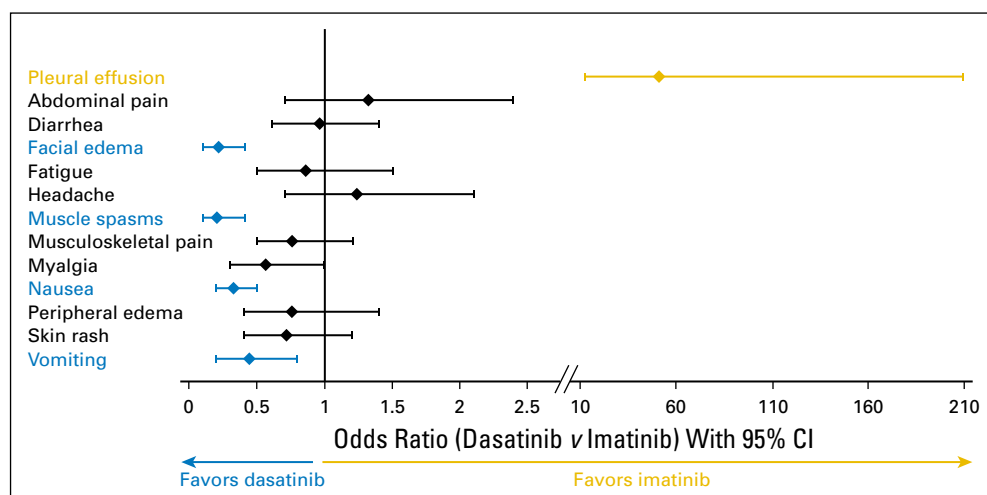
Because arterial ischemic events have been described during TKI therapy for CML,<sup>25</sup> cardiovascular, cerebrovascular, and peripheral vascular events were evaluated. Arterial ischemic events were uncommon in both the dasatinib (5%) and imatinib (2%) treatment arms (Appendix Table A4, online only). Seven of 10 cardiovascular ischemic events occurred within year 1 of dasatinib therapy; most patients restarted dasatinib without a recurrent

event. Additionally, two dasatinib-treated patients (imatinib,  $n = 0$ ) had a transient ischemic attack, and two imatinib-treated patients (dasatinib,  $n = 0$ ) had peripheral arterial disease. No patients experienced a stroke.

Twenty-six patients (10%) died in each arm by 5 years, a fraction within 30 days of their last treatment (eight patients [3%] in the dasatinib arm and five patients [2%] in the imatinib arm). Four deaths, three in dasatinib-treated patients and one in imatinib-treated patients, were reported after the start of subsequent CML therapy ( $n = 3$  on nilotinib;  $n = 1$  on nilotinib and imatinib after dasatinib discontinuation). Overall, causes of death included cardiovascular disease (dasatinib,  $n = 2$ ; imatinib,  $n = 1$ ); disease progression (dasatinib,  $n = 9$ ; imatinib,  $n = 17$ ); infection (dasatinib,  $n = 11$ ; imatinib,  $n = 1$ ); other malignancy, septic shock and cardiac failure, multiorgan failure, and whole-body swelling (dasatinib,  $n = 1$  each); stem-cell transplantation complications and unknown cause (imatinib,  $n = 2$  each); and severe chest pain, clinical deterioration and decrease in performance status, and fatal bleeding (imatinib,  $n = 1$  each). Four of 11 dasatinib-treated patients who died of infection died within 30 days of their last dose (*Klebsiella* meningococcal meningitis, sepsis, pneumonia, and unknown cause). The remaining seven patients died of various forms of infection (encephalitis, aspiration pneumonia, pulmonary infection, jaundice/malarial fever, sepsis, septic shock, and unknown cause) between 69 days and 4.5 years after their last dose, with two patients having transformed to AP/BP before death. Only one patient who died as a result of infection had neutropenia, and this patient discontinued dasatinib more than 4 years before death.

## DISCUSSION

The final study results from DASISION confirm that dasatinib-treated patients have high MR rates and that the achievement of  $BCR-ABL1 \leq 10\%$  (IS) at 3 months is predictive of significantly higher PFS and OS rates. The dasatinib arm had more patients achieve  $BCR-ABL1 \leq 10\%$  (IS) at 3 months and fewer CML-related deaths (nine of 26 patients  $v$  17 of 26 patients in dasatinib and imatinib arms, respectively). The benefit of dasatinib has been



**Fig 4.** Drug-related, nonhematologic adverse events (AEs) reported in  $\geq 10\%$  of patients. Odds ratios (dasatinib  $v$  imatinib) with 95% CIs are shown for AEs that occurred in  $\geq 10\%$  of patients. Blue favors dasatinib, and gold favors imatinib.

confirmed in additional randomized trials,<sup>26-28</sup> making the data supporting the overall benefit with dasatinib robust.

PFS and OS rates remain high and comparable between the two treatment arms, with more dasatinib patients achieving early treatment milestones. Patients with CML are now living almost as long as the general population.<sup>29</sup> Therefore, given high OS rates (approximately 90% at 5 years) and a majority of patients achieving CCyR, a larger population over a longer period of time may demonstrate a statistically significant survival difference. Another possible explanation for indistinguishable survival benefit is that 26% of patients were treated with the second-generation TKIs dasatinib (16%) or nilotinib (9%) after discontinuation of imatinib, which can rescue patients with imatinib failure.

Notably, in an intent-to-treat analysis, a disproportionate number of dasatinib-treated patients (n = 11) died as a result of infection compared with imatinib-treated patients (n = 1). Most infection deaths (n = 7 of 11 deaths) occurred between 69 days and 4.5 years after dasatinib was discontinued, including five patients who were receiving nilotinib or imatinib at the time of infection. Prior studies with dasatinib as initial therapy for CML have not reported a significant increase in risk of infections.<sup>27,28,30,31</sup> However, follow-up for these studies at the time of this report was either short or included only preliminary results. It will be important to prospectively and intentionally look at a possible imbalance in the occurrence of infections and, if present, determine a possible mechanism(s) for dasatinib-related infectious complications.

Few patients in either arm developed *BCR-ABL1* mutations. Different numbers of patients with mutations were identified here and in the 3-year mutational analysis of DASISION. Mutations assessed in the 3-year report were from a more diverse patient population, those with an on-treatment event (no cCCyR and no MMR within 12 months, five-fold increase in *BCR-ABL1* with loss of MMR, or loss of CCyR).<sup>32</sup> Here, T315I mutations were identified with dasatinib (n = 8) but not imatinib. Previous reports have demonstrated a 2% rate of T315I mutations after a median of 31 months on imatinib,<sup>33</sup> making the absence of this mutation in DASISION unexpected. One possible explanation for the disparity in T315I mutations between the two study arms is the decreased diversity in mutations that are resistant to dasatinib versus those that are resistant to imatinib, resulting in fewer mutants to dominate resistance mechanisms. It has been suggested that some mutations (ie, Y253H/F, E255K) may confer higher transformation potency in vitro than others (ie, T315I).<sup>32</sup> If true, one could speculate that the more proliferative clones would emerge. However, if these were suppressed by dasatinib, less proliferative, unsuppressed clones would predominate. Further studies are required to investigate this hypothesis. Most patients with mutations discontinued treatment because of progression or treatment failure, consistent with the 3-year analysis.<sup>32</sup>

The safety profile for dasatinib remains consistent, with no new safety signals identified after 5 years. Other than pleural effusion, the most common drug-related nonhematologic AEs were either similar between dasatinib and imatinib or lower with dasatinib. Pleural effusion was more common with dasatinib, occurred throughout this trial, and led to discontinuation in 6% of

patients. Almost all patients (96%) with pleural effusion achieved cCCyR, and 82% achieved MMR. These results suggest that, with adequate management, patients with pleural effusion may be able to remain on dasatinib. Serious, but rare, AEs have been reported with use of TKIs in CML, including hepatotoxicity<sup>34</sup> and renal dysfunction with imatinib,<sup>35</sup> PAH with dasatinib,<sup>24,36</sup> cardiac and vascular events with nilotinib,<sup>37</sup> and arterial and venous thrombosis and occlusions with ponatinib.<sup>38</sup> Some dasatinib-treated patients experienced PH. There were no reports of PAH fitting the criteria defined by WHO, which require right heart catheterization, although this procedure was only attempted in one patient, making the evaluation of true PAH incidence in this report inaccurate. As previously reported,<sup>39</sup> there may be an association between PH and pleural effusion because nine of 14 patients with PH also had pleural effusion. Awareness and investigation of PH are important aspects of proper management of dasatinib-treated patients.

Arterial ischemic events were not common in either treatment arm. No dasatinib-treated patients experienced peripheral arterial disease. Rates of cardiovascular ischemic events on dasatinib (4%) and imatinib (2%) were similar to those reported in the general population.<sup>40,41</sup> Nonetheless, physicians should be aware of these cardiovascular ischemic events, effectively manage comorbidities, and identify these events promptly.

AEs have been reported to increase nonadherence to TKIs.<sup>42,43</sup> The proportion of patients in DASISION who discontinued dasatinib or imatinib as a result of poor compliance or noncompliance was small. It is currently unclear whether patients treated in community practices would have similarly low levels of noncompliance to TKIs outside of a clinical trial. Given that noncompliance has been shown to negatively affect treatment responses and outcomes,<sup>43-46</sup> it is an important question to address in future studies to support successful treatment of CML.

In summary, the final, long-term results from DASISION demonstrated that patients taking dasatinib had faster and deeper MRs than patients taking imatinib. However, at the time of this final report, PFS and OS rates were similar for both cohorts. There were no new safety signals observed with dasatinib through 5 years or with longer follow-up. These results suggest that first-line dasatinib should continue to be considered a standard first-line therapy for patients with newly diagnosed CML-CP.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

#### AUTHOR CONTRIBUTIONS

**Conception and design:** All authors  
**Provision of study materials or patients:** All authors  
**Collection and assembly of data:** All authors  
**Data analysis and interpretation:** All authors  
**Manuscript writing:** All authors  
**Final approval of manuscript:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial

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**Jorge E. Cortes**

**Consulting or Advisory Role:** ARIAD, Bristol-Myers Squibb, Novartis, Pfizer

**Research Funding:** ARIAD (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst), Pfizer (Inst), Teva (Inst)

**Giuseppe Saglio**

**Consulting or Advisory Role:** Bristol-Myers Squibb, Novartis, ARIAD, Pfizer

**Hagop M. Kantarjian**

**Research Funding:** Pfizer (Inst), ARIAD, Amgen (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst)

**Michele Bacarani**

**Honoraria:** Bristol-Myers Squibb

**Consulting or Advisory Role:** Bristol-Myers Squibb

**Speakers' Bureau:** Bristol-Myers Squibb

**Jiří Mayer**

**Consulting or Advisory Role:** Novartis, Bristol-Myers Squibb

**Research Funding:** Novartis, Bristol-Myers Squibb

**Concepción Boqué**

**Honoraria:** Novartis, Bristol-Myers Squibb

**Consulting or Advisory Role:** Novartis

**Travel, Accommodations, Expenses:** Novartis, Bristol-Myers Squibb, Celgene

**Neil P. Shah**

**Research Funding:** Bristol-Myers Squibb, ARIAD, Pfizer, Daiichi Sankyo, Plexxikon

**Charles Chuah**

**Honoraria:** Bristol-Myers Squibb, Novartis

**Luis Casanova**

No relationship to disclose

**Brigid Bradley-Garelik**

**Employment:** Bristol-Myers Squibb

**Stock or Other Ownership:** Bristol-Myers Squibb

**George Manos**

**Employment:** Bristol-Myers Squibb

**Stock or Other Ownership:** Bristol-Myers Squibb

**Andreas Hochhaus**

**Honoraria:** Bristol-Myers Squibb, Novartis, Pfizer, ARIAD, Omniamed  
**Consulting or Advisory Role:** Novartis, Bristol-Myers Squibb, Pfizer, ARIAD

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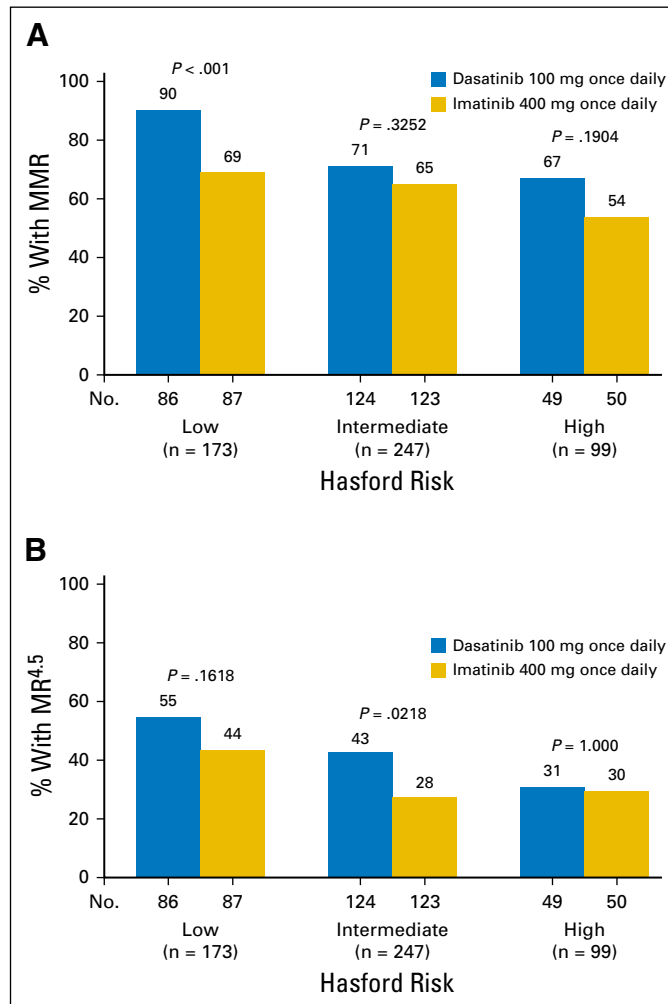
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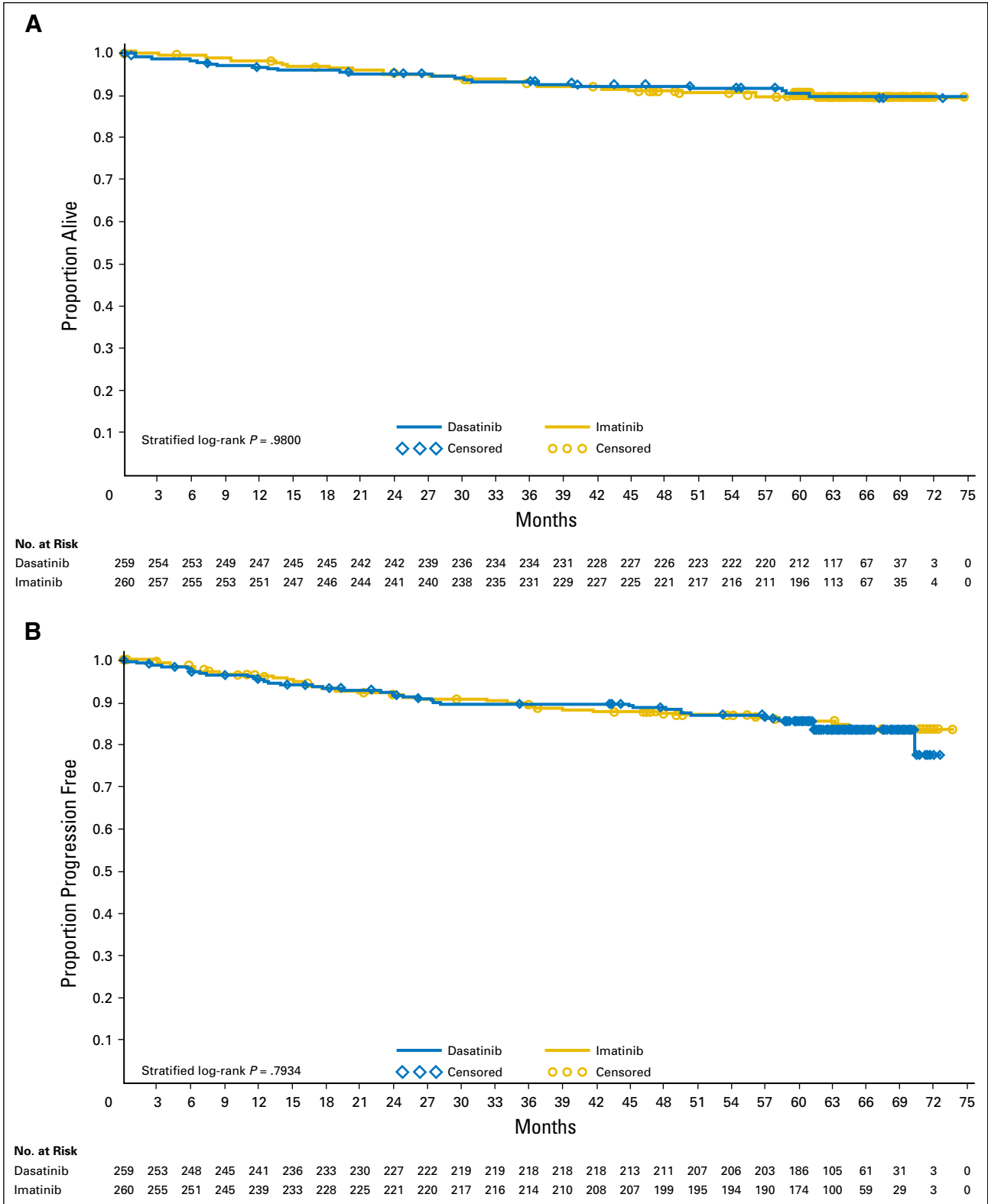
### Appendix

#### Methods

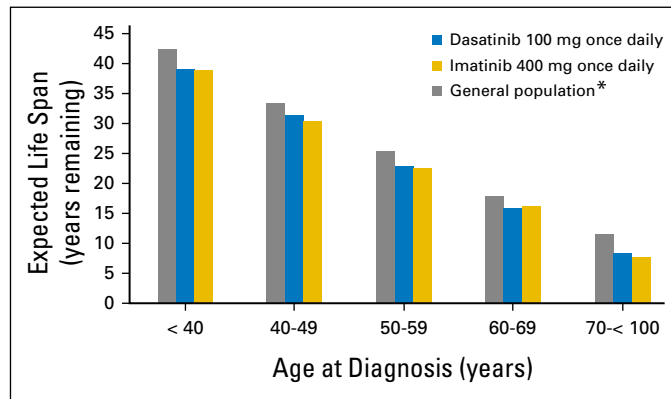
Key exclusion criteria were as follows: serious, uncontrolled medical disorders or active infections; a corrected QT interval of more than 450 milliseconds; history of a serious bleeding disorder unrelated to chronic myeloid leukemia; previous or concurrent malignancy (excluding adequately treated basal or squamous cell skin cancer, cervical carcinoma in situ, or stage I or II cancer in remission, or patients with previous cancer who have been disease free for  $\geq 3$  years); previous chemotherapy for peripheral stem-cell mobilization; and pleural effusion at baseline.



**Fig A1.** (A) Major molecular response (MMR) and (B) molecular response with a 4.5-log reduction in *BCR-ABL1* transcripts from baseline ( $MR^{4.5}$ ; *BCR-ABL1* transcript level  $\leq 0.0032\%$  [International Scale]) at any time by Euro (Hasford) risk score.



**Fig A2.** Kaplan-Meier curves for (A) overall survival and (B) progression-free survival in both treatment arms. A sensitivity analysis of progression-free survival was performed to include patients who discontinued treatment and experienced progression or died on treatment or during follow-up.



**Fig A3.** Expected survival by age at diagnosis for both treatment arms and a general population of patients without chronic myeloid leukemia. (\*) Expected life span estimates were adapted from Ludwig et al.<sup>22</sup>

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**Table A1.** AEs Leading to Treatment Discontinuation Regardless of Relationship to Study Treatment

AE	No. of Patients (%)	
	Dasatinib 100 mg Once Daily (n = 258)	Imatinib 400 mg Once Daily (n = 258)
Patients* with any AEt leading to discontinuation	50 (19)	26 (10)
Pleural effusion	15 (6)	1 (< 1)
Pulmonary hypertension	6 (2)	0
Blast phase in myelogenous leukemia	3 (1)	3 (1)
Thrombocytopenia	3 (1)	2 (1)
Dyspnea	2 (1)	0
Leukopenia	2 (1)	0
Acute myocardial infarction	2 (1)	0
Pericardial effusion	2 (1)	0
Chest pain	2 (1)	0
Diarrhea	1 (< 1)	1 (< 1)
Acute renal failure	1 (< 1)	1 (< 1)
Pleuritis	1 (< 1)	0
Pneumothorax	1 (< 1)	0
Pulmonary embolism	1 (< 1)	0
Lung adenocarcinoma	1 (< 1)	0
Transitional-cell carcinoma	1 (< 1)	0
Peripheral edema	1 (< 1)	0
Abdominal discomfort	1 (< 1)	0
Abdominal pain	1 (< 1)	0
Colitis	1 (< 1)	0
Pancreatic disorder	1 (< 1)	0
Bronchopneumonia	1 (< 1)	0
Infection	1 (< 1)	0
Meningoencephalitis, bacterial	1 (< 1)	0
Creatine phosphokinase increased	1 (< 1)	0
ECG QT prolonged	1 (< 1)	0
Diabetes mellitus	1 (< 1)	0
Renal failure	1 (< 1)	0
Optic neuritis	1 (< 1)	0
Blast cell proliferation	0	2 (1)
Neutropenia	0	2 (1)
Rash	0	2 (1)
Colon cancer	0	1 (< 1)
Nodal marginal zone B-cell lymphoma	0	1 (< 1)
Rectal carcinoma	0	1 (< 1)
Myocardial infarction	0	1 (< 1)
Asthenia	0	1 (< 1)
Performance status decreased	0	1 (< 1)
Alopecia	0	1 (< 1)
Erythema	0	1 (< 1)
Palmar-plantar erythrodysesthesia	0	1 (< 1)
Maculopapular rash	0	1 (< 1)
ALT increased	0	1 (< 1)
AST increased	0	1 (< 1)
Hypocalcemia	0	1 (< 1)
Hypophosphatemia	0	1 (< 1)
Cytogenetic abnormality	0	1 (< 1)
Toxic hepatitis	0	1 (< 1)

Abbreviation: AE, adverse event.

\*Patients may have had more than one AE.

†AEs listed were reported by investigators at the time of treatment discontinuation and were defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient. AEs did not necessarily have a causal relationship with study treatment.

**Table A2.** *BCR-ABL1* Mutations at the Time of Discontinuation

Mutation	Dasatinib 100 mg Once Daily (n = 258)			Imatinib 400 mg Once Daily (n = 258)		
	Progression (n = 18)	Treatment Failure (n = 10)	Other* (n = 219)	Progression (n = 23)	Treatment Failure (n = 14)	Other† (n = 221)
Mutation analysis attempted, No. (%)	18 (100)	9 (90)	173 (79)	21 (91)	13 (93)	180 (81)
No. of patients with mutation(s)‡	10	3	2	10	4	5
Specific mutations, No.						
M244V	0	0	0	1	0	1
L248V	0	0	0	0	1	0
Y253H	0	0	0	0	1	0
V299L	2	2	1	0	0	0
G250E	0	0	0	0	1	2
E255K/V	0	0	0	1	1	0
D276G	0	0	0	2	0	0
T315I	6	1	1	0	0	0
F317I/L	3	0	1	0	0	2
E355G	0	0	0	1	1	0
L359C/I/V	0	0	0	4	0	0
L387M	0	0	0	1	0	0
H396P/R	0	0	0	1	0	1
E450G	0	0	0	0	1	0
No mutation, No.	8	5	24	11	8	37
No amplification,§ No.	0	1	147	0	1	138

\*Includes study closure (n = 147); adverse event related to study drug (n = 42); adverse event unrelated to study drug (n = 12); withdrawal of consent and patient request (n = 4 each); insufficient molecular response (n = 3); pregnancy (n = 2); and poor compliance/noncompliance, lost to follow-up, loss of complete cytogenetic response, increased *BCR-ABL1*, and relocation to the United States (n = 1 each).

†Includes study closure (n = 162); adverse event related to study drug (n = 17); patient request (n = 10); poor compliance/noncompliance (n = 7); adverse event unrelated to study drug and no molecular response/loss of molecular response (n = 4 each); withdrawal of consent and suboptimal response (n = 3 each); lost to follow-up, insufficient cytogenetic response, and investigator request (n = 2 each); and pregnancy, recurrence of blasts in bone marrow, no complete molecular response, no major molecular response, and appearance of mutation (n = 1 each).

‡Mutations identified in dasatinib-treated patients were T315I (n = 8), V299L (n = 5), and F317I/L (n = 3). Mutations identified in imatinib-treated patients were F359C/I/V (n = 4); G250E (n = 3); M244V, E255K/V, D276G, F317L, E355G, and H396P/R (n = 2 each); and L248V, Y253H, L387M, and E450G (n = 1 each).

§Insufficient *BCR-ABL1* cDNA to assess mutations as a result of ongoing response.

**Table A3.** Incidence of PE in At-Risk Dasatinib-Treated Patients by the Year They Were Reported in the Study

Year of Treatment	No. of Patients at Risk	No. of PE Incidents (%)
≤ 1 year	258	20 (8)
>1 to ≤ 2 years	209	13 (6)
>2 to ≤ 3 years	184	11 (6)
>3 to ≤ 4 years	160	14 (9)
>4 to ≤ 5 years	141	12 (9)

Abbreviation: PE, pleural effusion.

**DASISION Final 5-Year Study Results**

**Table A4.** Any-Cause Arterial Ischemic Events

Event	No. of Patients (%)					
	Dasatinib 100 mg Once Daily (n = 258)			Imatinib 400 mg Once Daily (n = 258)		
	Any Grade	Grade 3 or 4	Grade 5	Any Grade	Grade 3 or 4	Grade 5
Any ischemic event	12 (5)	7 (3)	2 (1)	6 (2)	3 (1)	1 (< 1)
CV event*	10 (4)	5 (2)	2 (1)	4 (2)	2 (1)	1 (< 1)
TIA	2 (1)	2 (1)	0	0	0	0
PAD	0	0	0	2 (1)	1 (< 1)	0

Abbreviations: CV, cardiovascular; PAD, peripheral arterial disease; TIA, transient ischemic attack.

\*Includes myocardial infarction, angina pectoris, coronary artery disease, and acute coronary syndrome.