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ORIGINAL ARTICLE

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Treatment patterns and clinical outcomes of tyrosine kinase inhibitors in chronic-phase CML in clinical practice: 3-year European SIMPLICITY data

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Abstract

Objectives: SIMPLICITY (NCT01244750) is an observational study of patients with chronic-phase chronic myeloid leukemia (CP-CML) in routine clinical practice receiving first-line tyrosine kinase inhibitors (TKIs). We evaluated TKI treatment changes and how switching affects clinical response in patients recruited in Europe with ≥3 years of follow-up.

Methods: The SIMPLICITY European cohort (France, Germany, Italy, the Netherlands, Russia, and Spain) included 431 patients. 370 (86%) were followed for ≥3 years.

Results: Proportions of patients experiencing treatment interruptions, TKI switching, and discontinuations decreased over 3 years' follow-up. Intolerance was a key driver for treatment changes. Complete cytogenetic response (CCyR) was achieved in 87.5% of patients switching TKI within 3 years of initiation vs 91.7% of non-switchers. Major molecular response (MMR) was achieved in 82.4% of switchers vs 92.9% of non-switchers. Over 3 years, not switching TKI was a strong predictor for achieving CCyR or MMR (both $P < .05$). Three-year survival remained high, irrespective of treatment changes (95.3% switchers, 96.4% non-switchers).

Conclusions: European patients with CP-CML who do not switch TKI are more likely to achieve clinical response, while intolerance is a key driver for switching. Successful CML management may require careful selection of initial TKI, with early monitoring of response and intolerance.

KEYWORDS

dasatinib, imatinib mesylate, leukemia, chronic, BCR-ABL positive, myeloid, chronic-phase, observational studies

1 | INTRODUCTION

Chronic myeloid leukemia (CML) is a rare myeloproliferative neoplasm, with a crude incidence of 1.1 cases per 100 000 in Europe.[1] Tyrosine kinase inhibitors (TKIs) are a mainstay of treatment for chronic-phase CML (CP-CML).[2,3] Imatinib, a first-generation TKI, was the first TKI to receive regulatory approval for treatment of CP-CML. Since then, approved second-generation TKIs, including nilotinib and dasatinib, have been associated with higher and faster rates of cytogenetic and molecular responses and reduced rates of progression, but no survival advantage, compared with imatinib as first-line (1L) treatments in CP-CML patients (reviewed by Rosti et al[4]). Nonetheless, International guidelines recommend that CP-CML patients receiving TKI treatment are monitored regularly, modifying treatment based on response.[2,3,5] Such monitoring is necessary, both for assessing eligibility of patients for TKI discontinuation to enter treatment-free remission, and to ensure the early detection of subsequent disease recurrence.[3]

SIMPLICITY (NCT01244750) is an ongoing observational study in seven countries (France, Germany, Italy, the Netherlands, Russia, Spain, and United States) of patients with CP-CML seen in routine clinical practice and receiving 1L TKI treatment (imatinib, dasatinib, or nilotinib). The primary objective of SIMPLICITY is to understand TKI use and management patterns in routine clinical practice and treatment-related outcomes. Previous analyses of SIMPLICITY have highlighted that National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) recommendations on response monitoring have not been consistently translated into routine clinical practice, and that intolerance is the most common reason for treatment interruptions, discontinuations, and switching.[6,7] In the overall SIMPLICITY population, 18% of patients with at least 12 months of follow-up had no documented cytogenetic response (CyR) or molecular response (MR) monitoring during the first 6 months of TKI treatment, with a higher proportion of patients in the European cohort receiving a CyR or MR test in the first 6 months than in the US cohort (87% vs 79%).[6]

Here we report SIMPLICITY data for patients recruited at European sites who reached 3 years of follow-up, and evaluate interruptions, switching, and discontinuations patterns in TKI treatment and how switching TKI may affect clinical response, and we discuss these outcomes in the context of the full SIMPLICITY cohort.

Novelty Statements

What is the NEW aspect of your work?

We report changes in tyrosine kinase inhibitor (TKI) treatment and the effect of switching first-line TKI on clinical response over 3 years of follow-up in European patients with chronic-phase chronic myeloid leukemia (CP-CML) from the SIMPLICITY study.

What is the CENTRAL finding of your work?

TKI treatment changes decrease over 3 years of follow-up in European patients with CP-CML, and patients who do not switch TKI treatment are more likely to achieve clinical response.

What is (or could be) the SPECIFIC clinical relevance of your work?

Patients who respond to first-line TKI treatment may have better clinical outcomes than those who switch to another TKI due to intolerance or lack of clinical response; therefore, in line with European LeukemiaNet recommendations, care and early monitoring of response and management of intolerance may be key to successful CML treatment.

2 | METHODS

SIMPLICITY enrolled patients newly diagnosed with CP-CML (age ≥18 years at the time of diagnosis), initiating TKI treatment on or after October 1, 2010. Patients were grouped into three prospective cohorts according to their 1L TKI: imatinib, dasatinib, or nilotinib. SIMPLICITY also enrolled a retrospective cohort of patients who started 1L imatinib between January 2, 2008, and September 30, 2010. The design of SIMPLICITY has been described in detail previously.[6] Each of the prospective cohorts closed when approximately 400 CP-CML patients had been enrolled. Study sites included practices in Europe (France, Germany, Italy, the Netherlands, Russia, and Spain) and United States. This analysis reports data for CP-CML patients from the three prospective cohorts recruited and treated in Europe.

The study protocol was approved by the relevant institutional review boards and written patient consent obtained. Data were collected through completion of an electronic case report form.

"Treatment interruption" was defined as a gap in treatment of >1 day before restarting the same TKI, from the day the TKI was temporarily discontinued and ending the day before restarting. "Treatment discontinuation" was defined as cessation of TKI treatment that did not qualify as a treatment interruption. "Treatment switch" was defined as discontinuation of index TKI, followed by the start of second-line (2L) TKI during the follow-up period; all patients who switched TKI were deemed to have discontinued treatment. Treatment interruptions and discontinuations were analyzed with reference to the date of TKI discontinuation and TKI switch, according to the date of 2L TKI start.

Treatment changes were grouped according to whether changes occurred within 1 year of index TKI initiation (first year of treatment), between 1 and 2 years after index TKI initiation (second year of treatment), or between 2 and 3 years after index TKI initiation (third year of treatment). The reasons for TKI switching were reported, selected from the following categories: intolerance, primary resistance (failure to achieve a response), acquired resistance (loss of response), insurance/financial reasons, subject refusal, unrelated medical conditions, and "other."

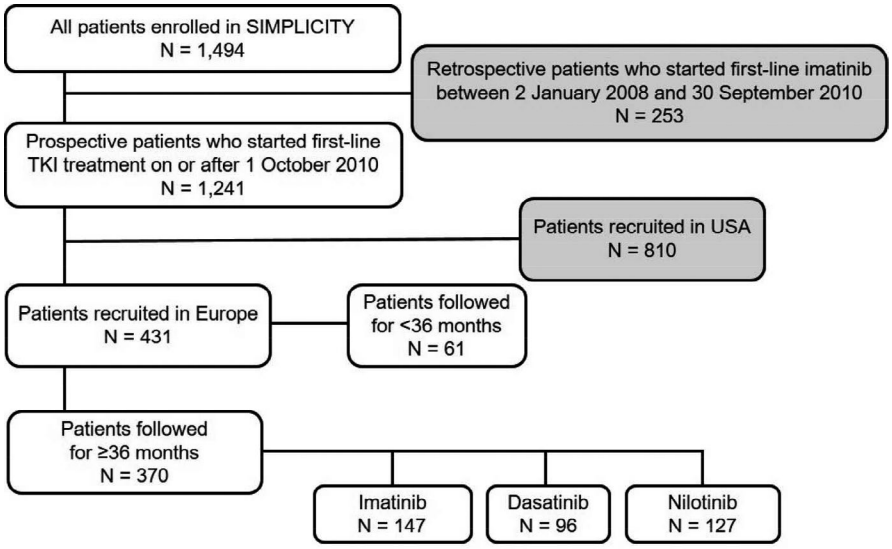

FIGURE 1 Patient flow diagram of the analyzed SIMPLICITY study population. TKI, tyrosine kinase inhibitor

TABLE 1 Baseline characteristics: European cohort patients

	Patients with ≥3 y of follow-up since initiating first-line TKI			
Characteristic	**Imatinib**	**Dasatinib**	**Nilotinib**	**All patients**
N	147	96	127	370
Male, n (%)	88 (59.9%)	51 (53.1%)	65 (51.2%)	204 (55.1%)
Median age at first-line TKI, years (IQR)	61.5 (46.7; 70.3)	57.4 (45.4; 72.8)	53.1 (45.3; 63.5)	57.2 (45.7; 68.9)
Age at first-line TKI, n (%)				
<50 y	42 (28.6%)	35 (36.5%)	49 (38.6%)	126 (34.1%)
50-64 y	46 (31.3%)	23 (24.0%)	51 (40.2%)	120 (32.4%)
≥65 y	59 (40.1%)	38 (39.6%)	27 (21.3%)	124 (33.5%)
Median time from first-line TKI to end of follow-up, months (IQR)	60.2 (60.0; 61.1)	55.3 (48.2; 60.3)	58.2 (44.5; 60.5)	60.0 (51.4; 60.8)
Minimum and maximum time from first-line TKI to end of follow-up, months	37.9, 64.1	38.9, 63.7	36.1, 71.6	36.1, 71.6
Race/Ethnicity, n (%)				
White non-Hispanic	115 (78.2%)	66 (68.8%)	84 (66.1%)	265 (71.6%)
Other/unknown	32 (21.8%)	30 (31.2%)	43 (33.9%)	105 (28.4%)
Practice type, n (%)				
Academic center	112 (76.2%)	73 (76.0%)	83 (65.4%)	268 (72.4%)
Private or community practice	35 (23.8%)	23 (24.0%)	44 (34.6%)	102 (27.6%)
Mean (±SD) number of comorbidities[a]	2.3 ± 2.1	1.6 ± 1.5	1.6 ± 1.6	1.9 ± 1.8

Note: Demographic information according to index TKI and the total SIMPLICITY population that had ≥3 y of follow-up since initiating TKI treatment.
Abbreviations: IQR, interquartile range; N, cohort size; n, sample size; SD, standard deviation; TKI, tyrosine kinase inhibitor.
[a]For patients with a baseline medical history form.

Monitoring patterns in the first, second, and third years following initiation of 1L TKI are presented for "non-switchers" according to index TKI, and switchers, according to the TKI patients were receiving at the time of best response.

Clinical response after the start of 1L TKI was assessed by CyR (karyotype or fluorescence in situ hybridization [FISH]) and by MR (only tests by polymerase chain reaction on the international scale [IS] were included), as determined by the treating physician and conducted at local laboratories in line with standard practice at the treatment center.

For eligible CyR testing, chromosome banding analysis results were reported if the number of metaphases examined was ≥20 and %Ph+ metaphases were known. Eligible FISH results were reported if the number of evaluated nuclei was ≥200 and %Ph+ cells were known. The "best" CyR was determined either by the earliest

complete CyR (CCyR), if achieved, or by the earliest partial CyR (PCyR), if achieved. If the patient did not achieve CCyR or PCyR, best CyR was characterized as the lowest of %Ph+ metaphases recorded during the specified follow-up period.

The "best" MR (on the IS) was determined by the earliest $MR^{4,5}$ (BCR-ABL < 0.0032%), if achieved, then the earliest MMR (BCR-ABL ≤ 0.1%) if achieved. If patients did not achieve $MR^{4,5}$ or MMR, the best MR was characterized as the lowest %BCR-ABL recorded during the specified follow-up period.

Proportions of patients achieving CCyR (0% Ph+ metaphases) and not achieving CCyR, and proportions of patients achieving MMR (BCR-ABL ≤ 0.1%) and not achieving MMR, are presented for best response achieved by 30 days after the initiation of index TKI, and by either 1, 2, or 3 years, in non-switchers, according to the index TKI, and in switchers according to the TKI at the time of best response. For both best CyR and best MR, results are presented for the most recent TKI at the best response for the switchers with a 30-day minimum treatment duration; otherwise for the TKI prior to the best response with a 30-day maximum treatment gap; if the specified TKI prior to documentation of the best response was the 1L TKI that was discontinued within 30 days of response assessment, switchers were recategorized as non-switchers.

Proportions of patients achieving CCyR, not achieving CCyR, achieving MMR and not achieving MMR, are presented for all patients with at least 1, 2, or 3 years of follow-up, and are presented for patients tested within the specified period for response in the non-switcher and switcher sub-cohorts.

Descriptive statistics were generated for the overall prospective population and by index TKI. Categorical data are presented as counts and percentages, and continuous data as mean ± standard deviation (SD), median, interquartile range, and range (minimum, maximum).

Saturated multivariable logistic regression models were used to identify factors independently associated with achievement of CCyR or achievement of MMR by 3 years. These factors included sex, age at diagnosis, TKI at best response, and timing of switching to 2L TKI. Separate regression analyses were performed as sensitivity analyses on non-switchers and switchers.

Cox survival analysis was also used to investigate the relationship between survival, and switching to 2L TKI, Sokal/Hasford risk score, sex, age at initiation of 1L TKI, choice of 1L TKI, early response monitoring (by 3 months from index TKI), and early achievement of MR < 10% (by 3 months from index TKI) at the end of year 3 of treatment for prospective switchers and non-switchers from the European cohort.

3 | RESULTS

Of the 1241 patients prospectively enrolled in SIMPLICITY between October 1, 2010, and September 5, 2018, 431 were treated in Europe, of whom 370 (86%) were followed for at least 3 years; 14% did not complete the follow-up period (reasons for dropout were not recorded prospectively). Of the group with 3 years of follow-up, 147 patients received 1L imatinib, 96 received 1L dasatinib, and 127 received 1L nilotinib (Figure 1). Median follow-up was 60.0 months (Table 1), and median age was 57.2 years. Patients receiving imatinib had the highest median age (61.5 years), followed by patients receiving dasatinib and nilotinib (median ages of 57.4 and 53.1 years, respectively). The overall mean (±SD) number of comorbidities was 1.9 (±1.8) and was highest for imatinib patients (2.3 [±2.1]).

3.1 | Treatment patterns in the first, second, and third years of TKI treatment

3.1.1 | Treatment interruptions

Treatment interruptions occurred most frequently within a year of initiating 1L TKI, occurring in 67 of 370 patients, compared with 23 patients in the second year and 14 in the third year of 1L TKI initiation (18.1%, 6.2%, and 3.8% of patients, respectively; Figure 2A). Treatment interruptions were generally more common in patients receiving imatinib than dasatinib or nilotinib, except in the second year of 1L TKI treatment during which interruptions were most common with dasatinib (Figure 2A).

3.1.2 | Treatment switching

The proportion of patients switching TKI was highest in the first year of 1L TKI treatment (58 of 370 patients), compared with that in the second (26 patients) and third (10 patients) years of TKI treatment (15.7%, 7.0,% and 2.7% of patients, respectively). This trend was seen for patients on 1L imatinib, dasatinib, or nilotinib (Figure 2B). The highest numbers of patients switching treatment in the first and second years of TKI treatment were those receiving 1L imatinib (in 35 and 13 patients, respectively). In the third year of TKI treatment, the highest numbers of patients switching were those receiving 1L dasatinib (4 patients) (Figure 3).

Reasons for switching TKI were provided for 55 of the 58 patients who switched in the first year of TKI treatment. Intolerance was the most common primary reason for switching, (reported in 40 patients) followed by primary resistance (8 patients) and acquired resistance (3 patients). This trend was observed in imatinib-treated patients, whereas the primary reason for almost all TKI switching for dasatinib- or nilotinib-treated patients was intolerance (11 of 11 dasatinib-treated patients and 9 of 10 nilotinib-treated patients).

In the second year of treatment, 26 patients switched TKI (reasons for switching were provided for 23 patients). Intolerance was the most common primary reason for switching, (reported in 10 patients) followed by primary resistance (7 patients) and acquired resistance (5 patients). Patients receiving dasatinib or nilotinib followed this trend, whereas primary resistance was the primary reason for switching in patients treated with imatinib (5 of the 12 patients).

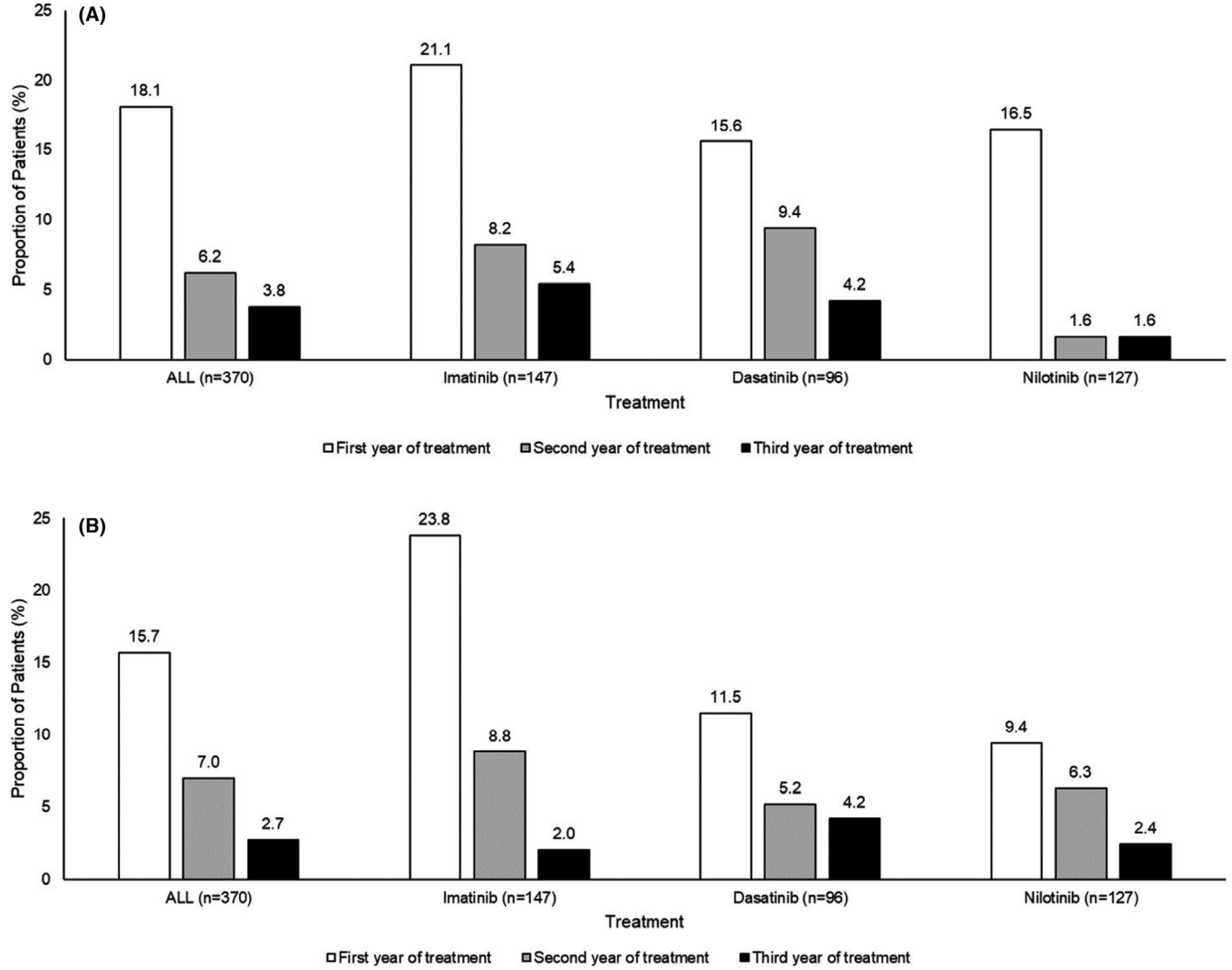

FIGURE 2 A, Treatment interruptions in the European cohort by TKI class and year of follow-up. TKI, tyrosine kinase inhibitor. B, Treatment switching in the European cohort by TKI class and year of follow-up. TKI, tyrosine kinase inhibitor

In the third year of treatment, 10 patients switched TKI (reasons for switching TKI treatment were provided for 8 patients). Intolerance and primary resistance were the most common defined primary reasons reported for switching (each reported in 2 patients), with acquired resistance reported in 1 patient (receiving imatinib). Additionally, 3 patients provided reasons for switching that were not directly related to treatment ("subject refusal," "unrelated medical conditions," and "other").

3.1.3 | Treatment discontinuations

The proportion of patients who discontinued 1L treatment for any reason was highest within a year of initiating 1L TKI (66 of 370 patients), compared with the proportion of those discontinuing in the second (30 patients) and third (16 patients) years (17.8%, 8.1%, and 4.3% of patients, respectively). This trend was seen for patients on 1L imatinib, dasatinib, and nilotinib (Figure S1). The patients who discontinued 1L TKI treatment included those who then switched to a 2L TKI (58 of the 66 who discontinued their 1L treatment were switchers).

The reasons for discontinuation in the first and second years after TKI initiation followed the same trend as the patients who switched TKI treatment, with intolerance (44 patients in the first year; 13 patients in the second year), primary resistance (9 and 7 patients, respectively), and acquired resistance (3 and 5 patients, respectively) being the most common primary reasons reported for discontinuation. The most common primary reason reported for discontinuation in the third year was not defined (categorized as "other": reported for 5 of 14 patients). Intolerance was the most common defined primary reason for discontinuation, (reported in 3 patients), followed by primary resistance (2 patients) and "refusal by subject" (2 patients).

3.2 | Clinical response to TKI treatment by 3 years

3.2.1 | Response monitoring patterns

In the first year of 1L TKI treatment, 221 (54.3%) of the 407 patients followed for this period were tested for CyR. Of the 354 patients

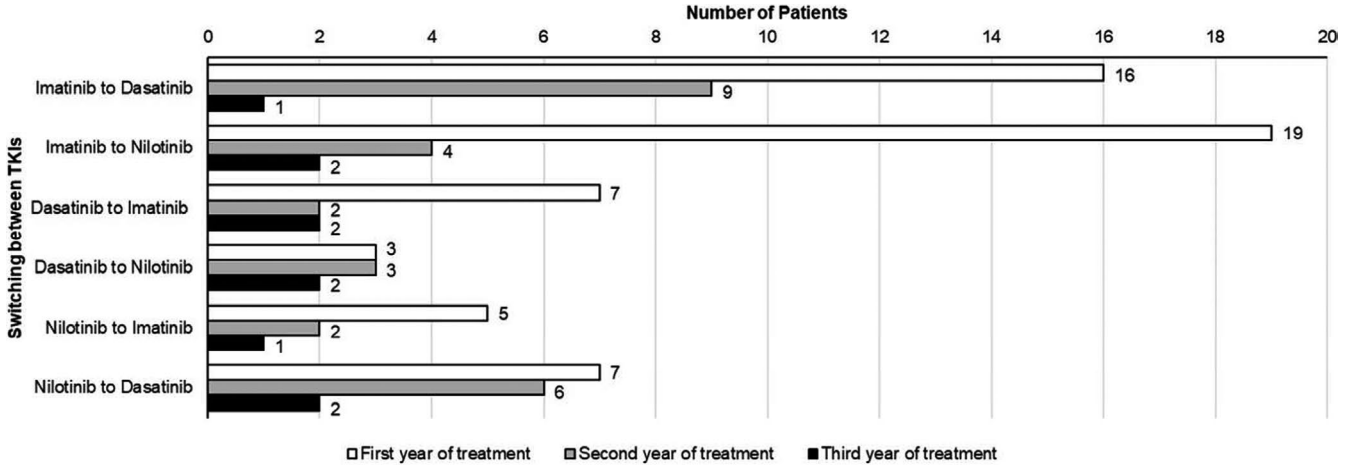

FIGURE 3 Treatment switching patterns from first- to second-line TKIs in the first, second, and third years of first-line TKI treatment in the European cohort. TKI, tyrosine kinase inhibitor

enrolled who were followed for ≥3 years, 217 (61.3%) had documented CyR testing (median 2.0 CyR tests per patient per year over the 3-year period). Within a year of 1L TKI initiation, 77.2% (n = 159) of the non-switchers and 60.0% (n = 9) of the switchers had been tested for CyR at least twice and/or up to four or more times.

Within a year of 1L TKI initiation, 360 (88.5%) of the 407 patients followed for this period were tested for MR. In the 354 patients with ≥3 years of follow-up, 335 (94.6%) had documented MR testing (median 2.0 MR tests per patient per year over the 3-year period). Within a year of 1L TKI initiation, 84.0% (n = 274) of the non-switchers and 79.4% (n = 27) of the switchers had been tested for MR at least twice and/or up to four or more times.

3.2.2 | Clinical response

In patients with documented CyR testing, 82.4% (n = 182) had achieved CCyR by 1 year, 91.3% (n = 209) by 2 years, and 91.2% (n = 198) by 3 years. At 3 years, the majority in this group had not switched TKI (88.9%; n = 193% vs 11.1%; n = 24 switchers). Of the 193 patients not switching TKI treatment, 91.7% (n = 177) had achieved CCyR by 3 years, compared with 87.5% (n = 21) of the 24 patients switching TKI treatment.

In patients with documented MR testing, 60.8% (n = 219) had achieved MMR by 1 year, 82.7% (n = 292) by 2 years, and 90.7% (n = 304) by 3 years. At 3 years, the majority in this group had not switched TKI (79.7%; n = 267% vs 20.3%; n = 68 switchers). Of the 267 patients not switching TKI treatment, 92.9% (n = 248) had achieved MMR by 3 years, compared with 82.4% (n = 56) of the 68 patients switching TKI treatment.

3.2.3 | Predictors of clinical response

Not switching to a 2L TKI within 3 years of initiation vs switching to 2L TKI between 6 months and 3 years was a strong predictor for achieving CCyR (odds ratio [OR] 3.92; 95% confidence interval [CI]: 1.14-13.46; $P = .030$). Gender was a weak predictor for achieving CCyR (female vs male; OR 0.40; 95% CI: 0.15-1.09; $P = .073$). Not switching to a 2L TKI within 36 months vs switching to 2L TKI between 6 and 36 months was also a strong predictor for achieving MMR (OR 4.07; 95% CI: 1.56-10.57; $P = .004$).

3.3 | Survival at 3 years of follow-up

After 3 years of follow-up, survival rate in the total prospective European cohort was 96.1%. Survival rates in patients were 95.7% (imatinib group), 95.9% (dasatinib group), and 96.9% (nilotinib group). In patients who did not switch 1L TKI within 3 years of follow-up, the survival rate was 96.4%, compared with 95.3% in those who had switched TKI. Cox survival analysis showed that there were no significant associations between 3-year survival and switching, generation of TKI, or lack of early response monitoring. Age at initiation of 1L TKI was a strong predictor of 3-year survival in the European cohort ($P < .001$) and in non-switchers ($P = .002$).

4 | DISCUSSION

This analysis describes the patterns of TKI treatment for CP-CML patients in Europe after 3 years of follow-up from the SIMPLICITY observational study. Treatment monitoring, clinical response outcomes, and predictors of clinical response are presented in the context of treatment patterns.

Patterns of treatment interruptions, discontinuations, and switching in this analysis were consistent with those seen for the overall SIMPLICITY cohort after 2 years of follow-up, which showed that a higher proportion of patients experienced these events in the first year of treatment than in the second.[7] These trends showing a decrease in these events in the second year extended to the third year, with the lowest proportion of European patients experiencing interruptions, discontinuations, and TKI

switching in the third year of treatment. As previously observed for the overall SIMPLICITY population,[7] the key drivers for treatment changes in the European cohort were intolerances to TKIs and, to a lesser extent, resistance to TKIs. Although the proportions of patients with changes in treatment for intolerance declined year-on-year, the contribution of resistance to discontinuation of treatment increased after the first year of treatment. Intolerance to TKI treatment typically occurs due to an increase of adverse events or development of an adverse event that cannot be managed through treatment of the symptom or dose reduction, thus leading to either TKI switching or discontinuation.[8] In this study, patients for whom intolerance was reported as the primary reason for treatment changes may also have underlying resistance to the index TKI that was not reported, which would also have an impact on the need for treatment changes. However, the data do suggest there are two phases of discontinuation: a short-term phase in which early intolerances are managed, followed by a later phase in which poor response and/or resistance are addressed.

SIMPLICITY has shown previously that monitoring of clinical response in the first year of TKI treatment is not necessarily performed as frequently as clinical guidelines suggest, both in the overall study population and in the European cohort.[6] In particular, the proportion of patients with at least 1 year of follow-up receiving early clinical response monitoring with either a CyR or MR test was 36% and 38% within the first 3 months, and 82% and 87% in the first 6 months, in the overall SIMPLICITY population and the European cohort, respectively.[6] Other observational studies in Europe, such as the European Treatment and Outcome Study (EUTOS) CML registry, have also shown the importance of response monitoring.[9] Absence of early clinical response monitoring means that a lack of response to TKI treatment cannot be identified, and action cannot be taken to change treatment. It is conceivable that treatment changes due to intolerances in some way mask changes that would have taken place for other reasons, showing that the observed rate of treatment switching due to treatment resistance is low. Infrequent monitoring is therefore a potential confounding factor in clinical practice. Monitoring is also necessary to assess when patients are able to enter treatment-free remission, and, if disease recurrence occurs, regular monitoring can ensure it is detected as early as possible.[3]

Previous data from routine clinical practice in the United States have shown that changes in treatment patterns can occur in up to one-third of patients on 1L imatinib, including switching to a 2L TKI in 21% of patients.[10] Rates of switching were lower in the SIMPLICITY European cohort (just under 16% in the first year after TKI initiation). In this population, we found that remaining on a 1L TKI treatment by the end of 3 years of follow-up was a significant predictor for achieving MMR and CCyR vs switching to another TKI between 6 months and 3 years. This observation indicates that patients who respond to and remain on 1L TKI treatment have better clinical outcomes than patients who switch to another TKI because of intolerance or lack of clinical response. This is consistent with the overall SIMPLICITY population by 3 years (Cortes et al; manuscript in preparation).

Survival after 3 years of follow-up in European patients was also comparable to the observed survival rate in the overall SIMPLICITY population after an equivalent time period (96.1% in the European cohort, 96.4% in the overall population; Mauro et al; manuscript in preparation). Early monitoring did not affect survival outcomes in the European population. While there was no observed correlation in this cohort between switching TKI treatment and survival, not switching was associated with achieving CCyR and MMR, response outcomes that are prognostic indicators for long-term survival. This suggests that the differences in survival between switchers and non-switchers may not have been captured in this 3-year study. A longer follow-up may therefore show greater differences in survival based on TKI switching status.

SIMPLICITY is a non-randomized study: As such, there is a risk of selection bias and confounding factors, and results should be interpreted in the context of clinical practice, and comparisons with randomized trials made with caution.[11] Limitations specific to SIMPLICITY have been discussed previously.[6,7]

In conclusion, TKI interruptions, discontinuations, and switching observed in the SIMPLICITY European cohort decreased over time, consistent with the overall SIMPLICITY population. Patients remaining on 1L TKI were more likely to achieve CCyR and MMR than those who switched. Intolerance was the most common reason given for switching from 1L TKI, particularly within the first year of treatment. Since few patients required alteration of therapy during the third year, and since remaining on therapy correlated with outcomes, careful selection of initial TKI therapy to maximize tolerability and addressing intolerance may be key to successful CML management.

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CONFLICT OF INTEREST

CGP has received grants and consultancy fees from BMS, and honoraria/grants from Pfizer. CC and CD are employees of BMS. GS and CG are employees of ICON Clinical Research. RH and RP declare no conflict of interest. MM reports research grants from BMS and Sanofi, and consultancy fees/honoraria from BMS, Pfizer, Novartis, Astellas Pharma, MSD, Genzyme, Medac, Elsalys, Chugai, and MaaT Pharma. SLG has received grants and/or consultancy fees from BMS, and has equity ownership of Cancer Outcomes Tracking and Analysis (COTA) Inc.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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