Treatment of chronic-phase chronic myeloid leukemia in patients randomized to dasatinib or imatinib after suboptimal responses to 3 months of imatinib therapy: final 5-year results from DASCERN

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Abstract

Early molecular response at 3 months is predictive of improved overall survival and progression-free survival in patients with chronic myeloid leukemia in the chronic phase. Although about one-third of patients treated with first-line imatinib do not achieve an early molecular response, long-term overall survival and progression-free survival are still observed in most patients. DASCERN (NCT01593254) is a prospective, phase IIb, randomized trial evaluating a switch to dasatinib in patients who have not achieved an early molecular response after 3 months of treatment with first-line imatinib. Early analysis demonstrated an improved major molecular response (MMR) rate at 12 months with dasatinib *versus* imatinib (29% *vs*. 13%, *P*=0.005). Here, we report results from the final 5-year follow-up. In total, 174 patients were randomized to dasatinib and 86 to remain on imatinib. Forty-six (53%) patients who remained on imatinib but subsequently experienced failure were allowed to cross over to dasatinib per protocol. At a minimum follow-up of 60 months, the cumulative MMR rate was significantly higher in patients randomized to dasatinib than those randomized to imatinib (77% *vs*. 44%, *P*<0.001). The median time to MMR was 13.9 months with dasatinib *versus* 19.7 months with imatinib. The safety profile was consistent with previous reports. These results demonstrate that switching to dasatinib after a suboptimal response to imatinib at 3 months leads to faster MMR, provides earlier deep molecular responses, and improves some outcomes in patients with chronic myeloid leukemia in the chronic phase.

Introduction

For patients with chronic myeloid leukemia in the chronic phase (CML-CP), achievement of early molecular response (EMR), defined as *BCR::ABL1* ≤10% International Scale (IS), at 3 months after initiating first-line treatment with a tyrosine kinase inhibitor (TKI) increases the probability of achieving deep molecular response (DMR) and is prognostic of favorable long-term progression-free survival (PFS) and overall survival (OS).[1-7] Prior studies have shown that in patients with suboptimal responses following frontline imatinib treatment, switching to the second-generation TKI nilotinib can result in improved responses.[8,9] Both NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

and European LeukemiaNet (ELN) recommendations for CML consider achievement of EMR an optimal response to frontline therapy.[10,11] One-third of patients treated with imatinib in the first line, however, do not achieve EMR.[12] The optimal management of these patients is not well defined, mostly due to the lack of available prospective studies addressing this clinical scenario.

In patients with newly diagnosed CML-CP, dasatinib demonstrated superior rates of major molecular response (MMR) (*BCR::ABL1* ≤0.1% [IS]) and DMR (MR^4: *BCR::ABL1* ≤0.01% [IS] and MR$^{4.5}$: *BCR::ABL1* ≤0.0032% [IS]) compared with imatinib.[1] These data suggest that a switch to dasatinib may be beneficial for patients who do not achieve EMR with imatinib after 3 months on treatment.

DASCERN (NCT01593254) is the first prospective, phase IIb randomized trial to examine the benefit of switching to dasatinib early in patients who have not achieved EMR after 3 months of first-line imatinib.[13] In an early analysis, the MMR rate at 12 months (primary endpoint) was over twice as high with dasatinib as with imatinib (29% *vs*. 13%, respectively; *P*=0.005).[13] The benefits of dasatinib *versus* imatinib were maintained at the 3-year follow-up of DASCERN in which the cumulative MMR rate was greater with dasatinib than with imatinib (67% and 40%, respectively), as was the cumulative rate of MR$^{4.5}$ (27% and 20%, respectively).[14] PFS and OS remained similar between the treatment arms.[14] The early switch from imatinib to dasatinib did not increase the incidence of treatment-emergent adverse events.[14] Here, we report results from the final 5-year follow-up of DASCERN.

Methods

Study design and eligibility

DASCERN is a randomized, open-label, multinational, phase IIb trial in adults with CML-CP (*Online Supplementary Figure S1*). The full study design and eligibility criteria have been published previously.[13] Briefly, eligible patients were aged ≥18 years, had a complete hematologic response but *BCR::ABL1* >10% (IS) at 3 months (confirmed by a central laboratory) after beginning first-line imatinib (400 mg once daily), and had an Eastern Cooperative Oncology Group performance status of 0-2.

Patients were randomized 2:1 to switch to dasatinib (100 mg once daily) or continue imatinib (≥400 mg once or twice daily with the option of dose escalation) ≤8 weeks after failure of therapy to meet EMR. Randomization occurred ≤8 weeks after the 3-month molecular assessment and was stratified by Sokal score (high, intermediate, low, unknown) and time from 3-month molecular assessment to randomization (≤4 *vs*. >4 weeks). Dose escalation for suboptimal responses (per ELN 2013 criteria) was permitted in both arms per investigator's discretion, provided no treatment intolerance.[15] Patients who remained on imatinib but subsequently experienced treatment failure per ELN 2013 recommendations (identified by the investigator) were allowed to cross over to dasatinib unless they had documented *BCR::ABL1* mutations resistant to dasatinib.[15]

Patients were followed every 3 months for 24 months, then every 6 months until month 60, then annually. Here, results are reported after the time since the last patient's first visit had equaled or surpassed 5 years.

All patients provided written informed consent in accordance with the Declaration of Helsinki and institutional guidelines before study entry. The study protocol was approved by the institutional review board and/or ethics committee of each participating center and the competent national authority.

Study endpoints

The primary endpoint, MMR at 12 months, has been previously reported.[13] Secondary endpoints were time to MMR, time to MR$^{4.5}$, PFS, and OS. Tertiary endpoints included MMR, MR^4, MR$^{4.5}$, safety, tolerability, benefit (assessed by response rates and survival) of an early switch to dasatinib after lack of EMR with imatinib *versus* a later switch after imatinib failure (per ELN 2013 recommendations), assessing development of *BCR::ABL1* mutations in both arms, and correlation of treatment adherence with disease response. Patients who discontinued study treatment had to be followed for outcome and/or survival data as required until death or conclusion of the study, although nine patients withdrew their consent to continue in the study, and 14 were lost to follow-up.

Evaluations and definitions

Time to MMR/MR$^{4.5}$ was the time from randomization to first polymerase chain reaction confirmation of MMR/MR$^{4.5}$ in all patients. PFS was the time from randomization to transformation to accelerated phase or blast phase (CML-AP/BP) or death from any cause, whichever occurred first. OS was the time from randomization to death. Safety and tolerability were reported descriptively with adverse events and serious adverse events assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Low, medium, or high treatment adherence was determined by the Morisky Medication Adherence Scale-8 items, a validated self-reported measure of medication adherence.

Statistical analysis

The intent-to-treat (ITT) population comprised all patients initially randomized to each arm, regardless of crossover. Time-to-event endpoints were estimated using Kaplan-Meier and Brookmeyer-Crowley methods, and were compared between arms using a two-sided stratified log-rank test. PFS and OS sensitivity analysis was performed; patients who crossed over to dasatinib from imatinib failure were censored at the date of crossover.

Table 1. Baseline characteristics.

Characteristic	Randomized to dasatinib N=174	Randomized to imatinib N=86	Imatinib (with crossover to dasatinib) N=46	Imatinib (no crossover) N=40
Age in years, median (range)	35 (18-82)	40 (18-73)	41 (18-70)	39 (19-73)
Age group, N (%)				
<65 years	166 (95.4)	82 (95.3)	45 (97.8)	37 (92.5)
≥65 years	8 (4.6)	4 (4.7)	1 (2.2)	3 (7.5)
Male, N (%)	133 (76.4)	70 (81.4)	36 (78.3)	34 (85.0)
Race, N (%)				
White	36 (20.7)	15 (17.4)	9 (19.6)	6 (15.0)
Black or African-American	4 (2.3)	3 (3.5)	3 (6.5)	0
Asian	127 (73.0)	63 (73.3)	32 (69.6)	31 (77.5)
Other	7 (4.0)	5 (5.8)	2 (4.3)	3 (7.5)
ECOG PS,[a] N (%)				
0	142 (81.6)	75 (87.2)	38 (82.6)	37 (92.5)
1	27 (15.5)	10 (11.6)	7 (15.2)	3 (7.5)
2	0	1 (1.2)	1 (2.2)	0
Sokal score, N (%)				
Low	47 (27.0)	26 (30.2)	10 (21.7)	16 (40.0)
Intermediate	51 (29.3)	26 (30.2)	17 (37.0)	9 (22.5)
High	44 (25.3)	19 (22.1)	11 (23.9)	8 (20.0)
Unknown	32 (18.4)	15 (17.4)	8 (17.4)	7 (17.5)
Time from diagnosis to randomization in months, median (range)[b]	4.4 (3.2-9.8)	4.4 (3.4-9.5)	4.5 (3.4-9.5)	4.3 (3.6-5.3)

[a]There were five patients randomized to dasatinib for whom the ECOG PS was not reported. [b]Imatinib monotherapy was started ≤6 months after diagnosis and randomization occurred ≤8 weeks after the 3-month molecular analysis. ECOG PS: Eastern Cooperative Oncology Group performance status.

Results

Baseline characteristics and patients disposition

A total of 1,128 patients were screened, of whom 262 were enrolled between September 2012 and January 2017 from 101 study sites across 15 countries. Of the enrolled patients, 174 were randomized to dasatinib and 86 to remain on imatinib. Baseline characteristics have been reported previously.[13] Median age was 37 years, and 73% of patients were Asian (Table 1).

At data cutoff (April 24, 2022), with a minimum follow-up of 60 months (median follow-up 80 months), all patients had discontinued the study, mostly due to study completion (N=176, 68%), study drug toxicity (N=26, 10%), or death (N=6, 2%) (Table 2, *Online Supplementary Figure S2*). Of the patients randomized to imatinib, 46 (53%) experienced subsequent treatment failure per ELN criteria and crossed over to the dasatinib arm. Twenty-one of these patients crossed over after failing to achieve an MMR, ten after loss of complete hematologic response or complete cytogenetic response, ten for other reasons, and five after loss of MMR with imatinib (Table 2); since the 3-year analysis, only one additional patient randomized to imatinib had crossed over to dasatinib. Kaplan-Meier estimate of the median (95% confidence interval [95% CI]) time to crossover was 9.5 (6.2-12.4) months. Median (range) treatment duration was 67.7 (0.1-104.1) months in patients randomized to dasatinib and 20.9 (0.9-94.5) months in patients randomized to imatinib. Median (range, interquartile range) daily dose was 99.7 (25.8-136.0, 91.7-100.1) mg in patients randomized to dasatinib and 400.0 (128.6-863.7, 387.9-479.6) in patients randomized to imatinib. Index drug dose interruptions, reductions, and escalations occurred, respectively, in 88 (51%), 20 (12%), and 26 (15%) patients randomized to dasatinib and 41 (48%), 20 (23%), and 12 (14%) patients randomized to imatinib. In patients who received dasatinib after crossing over from imatinib failure, index drug dose interruptions, reductions, and escalations after crossover occurred in 25 (54%), 13 (28%), and four (9%) patients, respectively.

Efficacy

The cumulative rate of MMR by any time in the ITT population was significantly higher in patients randomized to dasatinib *versus* imatinib (dasatinib, 134 [77%]; imatinib, 38 [44%]; $P<0.001$) (Figure 1, Table 3). Median (95% CI) time to MMR was 13.9 (11.6-17.6) months and 19.7 (14.2-26.4) months with dasatinib and imatinib, respectively. Among patients randomized to imatinib who subsequently crossed over to dasatinib, 30 (65%) achieved MMR with a median (95% CI) time to MMR after crossover of 21.2 (7.6-37.7) months. Among all patients who received dasatinib, including those who received it after crossing over from imatinib (N=220),

Table 2. Patients' disposition and treatment exposure.

	Randomized to dasatinib N=171[a]	Randomized to imatinib N=86	Imatinib (after crossover to dasatinib) N=46	Imatinib (no crossover) N=40
Discontinued treatment, N (%)	171 (100.0)	86 (100.0)	46 (100.0)	40 (100.0)
Study completion	115 (67.3)	61 (70.9)	29 (63.0)	32 (80.0)
Disease progression	7 (4.1)	2 (2.3)	2 (4.3)	0
Study drug toxicity	20 (11.7)	6 (7.0)	4 (8.7)	2 (5.0)
Death	3 (1.8)	3 (3.5)	3 (6.5)	0
Administrative reason	3 (1.8)	7 (8.1)	4 (8.7)	3 (7.5)
Other[b]	23 (13.5)	7 (8.1)	4 (8.7)	3 (7.5)
Discontinued study, N (%)	171 (100.0)	86 (100.0)	46 (100.0)	40 (100.0)
Study completion	146 (85.4)	77 (89.5)	38 (82.6)	39 (97.5)
Withdrew consent	7 (4.1)	0	0	0
Death	8 (4.7)	5 (5.8)	4 (8.7)	1 (2.5)
Lost to follow-up	9 (5.3)	4 (4.7)	4 (8.7)	0
Missing	1 (0.6)	0	0	0
Crossed over to dasatinib, N (%)	-	46 (53.5)	-	-
Treatment failure	-	46 (53.5)	-	-
Loss of MMR	-	5 (10.9)	-	-
Inadequate molecular response[c]	-	21 (45.7)	-	-
Loss of CHR or CCyR	-	10 (21.7)	-	-
Other[d]	-	10 (21.7)	-	-
Daily dose, mg, median (range)	99.7 (25.8-136.0)	400.0 (128.6-863.7)	93.9 (41.7-233.8)	400.0 (128.6-863.7)
Duration of treatment in months, median (range)	67.7 (0.1-104.1)	20.9 (0.9-94.5)	51.5 (0.2-84.9)	71.8 (0.9-94.5)
Dose modifications, N (%)				
Reductions	20 (11.7)	20 (23.3)	13 (28.3)	7 (17.5)
Interruptions	88 (51.5)	41 (47.7)	25 (54.3)	13 (32.5)
Escalations	26 (15.2)	12 (14.0)	4 (8.7)	4 (10.0)

[a]Three patients randomized to dasatinib were not treated. [b]Other reasons included adverse events unrelated to the study drug, patient's request, withdrawal of consent, loss to follow-up, achievement of maximum clinical benefit, poor/non-compliance, no longer meeting study criteria, and pregnancy. [c]Patients who met European LeukemiaNet 2013 criteria for failure. [d]Includes no cytogenetic response at 6 months, less than a partial cytogenetic response at 12 months, less than a complete cytogenetic response at 18 months, *BCR::ABL1* domain mutations poorly sensitive to imatinib, and other. MMR: major molecular response; CHR: complete hematologic response; CCyR: complete cytogenetic response.

164 (75%) achieved MMR. Treatment with dasatinib was associated with an increased likelihood of achieving MMR compared with imatinib (hazard ratio [HR]=2.3, 95% CI: 1.4-3.7, *P*=0.0006) and an early switch to dasatinib after suboptimal response to imatinib at 3 months significantly increased the likelihood of achieving MMR compared with a later switch after treatment failure (HR=1.2, 95% CI: 1.1-1.3, *P*=0.0011).

Cumulative MR^4 was observed in 92 (53%) and 27 (31%) patients randomized to dasatinib and imatinib, respectively (*P*=0.001) (Figure 2A). Only two (4%) patients who crossed over to dasatinib after experiencing treatment failure with imatinib achieved MR^4. Cumulative $MR^{4.5}$ was observed in 63 (36%) and 22 (26%) patients randomized to dasatinib and imatinib, respectively (Figure 2B). Among all patients who received dasatinib, including those who received it after crossing over from imatinib (N=220), 64 (29%) achieved $MR^{4.5}$. Only one (2%) patient who crossed over to dasatinib after experiencing treatment failure with imatinib achieved $MR^{4.5}$ at 41.7 months. Rates of MMR, MR^4, and $MR^{4.5}$ with dasatinib were similar between patients who reported low and medium adherence (*Online Supplementary Table S1*).

PFS at 60 months in the ITT population was 94% for both arms (Figure 3A) and 90% for patients randomized to imatinib who crossed over later to dasatinib (Figure 3B). OS at 60 months in the ITT population was 96% and 95% in patients randomized to dasatinib and imatinib, respectively (Figure 3C), and 94% in patients randomized to imatinib who crossed over later to dasatinib (Figure 3D).

Safety

Any-grade treatment-emergent adverse events occurred in 166 (97%) patients in the dasatinib group, 82 (95%) in the imatinib group, and 43 (93%) in the imatinib group after crossover to dasatinib (Table 4). Grade 3/4 treatment-emergent adverse events occurred in 95 (56%) patients in the

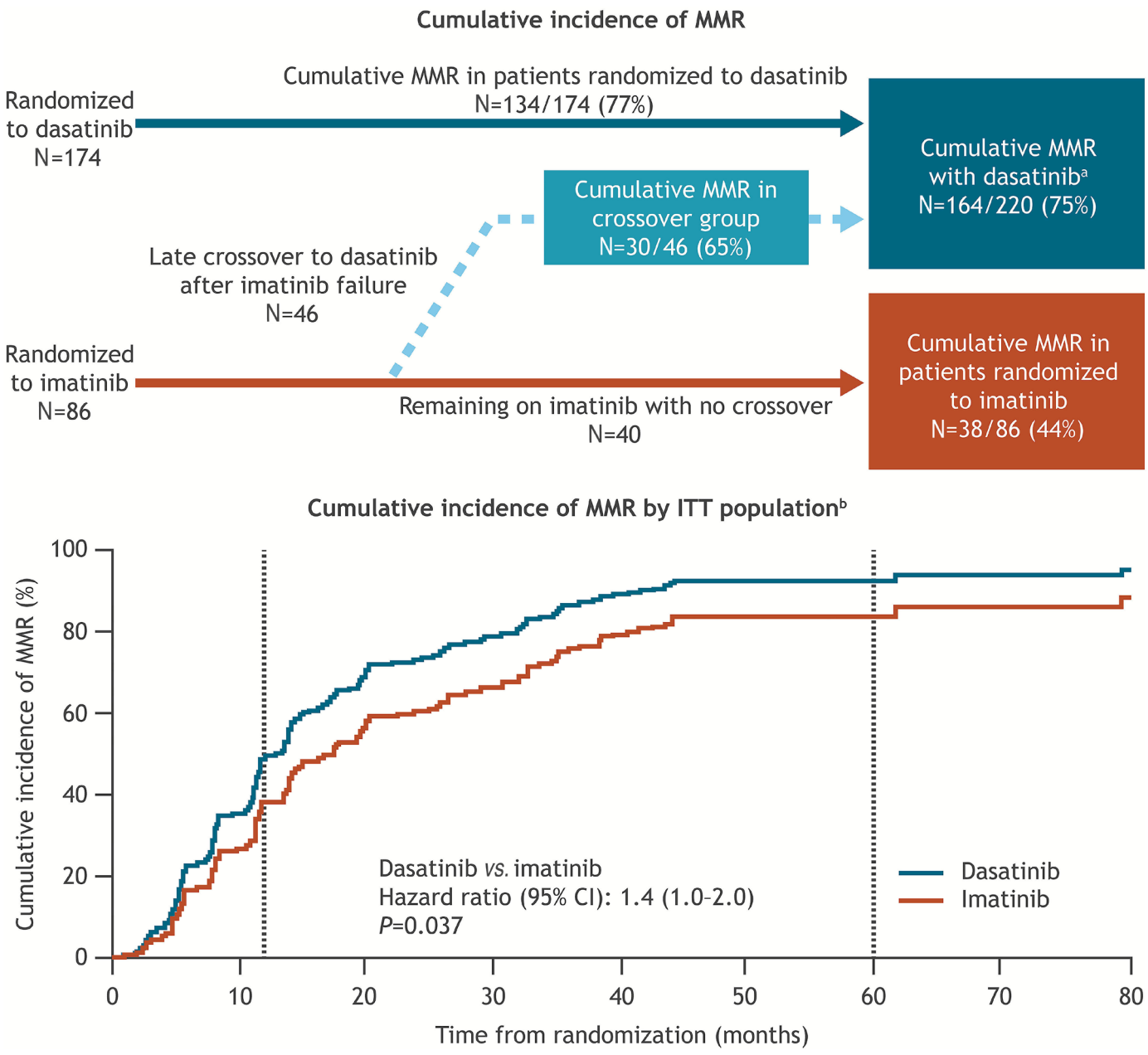

Figure 1. Cumulative incidence of major molecular response and major molecular response rates in the intent-to-treat population. [a]Four patients achieved then lost a major molecular response and subsequently crossed over to dasatinib. [b]The cumulative incidence curve accounts for competing risk and censored patients. ITT: intent-to-treat; MMR: major molecular response; 95% CI: 95% confidence interval.

dasatinib group, 50 (58%) in the imatinib group, and 26 (57%) in the imatinib group after crossover to dasatinib. Treatment-related adverse events with additional events reported since the 3-year follow-up included muscle spasms in patients in the imatinib group, diarrhea in patients in the imatinib group after crossover to dasatinib, headache in patients randomized to either treatment, and eyelid edema in patients randomized to either treatment.

Pleural effusion was reported in 31 (18%) patients in the dasatinib group, including ten patients since the 3-year follow-up, and in ten (22%) patients in the imatinib group after crossover to dasatinib, including five patients since the 3-year follow-up. Grade 3/4 pleural effusion was reported in six (4%) patients in the dasatinib group and two (4%) patients in the imatinib group after crossover to dasatinib. Three (2%) patients in the dasatinib arm discontinued due to pleural effusion. None of the patients in the imatinib group who did not cross over to dasatinib reported pleural effusion.

Pulmonary hypertension occurred in three (2%) patients in the dasatinib group and one (1%) in the imatinib group. Two (1%) patients in the dasatinib group experienced a grade 1 prolonged electrocardiogram QT interval. Cerebral ischemia occurred in one (0.6%) patient in the dasatinib group and coronary artery disease, ischemic stroke (after crossover to dasatinib), and peripheral ischemia were each reported in one (1.2%) patient in the imatinib group.

Hematologic treatment-emergent adverse events occurred in 88 (51%) patients in the dasatinib group, 17 (37%) in the imatinib group before crossing over to dasatinib, and 27 (59%) in the imatinib group after crossing over to dasatinib (Table 4). Grade 3/4 hematologic treatment-emergent adverse events occurred in 37 (22%) patients in the dasatinib group, nine (20%) in the imatinib group before crossing over to dasatinib, and 16 (35%) in the imatinib group after crossing over to dasatinib. Grade 3/4 neutropenia was experienced by 24 (14%), seven (15%), and 12 (26%) in the dasatinib, imatinib-before-crossover, and imatinib-af-

ter-crossover groups, respectively. Grade 3/4 thrombocytopenia was experienced by 18 (11%), four (9%), and six (13%) patients in the dasatinib, imatinib-before-crossover, and imatinib-after-crossover groups, respectively.

A total of nine and four patients in the dasatinib and imatinib groups, respectively, experienced transformation to CML-AP/BP. Of the patients in the imatinib group, three experienced transformation to CML-AP/BP after crossing over to dasatinib.

Treatment-emergent adverse events leading to study discontinuation occurred in 13 (8%) patients in the dasatinib group (grade 3/4, N=5 [3%]), five (6%) patients in the imatinib group (grade 3/4, N=1 [1%]), and three (7%) patients in the imatinib group after crossover to dasatinib (grade 3/4, N=1 [2%]) (*Online Supplementary Table S2*).

There were 16 (6%) deaths in total: 11 in the dasatinib group (6 occurred off-therapy and 2 were due to concomitant solid tumors), four in the imatinib group after crossover to dasatinib, and one in the imatinib group in a patient who did not cross over to dasatinib. The patient who received imatinib without crossing over to dasatinib died from severe sepsis. Among the other 15 deaths, four were due to disease progression, two were due to respiratory failure, and one each was due to study drug toxicity (pancytopenia leading to sepsis with pleural effusion), ischemic stroke and pneumonia, lung cancer, thyroid cancer, stroke, brain hemorrhage, and CML blastic transformation and central nervous system leukemic infiltration. Two deaths were from unknown causes. Overall, 3/11 (27%) deaths in patients randomized to the dasatinib arm *versus* 2/5 (40%) in patients randomized to imatinib were considered CML-related by the investigator.

Table 3. Outcomes by treatment arm.

Outcomes	Randomized to dasatinib N=174	Randomized to imatinib N=86
MMR, % (95% CI)		
By 12 months	29.9 (23.2-37.3)	14.0 (7.4-23.1)
By 24 months	57.5 (49.8-64.9)	36.0 (26.0-47.1)
By 36 months	67.2 (59.7-74.2)	39.5 (29.2-50.7)
By 48 months	75.9 (68.8-82.0)	44.2 (33.5-55.3)
By 60 months	75.9 (68.8-82.0)	44.2 (33.5-55.3)
By any time	77.0 (70.0-83.0)	44.2 (33.5-55.3)
MR^4, % (95% CI)		
By 12 months	8.6 (4.9-13.8)	5.8 (1.9-13.0)
By 24 months	17.8 (12.4-24.3)	14.0 (7.4-23.1)
By 36 months	31.0 (24.3-38.5)	20.9 (12.9-31.0)
By 48 months	41.4 (34.0-49.1)	24.4 (15.8-34.9)
By 60 months	46.6 (39.0-54.3)	30.2 (20.8-41.1)
By any time	52.9 (45.2-60.5)	31.4 (21.8-42.3)
$MR^{4.5}$, % (95% CI)		
By 12 months	5.2 (2.4-9.6)	3.5 (0.7-9.9)
By 24 months	10.9 (6.7-16.5)	8.1 (3.3-16.1)
By 36 months	16.7 (11.5-23.1)	14.0 (7.4-23.1)
By 48 months	23.6 (17.5-30.6)	18.6 (11.0-28.4)
By 60 months	29.3 (22.7-36.7)	19.8 (12.0-29.8)
By any time	36.2 (29.1-43.8)	25.6 (16.8-36.1)

MMR: major molecular response; 95% CI: 95% confidence interval; MR^4: 4-log reduction in *BCR::ABL1* or ≤0.01% International Standard; $MR^{4.5}$: 4.5-log reduction in *BCR::ABL1* or ≤0.0032% International Standard.

Discussion

Prior studies have shown that achievement of an EMR at 3 months after initiating first-line TKI treatment increases the probability of a DMR and is prognostic of favorable

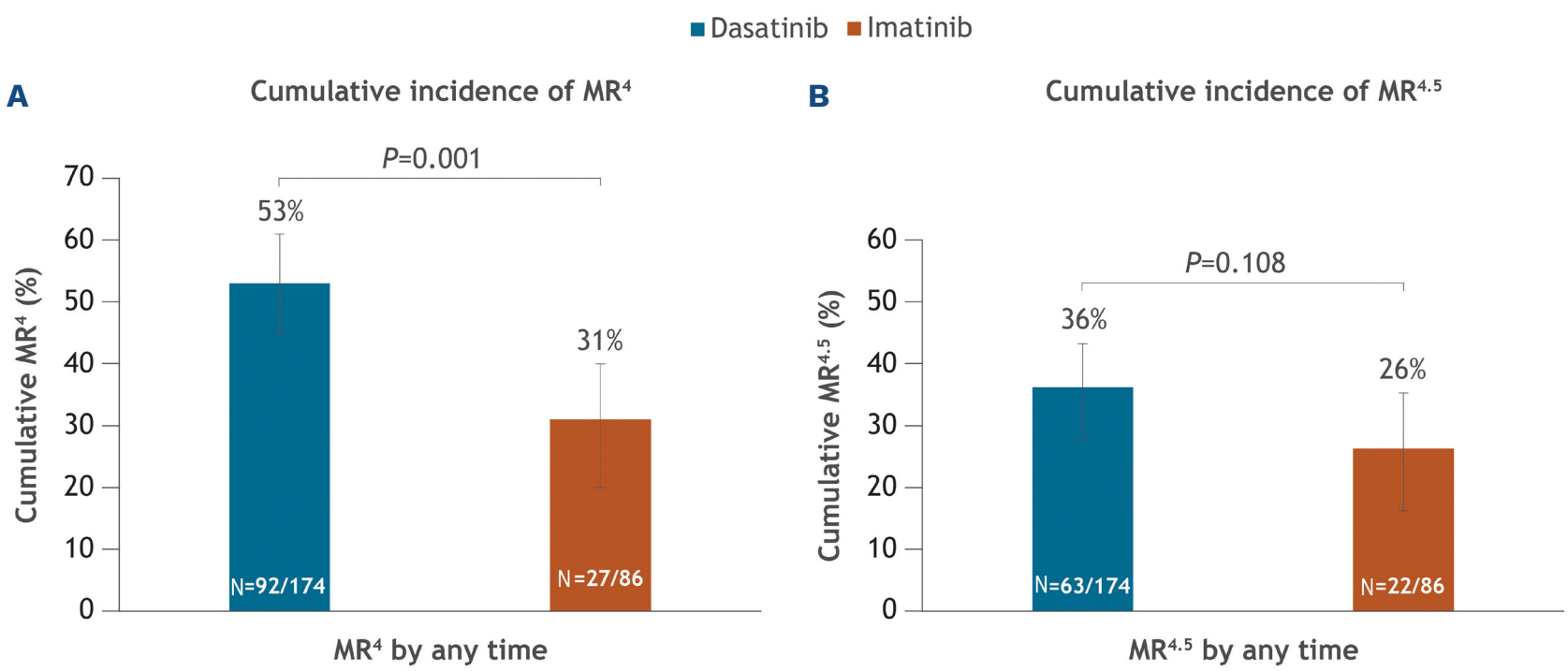

Figure 2. Deep molecular response by cumulative incidence of MR^4 (A) and $MR^{4.5}$ (B). Error bars indicate the 95% confidence interval. MR^4: 4-log reduction in *BCR::ABL1* or ≤0.01% International Standard; $MR^{4.5}$: 4.5-log reduction in *BCR::ABL1* transcript levels or ≤0.0032% International Standard.

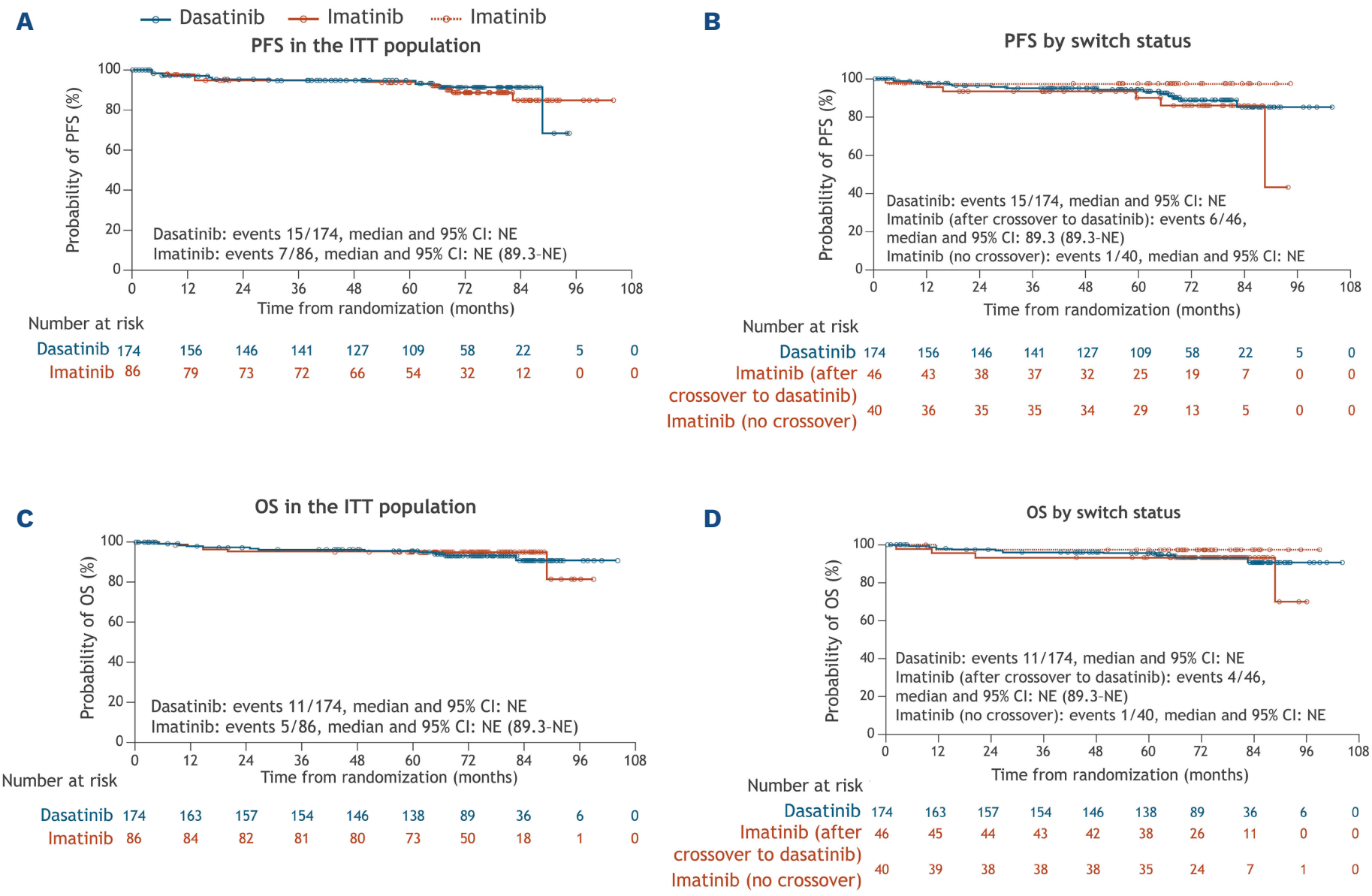

Figure 3. Survival outcomes in the intent-to-treat population and by switch status. (A, B) Progression-free survival in the intent-to treat population (A) and by switch status (B). Progression-free survival is defined as the time from randomization to progression or death, whichever occurred first. (C, D) Overall survival in the intent-to treat population (C) and by switch status (D). PFS: progression-free survival; ITT: intent-to-treat; 95% CI: 95% confidence interval; NE: not estimable; OS: overall survival.

long-term survival in patients with CML-CP.[1,2,7,16-18] In this study however, with the extent of follow-up available, the improved response observed with dasatinib *versus* imatinib did not result in improved survival, perhaps reflecting the high survival of patients who continued on imatinib. DASCERN is the first prospective study to investigate an early switch to dasatinib after suboptimal responses at 3 months with first-line imatinib. This 5-year follow-up shows a sustained clinical benefit from an early switch to dasatinib. MMR and DMR rates were higher in patients randomized to dasatinib than in those randomized to imatinib with a stable separation between groups throughout the study period, and more than half of the patients who remained on imatinib after a lack of EMR at 3 months experienced subsequent treatment failure per the ELN 2013 recommendations.[15] Upon crossing over to dasatinib, 65% of these patients achieved MMR, with similar 60-month PFS and OS rates as those of the dasatinib and imatinib ITT populations. Moreover, patients who crossed over to dasatinib after treatment failure with imatinib were still able to achieve MMR, although at a numerically lower rate than patients randomized earlier to dasatinib (65% *vs*. 77%). The safety profile was consistent with previous reports and the rate of grade 3/4 pleural effusions remained low.[13] These results demonstrate that the early improvements in MMR and DMR observed with dasatinib *versus* imatinib in DASCERN were sustained over a longer treatment duration, although these did not translate into improved OS or PFS. With longer follow-up, the results show a more apparent advantage of early switch *versus* later switch on DMR.

Patients who switched from imatinib to dasatinib after a lack of EMR at 3 months were more likely to achieve MR[4.5] (36%) than were patients who switched after imatinib treatment failure per the ELN 2013 recommendations (2%). Since the patients in DASCERN were previously treated with imatinib and were selected to have adequate tolerance without having progressed or experienced treatment failure, it is perhaps not unexpected that the rate of MR[4.5] would be lower than in patients treated with frontline dasatinib (42%) in the DASISION trial. Nonetheless, direct comparisons between the trials cannot be made due to different patient populations and study designs.[1] Our data

Table 4. Treatment-emergent adverse events.

TEAE[a] in ≥15% of patients N (%)	Randomized to dasatinib N=171[b]		Randomized to imatinib N=86		Imatinib (after crossover to dasatinib) N=46		Imatinib (no crossover) N=40	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with ≥1 TEAE	166 (97.1)	95 (55.6)	82 (95.3)	50 (58.1)	43 (93.5)	26 (56.5)	37 (92.5)	20 (50.0)
Non-hematologic TEAE								
Headache	40 (23.4)	3 (1.8)	9 (10.5)	0	6 (13.0)	0	2 (5.0)	0
Platelet count decreased[c]	36 (21.1)	12 (7.0)	24 (27.9)	11 (12.8)	12 (26.1)	10 (21.7)	11 (27.5)	1 (2.5)
Diarrhea	34 (19.9)	2 (1.2)	17 (19.8)	1 (1.2)	8 (17.4)	0	6 (15.0)	1 (2.5)
Pleural effusion	31 (18.1)	6 (3.5)	10 (11.6)	2 (2.3)	10 (21.7)	2 (4.3)	0	0
Upper respiratory tract infection	29 (17.0)	0	21 (24.4)	0	12 (26.1)	0	7 (17.5)	0
Hypophosphatemia	27 (15.8)	4 (2.3)	20 (23.3)	11 (12.8)	6 (13.0)	1 (2.2)	13 (32.5)	8 (20.0)
Neutrophil count decreased[c]	26 (15.2)	11 (6.4)	21 (24.4)	11 (12.8)	13 (28.3)	10 (21.7)	8 (20.0)	1 (2.5)
White blood cell count decreased[c]	26 (15.2)	6 (3.5)	20 (23.3)	3 (3.5)	10 (21.7)	2 (4.3)	7 (17.5)	0
Pyrexia	22 (12.9)	2 (1.2)	13 (15.1)	0	10 (21.7)	0	3 (7.5)	0
Rash	21 (12.3)	0	12 (14.0)	1 (1.2)	3 (6.5)	0	6 (15.0)	1 (2.5)
Blood creatine phosphokinase increased	19 (11.1)	4 (2.3)	13 (15.1)	1 (1.2)	4 (8.7)	1 (2.2)	6 (15.0)	0
Nausea	17 (9.9)	0	9 (10.5)	0	0	0	7 (17.5)	0
Alanine aminotransferase increased	14 (8.2)	0	11 (12.8)	3 (3.5)	3 (6.5)	2 (4.3)	6 (15.0)	1 (2.5)
Pneumonia	10 (5.8)	2 (1.2)	9 (10.5)	6 (7.0)	7 (15.2)	5 (10.9)	2 (5.0)	1 (2.5)
Hypocalcemia	10 (5.8)	0	10 (11.6)	0	2 (4.3)	0	6 (15.0)	0
Muscle spasms	3 (1.8)	0	12 (14.0)	0	1 (2.2)	0	7 (17.5)	0
Hematologic TEAE	88 (51.5)	37 (21.6)	47 (54.7)	21 (24.4)	27 (58.7)	16 (34.8)	19 (47.5)	4 (10.0)
Anemia	54 (31.6)	11 (6.4)	30 (34.9)	3 (3.5)	15 (32.6)	2 (4.3)	14 (35.0)	0
Neutropenia	42 (24.6)	24 (14.0)	28 (32.6)	15 (17.4)	20 (43.5)	12 (26.1)	7 (17.5)	1 (2.5)
Thrombocytopenia	40 (23.4)	18 (10.5)	16 (18.6)	10 (11.6)	10 (21.7)	6 (13.0)	4 (10.0)	2 (5.0)
Leukopenia	17 (9.9)	3 (1.8)	13 (15.1)	3 (3.5)	8 (17.4)	1 (2.2)	4 (10.0)	2 (5.0)

[a]By Common Terminology Criteria for Adverse Events preferred term. [b]Three patients randomized to dasatinib were not treated. [c]Laboratory assessments. TEAE: treatment-emergent adverse event.

also show that while it is common for patients to achieve MMR after a late switch to dasatinib (65%), it is not common for them to achieve MR[4] (4%) or MR[4.5] (2%), indicating that treatment-free remission would be less likely. These results therefore indicate that using dasatinib as early as possible provides benefit in patients with CML-CP. Nonetheless, given that the cumulative MMR rate in patients randomized to dasatinib was only ~10% higher than in patients who crossed later to dasatinib, decisions regarding treatment switch should give consideration to other factors such as whether a patient's comorbidities, potential adverse events, or transplantation status carry substantial risk.[19] Although reaching milestones is predictive of improved OS, patients not reaching them may still derive benefit from continued TKI treatment with good outcomes.[19,20] In the CML-IV study, 10-year OS rates were 82% in patients with 3-month *BCR::ABL* levels >10% *versus* 88% in patients with levels ≤10%, and 10-year PFS rates were 80% *versus* 87%, respectively.[21] When analyzed by therapy, the faster responses observed with 800 mg imatinib compared with the other treatment regimens did not result in a demonstrable survival advantage, and patients who received imatinib 400 mg had close to normal life expectancy regardless of the time to response.[21] The authors concluded that patient- and disease-related factors had a larger impact on survival than initial treatment selection and urged addressing non-CML survival determinants to prolong life.[21] Overall, data from other reports are mixed, with some supporting EMR at 3 months having superior prognostic value and therefore supporting early intervention strategies[6,22] and others suggesting that response at 6 months is a better predictor.[23] The most recent ELN recommendations in fact suggest that lack of EMR should be confirmed before deciding on a change in treatment.[11]

In the DASCERN study, PFS and OS were similar between treatment arms. Additionally, a numerically higher proportion of patients randomized to imatinib who subsequently crossed over to dasatinib experienced disease progression than patients who remained on imatinib or who were randomized to dasatinib, although this difference was not statistically significant. Notably, patients randomized to imatinib who achieved EMR and

remained on imatinib had PFS and OS similar to those seen in patients randomized to dasatinib. Although the improved response with an early switch to dasatinib did not translate into significantly improved PFS or OS, the achievement of deeper molecular responses is an endpoint of growing relevance to most patients and clinicians and is essential for consideration of treatment discontinuation and eventual treatment-free remission. The improved ability to achieve deep responses with an early switch in patients who otherwise have a lower probability of reaching this goal is a valuable benefit that should be considered during treatment decisions for patients without an EMR.

Findings from DASCERN expand on those of previous studies showing that patients with CML-CP could benefit from a switch to a second-generation TKI after a suboptimal response to imatinib. In the LASOR study, patients with a suboptimal response based on 2009 ELN criteria (which would be considered failure based on more recent editions of the ELN recommendations[11]) were randomized to receive nilotinib or to remain on imatinib with dose escalation.[24] The patients who received nilotinib had numerically but statistically non-significant higher complete cytogenetic response rates than those who remained on imatinib with dose escalation.[24] Furthermore, patients randomized to imatinib who crossed over to nilotinib had a numerically lower complete cytogenetic response rate than those randomized to nilotinib.[24] It should be noted that the treatment failure criteria for LASOR were different from those in DASCERN; while DASCERN only allowed crossover in patients who met ELN 2013 criteria for failure, LASOR allowed for a crossover from imatinib due to loss of response or intolerance, or for patients with no complete cytogenetic response after 6 months.[24]

A potential limitation of this study is that while the benefit of switching was clearly observed in many patients, it is possible that some patients who did not achieve EMR at 3 months with imatinib had an underlying biology conferring resistance to TKI in general, such as mutations in other cancer-associated genes; these were not investigated in patients in DASCERN. Also, the impact of patients' baseline characteristics on survival outcomes were not investigated, so the effect of these factors on the observed PFS and OS was unclear. Finally, as DMR may continue to improve beyond 5 years, the relatively short follow-up limits our ability to see the potential extended benefit of this intervention.

This study demonstrates that switching TKI when there is a lack of EMR at 3 months with imatinib can increase the probability of achieving optimal responses, with an early switch to dasatinib improving MMR and DMR rates.

Disclosures

JEC has received consultancy support from AbbVie, Biopath Holdings, Bristol Myers Squibb, Forma Therapeutic, Gilead, Novartis, Pfizer, Sun Pharma, and Takeda; has received honoraria from Novartis, Pfizer, and Takeda; has received research funding from AbbVie, Bristol Myers Squibb, Kartos, Novartis, Pfizer, Sun Pharma, and Takeda; and has stock ownership in Biopath Holdings. JWang is on the board of directors or advisory committee for AbbVie and has received consultancy support from AbbVie and AstraZeneca. AH has received research funding from Bristol Myers Squibb, Incyte, Novartis, and Pfizer. D-WK has received consultancy support, honoraria, research funding, and speakers' bureau support from Bristol Myers Squibb, Il-Yang, Novartis, Otsuka, and Pfizer. JR has received financial support from Amgen, Cepheid, HTG, Novartis, and Nuprobe. MS has received consultancy support from AbbVie, Bristol Myers Squibb, CTI, Geron, Novartis, Ryvu Therapeutics, Sierra Oncology, Taiho Pharmaceutical, Takeda, and TG Therapeutics; is an equity holder in the publicly-traded companies Karyopharm Therapeutics and Ryvu Therapeutics; has received research funding from ALX Oncology, Astex Pharmaceuticals, Incyte, and TG Therapeutics; and has received travel expenses from AbbVie, Astex, Incyte, Ryvu Therapeutics, Sierra Oncology, and TG Therapeutics.

PM-R is an employee and equity holder in the publicly-traded company Bristol Myers Squibb. OS is an employee at Bristol Myers Squibb. GS is on a speakers' bureau for Novartis. QJ, JWeng, HZ, and XL have no conflicts of interest to disclose.

Contributions

JEC, AH, JR, and GS were part of the Steering Committee. QJ, JWang, JWeng, HZ, and XL enrolled patients. D-WK was part of the Steering Committee and enrolled patients. PMR and OS collected and interpreted data. All authors provided directions and guidance to manuscript writing and reviewed, edited, and approved the final manuscript.

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Data-sharing statement

Bristol Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

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