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ORIGINAL ARTICLE

BCR-ABL1 mutation development during first-line treatment with dasatinib or imatinib for chronic myeloid leukemia in chronic phase

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BCR-ABL1 mutations are a common, well-characterized mechanism of resistance to imatinib as first-line treatment of chronic myeloid leukemia in chronic phase (CML-CP). Less is known about mutation development during first-line treatment with dasatinib and nilotinib, despite increased use because of higher response rates compared with imatinib. Retrospective analyses were conducted to characterize mutation development in patients with newly diagnosed CML-CP treated with dasatinib ($n = 259$) or imatinib ($n = 260$) in DASISION (Dasatinib versus Imatinib Study in Treatment-Naive CML-CP), with 3-year minimum follow-up. Mutation screening, including patients who discontinued treatment and patients who had a clinically relevant on-treatment event (no confirmed complete cytogenetic response (cCCyR) and no major molecular response (MMR) within 12 months; fivefold increase in *BCR-ABL1* with loss of MMR; loss of CCyR), yielded a small number of patients with mutations (dasatinib, $n = 17$; imatinib, $n = 18$). Dasatinib patients had a narrower spectrum of mutations (4 vs 12 sites for dasatinib vs imatinib), fewer phosphate-binding loop mutations (1 vs 9 mutations), fewer multiple mutations (1 vs 6 patients) and greater occurrence of T315I (11 vs 0 patients). This trial was registered at www.clinicaltrials.gov as NCT00481247.

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INTRODUCTION

Chronic myeloid leukemia (CML) has become a manageable chronic disease with the advent of BCR-ABL1 inhibitors; however, mutations in the *BCR-ABL1* gene may confer resistance to inhibitors, potentially limiting their effectiveness against expansion of specific leukemic clones.[1–4] Although the BCR-ABL1 inhibitor imatinib has demonstrated significant efficacy in newly diagnosed patients with CML in chronic phase (CML-CP), primary and secondary resistance to imatinib was observed (no initial response or loss of an established response), resulting in unfavorable long-term outcomes.[5,6] Patients treated with imatinib are susceptible to numerous mutations that reduce the binding of imatinib,[7–9] and *BCR-ABL1* mutations may be responsible for 9–48% of primary resistance and 10–68% of secondary or acquired resistance to imatinib.[10–13] Dasatinib, nilotinib, bosutinib and ponatinib have enabled many patients, including those with mutations, to overcome imatinib resistance; however, each lack efficacy against a small number of different leukemic clones, and all except ponatinib lack efficacy against T315I.[3,4,14–17]

Dasatinib and nilotinib are also approved for the treatment of newly diagnosed CML-CP patients in many countries.[18–21] Compared with imatinib, dasatinib and nilotinib in the first-line setting are associated with faster and deeper molecular responses and reduced risk of transformation to accelerated phase/blast phase (AP/BP).[22,23] Although a narrow spectrum of mutations developing during imatinib treatment are known to confer resistance to subsequent treatment with dasatinib or nilotinib, less is known qualitatively or quantitatively regarding the spectrum of mutations emerging during first-line treatment.[3,4,24–26]

The first-line phase 3 trial DASISION (Dasatinib versus Imatinib Study in Treatment-Naive CML-CP) demonstrated that dasatinib significantly improved early cytogenetic and molecular response rates compared with imatinib in the treatment of newly diagnosed CML-CP patients.[23,24,27] With a minimum 2-year follow-up in DASISION, mutational analyses in patients who discontinued treatment for any reason identified 10 mutations in each treatment arm affecting three amino acids in dasatinib-treated patients and nine amino acids in imatinib-treated patients.[24]

To identify patients potentially at higher risk for developing mutations, mutational analyses based on a minimum 3-year follow-up were conducted for patients in DASISION who had discontinued treatment for any reason and for those on treatment with clinically relevant events (defined as no confirmed complete cytogenetic response (cCCyR) and no major molecular response (MMR) within 12 months; a fivefold increase in *BCR-ABL1* transcript levels with loss of MMR; loss of CCyR). Potential relationships between the development of mutations, response dynamics and long-term patient status were also explored.

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SUBJECTS AND METHODS

DASISION (CA180-056; ClinicalTrials.gov: NCT00481247) is an ongoing, open-label, phase 3 randomized trial for which patient characteristics and eligibility criteria have been described.[27] Briefly, adults with cytogenetically confirmed Philadelphia chromosome-positive (Ph+) CML-CP diagnosed within 3 months who had adequate hepatic and renal function and no serious medical conditions were eligible. With the exception of anagrelide or hydroxyurea, no prior CML therapy was permitted. The trial was approved by all institutional review boards and ethics committees, and all patients gave written informed consent before randomization in accordance with the Declaration of Helsinki.

In the study, 519 patients with newly diagnosed CML-CP were randomized 1:1 to dasatinib 100 mg once daily ($n = 259$) or imatinib 400 mg once daily ($n = 260$). With a two-sided $\alpha = 0.05$ and power of 90%, 518 subjects were needed to show a statistically significant difference in 12-month CCyR rates between the two arms when the 12-month CCyR rates in the imatinib 400 mg once daily arm and the dasatinib 100 mg once daily arm were assumed to be 69% and 81%, respectively. Study treatment was discontinued for protocol-defined disease progression (increasing white blood cell count, loss of complete hematologic response, loss of major cytogenetic response, AP/BP criteria met, death from any cause during treatment), treatment failure (no hematologic response at 3 months, no complete hematologic response or cytogenetic response at 6 months, no partial cytogenetic response at 12 months, no CCyR at 18 months),[28] unacceptable toxicity, patient/investigator decision or pregnancy.

Treatment interruptions and dose reductions were permitted for managing adverse events. Dose escalations to dasatinib 140 mg once daily or imatinib 600–800 mg/day were permitted for suboptimal response at 3–18 months.[28] The primary end point was cCCyR rate by 12 months (the confirming assessment could be after 12 months). A cCCyR was defined as CCyR documented on two consecutive assessments at least 28 days apart. Key secondary end points included time in cCCyR, rates of MMR, defined as a *BCR-ABL1* transcript level in peripheral blood on international scale $\leqslant 0.1\%$, corresponding to ≥ 3-log reduction from the standardized baseline, at any time, times to cCCyR or MMR and durations of progression-free survival and overall survival. Transformation to AP/BP was defined according to the European LeukemiaNet (ELN) 2006 criteria (clonal evolution was not included).[28]

Mutational analysis

In DASISION, *BCR-ABL1* mutational analyses were to be conducted in all patients receiving first-line dasatinib or imatinib at baseline and the end of treatment. Here, we also conducted *BCR-ABL1* mutational analyses in the subset of patients who were considered more likely to have a mutation according to ELN recommendations.[12] This analysis included patients on treatment who had at least one clinically relevant event (no cCCyR within 12 months; no MMR within 12 months; fivefold increase in *BCR-ABL1* transcript levels with loss of MMR; loss of CCyR), and/or who discontinued treatment for any reason (Table 1). Patients may have been included in both categories having (1) a clinically relevant on-treatment event and (2) discontinued treatment. Stored specimens taken closest to the event were analyzed retrospectively for the presence of mutations (for patients who discontinued treatment, samples were analyzed within 45 days, before or after discontinuation). For those patients in whom a mutation was identified, all stored specimens from baseline to the final sample collected were retrospectively analyzed for the presence of mutations. Mutational analyses were conducted at a central independent laboratory (MolecularMD, Portland, OR, USA) using direct sequencing on peripheral blood samples after amplification of the ABL tyrosine kinase domain (amino acids 35–510) by reverse transcription PCR.[29] When a mutation was initially detected in a patient sample, repeat testing from the RNA was performed to verify the presence of the identified mutation. Mutation data were blinded for samples collected at baseline and end of treatment. The remaining samples were analyzed retrospectively.

Molecular response

BCR-ABL1 transcript levels in peripheral blood were assessed using quantitative real-time PCR by MolecularMD. Patients with typical *BCR-ABL1* transcripts b2a2 and b3a2 were eligible for molecular response analysis. Data are expressed on the international scale.[29,30]

Table 1. Triggers for mutational analysis: DASISION 3-year database

On-treatment, clinically relevant events	*Off-treatment, reason for discontinuation from study*
No confirmed CCyR within 12 months	Disease progression[a]
No MMR within 12 months	Maximum clinical benefit[b]
Fivefold increase in *BCR-ABL1* transcript levels with loss of MMR	Intolerance Treatment failure
Loss of CCyR[c]	Adverse event unrelated to study drug Withdrew consent Pregnancy Loss to follow-up Poor/noncompliance Subject request to discontinue

Abbreviations: CCyR, complete cytogenetic response; DASISION, Dasatinib versus Imatinib Study in Treatment-Naive CML-CP; MMR, major molecular response. [a]Increasing white blood cell count, loss of complete hematologic response (CHR), loss of major cytogenetic response, transformation to accelerated phase/blast phase and death. [b]Any subject who received study therapy and then discontinued treatment for intolerance (recurrent $\geq$ grade 3 hematologic toxicity or $\geq$ grade 2 nonhematologic toxicity despite dose reduction necessitating discontinuation of therapy) or treatment failure (lack of hematologic response at 3 months, lack of CHR or CyR at 6 months, lack of partial cytogenetic response at 12 months and lack of CCyR at 18 months). [c]As of last patient status; patients with interim loss of CCyR who subsequently regained a CCyR were not included.

Patient status

For patients with mutations detected based on 3-year minimum follow-up, status was assessed based on extended follow-up (minimum 4 years), including *BCR-ABL1* transcript level and current treatment dose for patients still on treatment, and included survival status (alive or dead, reason for death), current treatment and transformation to AP/BP for patients who discontinued treatment.

RESULTS

After a 3-year minimum follow-up, 169 of 259 (65%) randomized patients in the dasatinib arm and 194 of 260 (75%) in the imatinib arm of the study were identified with events that warranted mutational analysis (Table 2). *BCR-ABL1* mutations were detected in a minority of patients in both arms (dasatinib, $n = 17/169$ (10%); imatinib, $n = 18/194$ (9%): Table 2 and Figure 1). Patients receiving dasatinib had a more narrow spectrum of mutations (affecting four sites) compared with those receiving imatinib (affecting 12 sites) and fewer phosphate-binding loop (P-loop) mutations (1 (G250E) vs 9 (G250E, $n = 3$; L248V, $n = 1$; E255K/V, $n = 4$; Y253H, $n = 1$), respectively). The G250E mutation seen with dasatinib was identified in a single patient sample collected 12 months after the start of treatment and was not detected in samples collected thereafter. The patient was screened owing to no MMR within 12 months and a fivefold increase in *BCR-ABL1* transcript level with the loss of a subsequent MMR. His molecular and cytogenetic responses subsequently improved following dose escalation to 140 mg, and he remains on treatment as of last follow-up (>4 years after start of treatment). Fewer patients on dasatinib ($n = 1$) had two *BCR-ABL1* mutations detected in tandem or as separate clones compared with patients on imatinib ($n = 6$). The T315I mutation was only identified in the dasatinib arm ($n = 11$).

Characteristics of patients with mutations

The majority of patients with mutations had their first mutation detected within 12 months of the start of treatment (Figure 2): in the dasatinib arm, 65% (11/17) had a mutation detected within

Table 2. DASISION 3-year mutational analysis

	Dasatinib 100 mg once daily, N = *259*	*Imatinib 400 mg once daily,* N = *260*
Patients identified for mutational analysis, *n* (%)	169 (65)	194 (75)
Patients with samples analyzed for mutations, *n*	155	183
Patients with samples not analyzed,[a] *n*	14	11
Patients with mutations detected (total), *n*	17	18
Mutations detected[b] (*n*)	G250E (1), V299L (3), T315I (11), F317I/L (3)	M244V (1), L248V (1), G250E (3), Y253H (1), E255K/V (4), D276G (1), M351T (3), E355G (2), F359C/I/V (5), L387M (1), H396P (1), E450G (1)

Abbreviation: DASISION, Dasatinib versus Imatinib Study in Treatment-Naive CML-CP. [a]Alternate transcript; *BCR-ABL1* too low to test; other. [b]Includes patients with two mutations: one dasatinib (V299L/F317I) and six imatinib (L248V/E355G, E255V/E450G, E255K/M351T, Y253H/E255V, D276G/F359C and M351T/F359V).

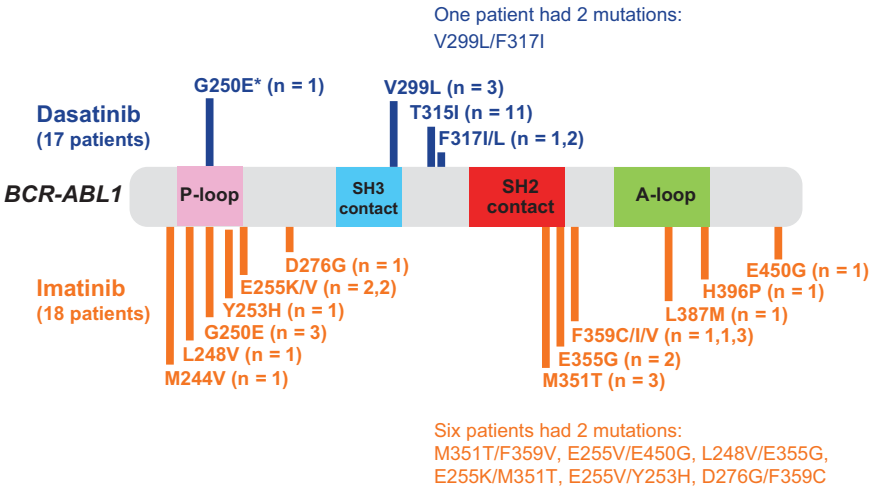

Figure 1. Distribution of mutations detected in DASISION at 3 years by treatment arm and *BCR-ABL1* location. *Identified in one sample collected 1 year after treatment start; no mutation was detected in a second sample collected the same day or in a sample collected 2 years later.

12 months and 94% (16/17) had a mutation detected within 24 months (range, 3–30 months); in the imatinib arm, 67% (12/18) had a mutation detected within 12 months and 72% (13/18) had a mutation detected within 24 months (range, 5–36 months). In addition, 76% (13/17) of dasatinib-treated patients and 61% (11/18) of imatinib-treated patients had a mutation detected shortly before the trigger for mutational analysis was observed ($\leqslant$3 months prior). The majority of patients with mutations had more than one of the defined clinically relevant on-treatment events, with most failing to achieve or maintain a molecular or cytogenetic response (Table 3).

Among patients with mutations in the dasatinib arm, a greater percentage had high baseline Euro (Hasford) scores (41%; Table 4) compared with all randomized patients (19% high, 47–48% intermediate and 33% low).[27] In the dasatinib arm, Euro (Hasford) scores among patients with T315I were evenly distributed (4 high, 3 intermediate and 4 low); however, among patients with other mutations, more had high baseline scores (n = 3: 1 G250E, 1 V299L and 1 V299L/F317I) than intermediate (n = 2: 1 F317L and 1 V299L) or low (n = 1: F317L). Euro (Hasford) scores among patients with mutations in the imatinib arm showed a similar distribution as for all randomized patients (Table 4), with no clear trends with regard to the incidence of specific mutations, double mutations or P-loop mutations. Analysis of molecular and cytogenetic response dynamics showed that most patients with mutations had little or no initial response or experienced a transient modest response often deep enough to achieve a CCyR but not an MMR (Table 4).

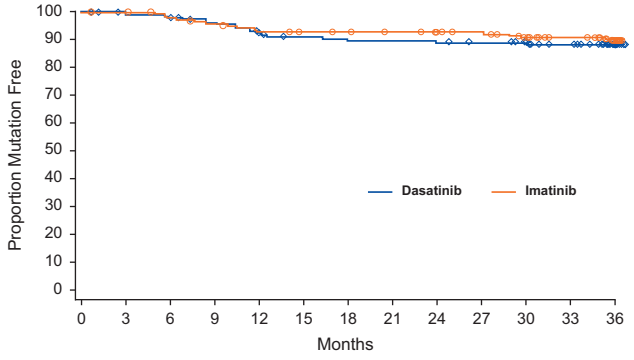

Figure 2. Detection of mutations over time. Kaplan–Meier curve of the detection of mutations for both dasatinib- and imatinib-treated patients tested for mutations. Dasatinib-treated patients with samples analyzed for mutations: n = 155; imatinib-treated patients with samples analyzed for mutations: n = 183. Patients were censored when they were no longer at risk for developing a mutation.

Long-term patient status

For patients with mutations identified based on 3-year minimum follow-up, an extended 4-year minimum follow-up was conducted. This extended follow-up of patients with mutations showed poor outcomes regardless of treatment (dasatinib vs imatinib) and high rates of treatment discontinuation (dasatinib,

Table 3. Clinically relevant on-treatment events, reasons for discontinuation and current status in patients with mutations in DASISION

	Dasatinib 100 mg once daily, n = *17*	*Imatinib 400 mg once daily,* n = *18*
Clinically relevant on-treatment events, n[a]	14	16
No MMR within 12 months	12	16
No cCCyR within 12 months	8	12
Loss of CCyR	6	4
Fivefold *BCR-ABL1* increase with loss of MMR	2	1
Discontinued treatment, n	14	14
Protocol-defined disease progression	11	8
Lost MCyR	4	4
Transformed to AP/BP	4	3
Lost CHR	1	1
Increased WBC count	1	—
Death	1	—
Treatment failure	1	4
No PCyR, 12 months	—	2
No CCyR, 18 months	1	2
Other	2[b]	2[c]
Patient status (4-year minimum follow-up), n		
Off treatment	14	14
Alive	8	10
Dead	6	4
On treatment	3	4
% Mutation detected at trigger plus molecular response at last analysis	90% G250E[d]; 0.02% *BCR-ABL1*^{IS} 40% T315I[d]; 0.039% *BCR-ABL1*^{IS} 80% T315I[d]; 0.013% *BCR-ABL1*^{IS}	80% F359I[d]; 1.03% *BCR-ABL1*^{IS} 100% G250E[d]; 11.3% *BCR-ABL1*^{IS} 90% G250E[d]; 7.7% *BCR-ABL1*^{IS} 20% F359V[d]; 20.5% *BCR- ABL1*^{IS}

Abbreviations: AP/BP, accelerated phase/blast phase; cCCyR, confirmed complete cytogenetic response; CCyR, complete cytogenetic response; CHR, complete hematologic response; DASISION, Dasatinib versus Imatinib Study in Treatment-Naive CML-CP; IS, international scale; MMR, major molecular response; MCyR, major cytogenetic response; PCyR, partial cytogenetic response; WBC, white blood cell. [a]Patients may have had multiple events. [b]One no CyR, one lost CCyR. [c]One poor/noncompliance, one patient request. [d]Estimated percentage of the mutation quantified in the sample.

$n = 14/17$; imatinib, $n = 14/18$). The primary reason for discontinuation of patients with mutations was protocol-defined disease progression (dasatinib, $n = 11$; imatinib, $n = 8$; Table 3). Of all patients in DASISION who discontinued because of protocol-defined disease progression, patients with mutations accounted for 61% on dasatinib ($n = 11/18$) and 42% on imatinib ($n = 8/19$).

The patients with mutations who discontinued because of transformation to AP/BP (a subset of patients who discontinued because of disease progression) all died: four dasatinib patients (three who had T315I and one who had F317I) and three imatinib patients (two mutations each: M351T/F359V, E255K/M351T and D276G/F359C). The remaining deaths among patients with mutations (dasatinib, infection, $n = 2$; imatinib, complication following allogenic stem cell transplant, $n = 1$) were not related to BCR-ABL1 inhibitor therapy. The one dasatinib patient with two mutations (V299L/F317I) was the only patient with a mutation identified who transformed to AP/BP after dasatinib discontinuation; this patient had discontinued treatment because of loss of complete hematologic response, transformed after switching to nilotinib, then received allogeneic hematopoietic stem cell transplantation and was alive at last follow-up. The remaining three imatinib patients with two mutations discontinued treatment because of poor cytogenetic response (two with no partial cytogenetic response by 12 months, one with no major cytogenetic response by 18 months), switched to dasatinib ($n = 2$) or nilotinib ($n = 1$) and were alive at last follow-up.

Although most patients who had mutations detected were off study at the time of this analysis, there were three patients in the dasatinib arm and four patients in the imatinib arm who remained on study treatment. The three patients with mutations in the dasatinib arm who remained on treatment had a good molecular response (*BCR-ABL1* transcript levels $\leqslant 0.1\%$ (MMR); Table 3); however, the four patients with mutations in the imatinib arm who remained on treatment had *BCR-ABL1* transcript levels $> 1\%$ (Table 3). The presence of a mutation and the failure to achieve *BCR-ABL1* $< 1\%$ represent treatment failure under the current ELN recommendations and should lead to a switch to another tyrosine-kinase inhibitor.[12,31]

DISCUSSION

This retrospective study based on 3-year minimum follow-up in the DASISION trial showed that *BCR-ABL1* mutations were identified in only a small number of patients (dasatinib, $n = 17$; imatinib, $n = 18$), even though the criteria for mutational analysis were expanded from that used in previous reports of DASISION (clinically relevant on-treatment events, discontinuation because of any reason) to include a large number of patients in this analysis. Consistent with results of *in vitro* studies and previous findings in the second-line setting,[3,32–38] a narrower spectrum of mutations was detected in patients who received first-line dasatinib compared with imatinib. Notably, the number of patients who carried more than one mutation was higher with imatinib. Patients with more than one *BCR-ABL1* mutation generally have a poorer outcome compared with patients harboring only one *BCR-ABL1* mutation.[39,40] In this mutational analysis, all patients with two *BCR-ABL1* mutations discontinued study treatment (dasatinib, $n = 1$; imatinib, $n = 6$) either because of protocol-defined disease progression (dasatinib, $n = 1$; imatinib, $n = 3$) or treatment failure (imatinib, $n = 3$), and 3 (imatinib) subsequently died. Compared with dasatinib, more patients treated with imatinib also had P-loop mutations. Mutations in the P-loop of the *BCR-ABL1* kinase domain have been shown to be associated with poor prognosis.[8]

Table 4. Baseline Euro (Hasford) risk score and response dynamics in patients with mutations

	Dasatinib 100 mg once daily, n = *17*	*Imatinib 400 mg once daily,* n = *18*
Euro (Hasford) score, n *(% of patients)*[a]		
Low (⩽780)	5 (29)	6 (33)
Patients at risk	86	87
Intermediate (>780 to ⩽1480)	5 (29)	8 (44)
Patients at risk	124	213
High (>1480)	7 (41)	4 (22)
Patients at risk	49	50
Best cytogenetic response, n		
CCyR	10	10
PCyR	1	4
< PCyR	6	4
Best molecular response, n		
MMR	2	1
BCR-ABL1 ⩽10% at 3 months	10[b]	6[c]
Treatment milestone		
cCCyR by 12 months		
Achieved	6	4
Not achieved	11	14
MMR at 12 months		
Achieved	0	0
Not achieved	17	18

Abbreviations: cCCyR, confirmed complete cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response; PCyR, partial cytogenetic response. [a]Investigator-reported Euro (Hasford) risk score. [b]*BCR-ABL1* transcript levels not available for one patient. [c]Three-month *BCR-ABL1* transcript levels not available in two patients.

Of note, the effectiveness of dasatinib against P-loop mutations varies: not all patients with P-loop mutations at the time of imatinib discontinuation have improved responses with dasatinib,[11,41,42] and P-loop mutations have been shown to emerge during second-line treatment with dasatinib, including G250E, Q252H and L248V.[3,34,40] Hence, the detection of a G250E mutation in the dasatinib arm is not surprising, and the absence of other P-loop mutants could be because of the small number of patients with mutations identified.

In this analysis, the T315I mutation was identified in the dasatinib arm ($n = 11$) but not the imatinib arm ($n = 0$). The lack of T315I mutations in the imatinib arm of DASISION is inconsistent with other reports, including the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients) trial.[7–11,25,26,43] With 2 and 3 years of follow-up in ENESTnd, a similar number of patients had a T315I mutation in the nilotinib and imatinib arms of the study (nilotinib 300 mg twice daily, $n = 3$; nilotinib 400 mg twice daily, $n = 2$; imatinib 400 mg once daily, $n = 3$).[25,26] However, differences in methodology, patient population, small numbers and geographical distribution between DASISION and ENESTnd make interpretation of cross-study comparisons difficult.[43] Mutation data from ongoing first-line trials by MD Anderson Cancer Center (CA180-040; NCT00254423)[44] and the Southwest Oncology Group (SWOG S0325; NCT00070499)[45] are expected to provide additional information regarding the development of mutations in patients with newly diagnosed CML-CP treated with dasatinib.

One hypothesis for the greater number of T315I mutations detected with dasatinib ($n = 11$) compared with imatinib ($n = 0$) derives from differences in competitive advantage between mutant clones observed in *in vitro* cell assays. Select mutant clones (for example, P-loop mutations Y253F, E255K) were found to have higher transformation potency and proliferation rate compared with T315I, even in the absence of BCR-ABL1 inhibitors.[46] Assuming that imatinib has lower activity against these mutations compared with dasatinib,[1,24,34,41,47] mutant clones with select P-loop mutations may expand more rapidly than clones with the T315I mutation when exposed to imatinib compared with dasatinib.

Consistent with this idea, some P-loop mutations have been shown to arise faster during imatinib treatment than the T315I mutation,[48] and T315I is less common than all P-loop mutations in CML-CP patients with imatinib resistance.[11,42,47–49] In addition, dasatinib suppresses P-loop mutations to a greater extent than T315I;[34,50–53] therefore, T315I may be able to develop during dasatinib treatment with relatively little competition from rapidly proliferating clones.

Patients with mutations in DASISION typically had a poor outcome, with high rates of discontinuation (82% dasatinib, 78% imatinib), transformation (24 and 17%) and death (35 and 22%) by 4-year minimum follow-up. The majority of mutations were identified early, usually within the first 12 months of treatment (dasatinib: 65%; range, 3–30 months; imatinib: 67%; range, 5–36 months).

Despite the fact that mutations were detected in a small percentage of patients considered to be more likely to develop mutations, the data from the DASISION 3-year mutational analysis reported here suggest that patients with CML-CP who fail to achieve and maintain treatment response at key milestones should be considered for mutation screening. This is consistent with current CML treatment guidelines.[12,31,54] Recent CML guideline updates from the National Comprehensive Cancer Network and recommendations from ELN advise mutational analysis be performed for patients with inadequate molecular or cytogenetic response.[12,31,54] The recent CML recommendations also suggest that patients with an inadequate response or treatment failure (inclusive of mutation development) may be considered for an alternative treatment.

Mutational testing is anticipated to become more widely used to select second-line treatment in the community setting, especially with the approval of ponatinib for treatment of patients with CML or Ph+ acute lymphoblastic leukemia with resistance or intolerance to prior tyrosine-kinase inhibitor therapy. Ponatinib has demonstrated activity against T315I/A in preclinical assays,[55] and patients with the T315I mutation respond well to ponatinib, unlike patients with T315I treated with other BCR-ABL1 inhibitors.[15,17] In addition, with the introduction of generic imatinib into the market in 2016, choosing the most appropriate second-line tyrosine-kinase inhibitor for patients, based on factors such as mutation status, will become increasingly important. Allowing physicians the option to choose the most suitable second-line therapy may ensure improved outcomes and decreased health-care costs.[56] More sensitive detection methods (for example, next-generation sequencing) may allow mutations that were not evident through conventional sequencing to be detected following a significant rise in *BCR-ABL1* levels;[2] however, further data are needed to determine the clinical relevance of low-level mutations for patient outcomes.[2,40,57–60]

Mutational testing provides arguably the most important measure for treatment selection in patients with CML, especially when selecting an alternative therapy because of current treatment failure. In patients with less-resistant mutations, other factors, such as patient comorbidities, the potential for cross-intolerance and adherence, should also be considered to ensure patients achieve good long-term outcomes.

CONFLICT OF INTEREST

TPH has received honoraria and research funding from ARIAD, Bristol-Myers Squibb (BMS) and Novartis. GS has acted as a consultant for and received honoraria from ARIAD, BMS, Celgene, Novartis and Pfizer. AQ-C has acted as a consultant for ARIAD, BMS and Novartis. MJM has received research funding from ARIAD, BMS and Novartis; and has acted as a consultant or speaker for and received honoraria from ARIAD, BMS, Novartis and Pfizer. D-WK received research funding and honoraria from ARIAD, BMS, ILYANG, Novartis and Pfizer; has received funding for travel/accommodations/meeting expenses from BMS; and has served as a consultant and board member for BMS and Novartis. JHL has received research support from ARIAD, BMS, Merck (Schering), Novartis, Pfizer (Wyeth), Roche and TEVA (ChemGenex); has served as a speaker or consultant for ARIAD, BMS, Merck, Novartis, Pfizer, Roche and TEVA; and is a stockholder of ARIAD. MBB-G is an employee of BMS and as employment benefit has received shares in BMS stock. JU was an employee of BMS at the time of analysis. AH has received research funding from ARIAD, BMS, MSD, Novartis and Pfizer. The authors did not receive financial compensation for authoring the manuscript.

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AUTHOR CONTRIBUTIONS

All authors provided feedback and guidance on the analysis and interpretation of the results, contributed to the drafting of and critically reviewed the manuscript and provided final approval for submission. TPH, AH and JU designed the analysis.

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