**Real-world tyrosine kinase inhibitor treatment pathways, monitoring patterns and responses in patients with chronic myeloid leukaemia in the United Kingdom: the UK TARGET CML study**

**Running title:** Tyrosine kinase inhibitor use in the real world

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**Abstract**

Management of chronic myeloid leukaemia (CML) has recently undergone dramatic changes, prompting the European LeukemiaNet (ELN) to issue recommendations in 2013; however, it remains unclear whether real-world CML management is consistent with these goals. We report results of UK TARGET CML, a retrospective observational study of 257 patients with chronic-phase CML prescribed a first-line TKI between 2013 and 2017, most of whom received first-line imatinib (n=203). Although 44% of patients required ≥1 change of TKI, these real-world data reveal that molecular assessments were frequently missed, 23% of patients with ELN-defined treatment failure did not switch TKI and kinase domain mutation analysis was performed in only 49% of patients who switched TKI for resistance. Major molecular response (MMR; *BCR-ABL1*IS ≤0.1%) and deep molecular response (DMR; *BCR-ABL1*IS ≤0.01%) were observed in 50% and 29%, respectively, of patients treated with first-line imatinib and 63% and 54% receiving a second-generation TKI first line. MMR and DMR were also observed in 77% and 44% of evaluable patients with ≥13 months’ follow-up receiving a second-generation TKI second line. We found little evidence that cardiovascular risk factors were considered during TKI management. These findings highlight key areas for improvement in providing optimal care to patients with CML.

**Keywords:** tyrosine kinase inhibitor, chronic myeloid leukaemia, real-world study, molecular response, management

**Introduction**

Tyrosine kinase inhibitors (TKIs) have revolutionised outcomes for patients with chronic myeloid leukaemia in chronic phase (CML-CP), with survival rates approaching those of the general population (Bower*, et al* 2016, Hoglund*, et al* 2013, Sasaki*, et al* 2015). Consequently, key considerations for optimal patient care have evolved considerably. While the primary aim remains achievement of molecular response that minimises the risk of disease progression (Baccarani*, et al* 2013), increasingly, complications of the treatment need to be considered. It is therefore essential for physicians to understand the best use of the available ABL1-targeting TKIs (Baccarani*, et al* 2013). This is the principal purpose of the most recent European LeukemiaNet (ELN) recommendations, which increased focus on molecular responses at 3, 6 and 12 months, with patients’ responses categorized as optimal, warning or failure (Baccarani*, et al* 2013). Patients experiencing failure are at particular risk of disease progression, and the guidelines recommend that such patients switch treatment and undergo assessment for *BCR-ABL1* kinase domain mutations (Baccarani*, et al* 2013).

While the current ELN guidelines state that patients must achieve a major molecular response (MMR; *BCR-ABL1* ≤0.1% on the International Scale [IS]) by 12 months for their response to be considered optimal (Baccarani*, et al* 2013), deeper levels of response, including MR4 (*BCR-ABL1*IS ≤0.01%) and MR4.5 (*BCR-ABL1*IS ≤0.0032%) are also recognized as important milestones (Cross*, et al* 2012, Etienne*, et al* 2014, Hehlmann*, et al* 2014). Some patients with a sustained deep molecular response (DMR; MR4 or better) may be eligible to attempt treatment-free remission (TFR) (Hochhaus*, et al* 2017b, Mahon 2017, NCCN 2019, Rea*, et al* 2018). Clinical trials have demonstrated that patients are more likely to achieve optimal and deeper responses to first-line therapy at key ELN milestones when second-generation (2G) TKIs are used rather than imatinib; however, achievement of responses in real-world practice is less well explored, particularly in the second-line setting (Cortes*, et al* 2018a, Cortes*, et al* 2016, Hochhaus*, et al* 2016). Achievement of ELN-defined responses and how ELN guidelines are implemented in real-world settings are infrequently explored.

An increased risk of cardiovascular (CV) adverse events (AEs) has been described in patients taking 2G- or 3G-TKIs compared with imatinib, especially in patients with preexisting CV risk factors (Chai-Adisaksopha*, et al* 2016, Cortes*, et al* 2018b, Cortes*, et al* 2016, Hochhaus*, et al* 2016, Lipton*, et al* 2016). Given the excellent long-term outcomes in CML, comorbidities are now a major consideration (Jabbour*, et al* 2014, Saussele*, et al* 2015). However, in UK routine clinical practice, it is unclear how physicians assess and manage CV risk factors or how CV risk factors affect TKI management.

UK TARGET CML (CAMN107CGB12) is a retrospective observational study of baseline assessment of patients with CML-CP, TKI treatment pathways, response monitoring patterns and response rates in routine UK National Health Service (NHS) clinical practice; we compared findings with ELN 2013 recommendations (Baccarani*, et al* 2013).

**Methods**

*Study design*

This retrospective noninterventional study was conducted at 21 UK NHS secondary and tertiary care centres. Data were collected from paper and electronic records. Inclusion criteria included CML-CP diagnosis at start of first-line TKI, age ≥18 years and ≥6 months of follow-up from date of first TKI (between January 2013 and April 2017). Patients prescribed first TKI in a clinical trial and patients in accelerated phase (AP) or blast phase (BP) before initiation of first TKI were excluded.

Objectives were to describe TKI treatment pathways in the UK, patient characteristics, practices for assessing and managing CV risk factors before TKI treatment, responses to first- and second-line TKI therapy at ELN time points, adherence to ELN 2013 recommendations and disease progression frequency and management. AE data were not collected.

Data were analysed using descriptive statistics, with a cutoff date of June 6, 2018, using Microsoft Excel and STATA (version 13; StataCorp LLC, College Station, TX). A study size of 200-250 patients in approximately 20 centres (maximum of 40 patients/centre) was expected to give a representative sample of patients in the UK and provide reliable quantitative and qualitative variables.

Responses were categorized as optimal, warning or failure according to ELN 2013 recommendations (Baccarani*, et al* 2013). If *BCR-ABL1* transcript levels were not available on the IS, unconverted *BCR-ABL1*/*ABL1* percentages were used to reflect real-world practices at that centre (all centres used *ABL1* as a reference gene). Two of 14 centres (14%) reported on the IS in 2013; increasing to 17/21 (81%) in 2017.

**Results**

*Patient demographics and baseline characteristics*

Two-hundred-fifty-seven patients (186 from 14 tertiary centres and 71 from 7 general hospitals) were enrolled between November 2015 and September 2017. Median follow-up by the data cutoff was 32.9 months (range, 12.6-58.6). Baseline characteristics are shown in **Table I**. Clinical characteristics (other than white blood cell [WBC] counts) and risk scores at diagnosis were not well documented.

The first-line TKI was imatinib in the majority of patients (79%); reasons for first-line TKI choice were recorded for <50% of patients: clinician preference, “standard first-line choice” and “good results expected” were the most frequently cited reasons (**Supplementary Table I**). First-line imatinib and 2G-TKIs were prescribed to 31/42 (74%) and 11/42 (26%) patients with high Sokal scores, respectively, and 23/34 (68%) and 11/34 (32%) with high European Treatment and Outcomes Study (EUTOS) scores. Patients receiving a first-line 2G-TKI were younger than those receiving first-line imatinib.

*CV risk factors and other documented comorbidities at baseline*

Among all patients, 149 (58%) had ≥1 recorded comorbidity at baseline (**Table I**). Seventy-four patients (36%) receiving imatinib had CV comorbidities at baseline vs 7 (13%) receiving a 2G-TKI (**Table II**). Only 74 patients (29%) had baseline blood pressure documented; 33 (45%) had stage ≥2 hypertension (**Supplementary Table II**) (Whelton*, et al* 2018).

Exact levels of baseline blood glucose were documented in 58 patients (23%); documentation occurred more often in patients treated with first-line 2G-TKI (20/54 [37%]) vs imatinib (38/203 [19%]). Baseline low-density lipoprotein and total cholesterol levels were recorded in 23 (9%) and 40 (16%) patients. CV risk assessment tool use was documented for 10 patients (4%), with the validated QRISK2 tool used in 3 (1%).

*Response monitoring practices*

Within 12 months of starting first-line TKI, 250 patients (97%) had ≥1 real-time quantitative polymerase chain reaction (RQ-PCR) assessments and 221 patients (86%) had ≥3 RQ-PCR assessments. Two-hundred-four (79%), 177 (69%), and 162 (63%) patients had assessments at the 3-, 6-, or 12-month ELN milestones (regardless of TKI line), respectively. Cytogenetic testing (chromosome banding analysis or fluorescence in situ hybridization) was conducted less frequently. Frequency of assessments at ELN milestones on first and second TKI are described in **Table III**.

*First-line TKI therapy*

Median follow-up duration on first-line TKI and molecular responses to first-line TKI therapy are shown in **Table IV**. Time to discontinuation of first TKI for patients on imatinib vs 2G-TKI is shown in **Fig 1**. For patients receiving imatinib or nilotinib, respective median starting doses were 400 or 600 mg/day; 24/203 (12%) and 8/50 (16%) had dose reductions, while 14% and 12% had dose interruptions.

Quantifiable molecular or cytogenetic assessments were performed at ≥1 ELN milestone during first-line TKI in 223 patients (87%) (**Fig 2**). Forty-eight patients had ≥1 failure; 11 (23%) remained on first-line TKI (median follow-up, 13.8 months [IQR, 12.8-25.9]), and 37 (77%) switched TKIs (median follow-up, 25.1 months [IQR, 14.3-32.6]).

*Second-line TKI therapy*

At least one TKI switch occurred in 113 patients (44%); 54 (21%) switched more than once. Reasons for the first switch were resistance in 73 (65%), intolerance in 38 (34%) and other reasons in 2 (2%) (**Supplementary Table III**). *BCR-ABL1* kinase domain mutational analysis was performed prior to the first switch in 24 patients (21%), including 20 (27%) who switched due to resistance and 4 (10%) who switched due to intolerance or other reasons. Thirteen patients (12%) switched to imatinib, 68 (60%) to nilotinib, 20 (18%) to dasatinib, 11 (10%) to bosutinib and one (1%) to ponatinib (**Supplementary Table IV)**. For patients receiving second-line imatinib, nilotinib, dasatinib and bosutinib, median starting doses (range) were 400 (200-400), 600 (200-800), 100 (50-100) and 300 (100-500) mg/day, respectively.

Median follow-up duration after switching to second TKI was 23.7 months (range, 1.2-54.1) (**Table V**). MMR at any time and DMR at any time were observed in 37/51 (73%) and 21/51 (41%) patients with ≥13 months’ follow-up on second line. Molecular responses to second-line TKI for all patients regardless of follow-up duration are shown in **Supplementary Table V**.

Of 113 patients who switched TKI at least once, 18 (16%) had failure on second-line TKI (**Supplementary Fig 1**); 7 (39%) remained on that TKI (median follow-up, 24.3 months [IQR, 11.6-31.0]), while 11 (61%) switched again (median follow-up, 27.5 months [IQR, 16.4-33.8]).

*Overall TKI pathways*

Among all patients, 144 (56%) received only a first-line TKI, and 59 (23%), 35 (14%), 16 (6%) and 3 (1%) received 2, 3, 4 and 5 TKIs, respectively; sequences of TKI received are described in **Supplementary Table IV**. Eleven patients received the same TKI in multiple lines of therapy.

*Disease progression*

Ten patients progressed to AP and/or BP, and 15 patients died (10 in CP and 5 after progression). Survival outcomes and treatments to manage progression are summarized in **Fig 3**.

**Discussion**

The management of CML has undergone dramatic changes; however, it remains unclear whether real-world practice in the UK has evolved with these developments. We conducted the UK TARGET CML study to assess this question, with a particular focus on (1) TKI treatment pathways, (2) implementation of ELN recommendations for molecular-based patient management, (3) attainment of DMR with first- and second-line TKI in real-world practice and (4) assessment of baseline CV risk factors.

Despite relatively short median follow-up (<33 months), almost half of patients switched from first-line TKI, most often due to resistance (65%). In addition, 21% of patients received ≥3 lines of TKIs. This frequency of TKI switching was somewhat higher than that observed in prospective clinical trials, such as the pivotal trial of frontline imatinib (International Randomized Study of Interferon and STI571 [IRIS]), which reported that 34% of patients discontinued treatment after 6 years follow-up, although no other alternative TKI was available at the time of IRIS recruitment (Hochhaus*, et al* 2009). In IRIS long-term follow-up (median, 10.9 years), imatinib discontinuation was most frequently attributed to unsatisfactory therapeutic effect (15.9%), withdrawal of consent (10.3%), or AEs (6.9%) (Hochhaus*, et al* 2017a). Similarly, in the frontline trial of nilotinib (Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients [ENESTnd]), treatment discontinuations were most frequently due to suboptimal response/treatment failure or AEs/abnormal laboratory values (12% each by the 5-year data cutoff among patients allocated to nilotinib 300 mg twice daily) (Hochhaus*, et al* 2016). We found that in real-world practice, approximately half of patients required a change of TKI, highlighting the importance of optimal monitoring of molecular responses and treatment-related side effects to ensure proper use of TKIs and timely switching. These data also demonstrated the ongoing challenge of establishing a satisfactory, long-term treatment, with multiple TKI switches being common.

Although 58% of patients had a recorded comorbidity, patients generally had poorly documented baseline clinical characteristics and prognostic scores. Demographic and baseline characteristics were not dissimilar from those of other real-world cohorts (Goldberg*, et al* 2017, Hoglund*, et al* 2013, Nesr*, et al* 2018), although prognostic scores were better documented (98%) in the Swedish CML registry (Hoglund*, et al* 2013). CV events have been reported to be increased with 2G-TKIs (Chai-Adisaksopha*, et al* 2016, Cortes*, et al* 2016, Hochhaus*, et al* 2016), and CV risk factors should therefore be carefully considered when choosing a TKI. Even with first-line imatinib, it is important to assess CV risk given that approximately half of patients will require a switch to a 2G-TKI at some point. Although late complications with 2G-TKIs were not fully understood or evaluable at the time of ELN 2013, the guidelines nevertheless recommended continued clinical monitoring of all patients. Several CV risk factors were very poorly documented in our cohort, and any use of validated CV risk tools, such as QRISK2, was rarely documented. Baseline blood pressure was documented in less than one-third of patients; when baseline blood pressure was recorded, it was often elevated, with 3 patients in hypertensive crisis, illustrating the importance of documenting this parameter so that hypertension can be managed appropriately. However, some evidence was observed that CV comorbidities at baseline played a role in first-line TKI choice, with patients appearing more likely to receive first-line imatinib if a CV comorbidity was documented.

Currently the UK National Institute for Health and Care Excellence (NICE) recommends NHS funding in England of imatinib, nilotinib or dasatinib in the first line, and nilotinib, dasatinib, bosutinib or ponatinib in later lines (Health and Care 2018). In this cohort, first-line treatment was mostly imatinib or nilotinib (<2% received first-line dasatinib), and second-line treatment was mostly nilotinib, reflecting NICE recommendations at the start of treatment for these patients (dasatinib was not routinely available). Patients were more likely to receive first-line 2G-TKIs than imatinib if they were younger and had no documented comorbidities. Overall, prognostic scores were poorly documented despite strong evidence that these risk scores remain highly predictive of disease response in the TKI era (Hochhaus*, et al* 2016). We did not find evidence that prognostic scores played a major role in first-line TKI choice, with a majority of patients identified as high risk by Sokal, EUTOS or Hasford criteria being treated with imatinib. Overall, 4% of patients progressed to AP and/or BP, corresponding well with the results of the Swedish CML registry (3% by 12 months) (Hoglund*, et al* 2013).

One key finding of this study is that ELN 2013 monitoring recommendations were not consistently implemented. Patients frequently did not have assessments at recommended time points. This finding is consistent with those from the SIMPLICITY study, which reported that monitoring was conducted less frequently than recommended, though with higher frequency in Europe than the United States (Goldberg*, et al* 2017). This finding is important because a previous study showed that patients without frequent molecular monitoring were at higher risk of disease progression (Goldberg*, et al* 2013). In addition, frequent molecular monitoring (3-4 times per year) was associated with greater TKI treatment adherence in patients with CML (Guerin*, et al* 2014).

Overall, in our study, 86% of patients had ≥3 molecular response tests during their first year of TKI treatment, while SIMPLICITY reported 46% for Europe (Goldberg*, et al* 2017), a finding that potentially reflects UK-specific practice or changes in practice over time (UK patients who were first treated in 2013-2017 were compared with SIMPLICITY patients first treated in 2010-2015). Furthermore, our UK study observed a relatively high level of testing for early molecular response (EMR) at 3 months (81%) compared with SIMPLICITY (32%), indicating rapid adoption of molecular monitoring at early milestones in the UK (Goldberg*, et al* 2017).

However, despite a generous 1-month window applied around ELN milestones, a large proportion of patients (≈20%-30%) were still without evaluable molecular or cytogenetic test results at any given time point during their first year of TKI treatment. Moreover, 13% of patients had no evaluable molecular or cytogenetic result at any ELN milestone during the first year of TKI treatment.

ELN recommended that a patient with ELN-defined failure should have their TKI switched to reduce the risk of progression. Nevertheless, a number of patients in TARGET remained on first-line TKI despite ELN-defined treatment failure.

Strikingly, *BCR-ABL1* kinase domain mutational analyses, recommended by ELN in warning or failure, were infrequently performed even in patients with documented resistance, despite the known importance of mutation status for subsequent TKI selection. Patients did not always have recommended baseline assessments such as qualitative PCR despite its importance in determining *BCR-ABL1* transcript type, which can affect future molecular monitoring, especially at the low levels before consideration for TFR. Furthermore, although bone marrow and cytogenetic analysis still have an essential role in assessment of patients at baseline, many patients were managed without bone marrow or cytogenetic analysis. Bone marrow evaluation before TKI switching was infrequently performed, which may reflect the current use of PCR thresholds for interpretation of resistance.

Clinical trials have shown that 2G-TKIs lead to improved rates of molecular responses compared with imatinib (Cortes*, et al* 2018a, Cortes*, et al* 2016, Hochhaus*, et al* 2016). In this cohort, observed rates of EMR and MMR at ELN milestones and DMR at any time during first-line TKI were higher with 2G-TKIs than with imatinib, confirming the results in this real-world setting. While EMR and MMR were defined as optimal responses in ELN 2013 (Baccarani*, et al* 2013), treatment goals are evolving to include deeper responses and TFR (Hochhaus*, et al* 2017b, NCCN 2019, Rea*, et al* 2018). Studies have shown that deeper molecular responses were associated with improved outcomes compared with complete cytogenetic response (Etienne*, et al* 2014, Hehlmann*, et al* 2014), and a sustained DMR is a prerequisite for attempting TFR in both clinical practice guidelines (Hochhaus*, et al* 2017b, NCCN 2019, Rea*, et al* 2018) and clinical trials (Mahon*, et al* 2018, Ross*, et al* 2018). Clinical studies have demonstrated that 2G-TKIs can also lead to improved rates of DMR in the second line (Hughes*, et al* 2017). Results from our study showed that patients switching from first-line treatment may achieve not only optimal responses but also deeper responses, including patients with prior resistance or ELN-defined failure.

A criticism of observational studies is the increased risk of selection bias and confounding, precluding the robust analysis and conclusions provided by randomized controlled trials. However, real-world evidence plays an important role in allowing physicians to reflect on current practice. Our study demonstrated that almost half of patients required TKI switch in real-world practice and that optimal and deep responses can be achieved by patients who switch. However, inadequate CV risk assessment, response monitoring, and mutational analysis increased the risk of inappropriate patient management and, as such, the findings of this study highlighted key areas for improvement in care for patients with CML. Further consideration for improving implementation of guidelines in real-world clinical practice is warranted.

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**Competing interests**

AJM has participated in advisory boards for Novartis, Bristol-Myers Squibb (BMS) and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis. REC has participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis, BMS and Pfizer. NCPC has participated in advisory boards for Novartis, BMS and Pfizer; received honoraria from Novartis, BMS, Pfizer and Ariad/Incyte; and received research funding from Novartis, BMS and Pfizer. FD received honoraria and travel, accommodations and expenses from Novartis. MFMM participated in advisory boards for Novartis and received honoraria from Novartis, Pfizer and BMS. SM has participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis. GC has participated in advisory boards for Novartis. FW received educational grants from Pfizer and Novartis. MR has participated in advisory boards and received honoraria from Novartis. JB has participated in advisory boards and received honoraria from Novartis, Pfizer and Incyte. FLD has received honoraria and travel expenses from Novartis and Pfizer. SA has participated in advisory boards and received honorarium, travel and accommodations from Novartis. MD has received honoraria from Novartis and Pfizer, and research funding from Novartis. JT has received support for conference attendance from Novartis. BH has participated in advisory boards for Novartis, Pfizer and BMS. FMW has received honoraria, travel, accommodation and expenses from Novartis. DM has received honoraria from Incyte, Novartis, Pfizer and BMS. JR and SJC are employees and shareholders of Novartis. LF is a former employee and shareholder of Novartis. FG is an employee of OPEN VIE contracted by Novartis. PN, GC and FW declared no conflict of interest.

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**Table I. Patient demographics and baseline characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All patients  (N=257) | First-line imatinib  (n=203) | First-line  2G-TKI  (n=54) | First-line nilotinib  (n=50) |
| Sex, n (%) |  |  |  |  |
| Male | 144 (56) | 119 (59) | 25 (46) | 24 (48) |
| Female | 113 (44) | 84 (41) | 29 (54) | 26 (52) |
| Age at initiation of first-line TKI, median (range [IQR]), years | 53.5  (18.4 - 92.4 [38.8-65.8]) | 55.4  (18.4 - 92.4 [39.9-67.4]) | 45.8  (20.3- 79.5 [36.4-59.6]) | 45.1  (20.3 -79.5 [36.1-59.6]) |
| Time from CML diagnosis to start of first TKI, median (IQR), days | 7.0 (1.0-20.0) | 8.0 (2.0-20.3) | 6.0 (1.0-11.0) | 6.0 (1.0-11.0) |
| Assessments prior to first-line TKI, n (%) |  |  |  |  |
| RQ-PCR | 169 (66) | 140 (69) | 29 (54) | 26 (52) |
| Qualitative PCR (b2a2, b3a2, other) | 140 (54) | 107 (53) | 33 (61) | 30 (60) |
| CBA | 180 (70) | 146 (72) | 34 (63) | 31 (62) |
| FISH | 155 (60) | 117 (58) | 38 (70) | 34 (68) |
| CBA or FISH (bone marrow) | 154 (60) | 119 (59) | 35 (65) | 32 (64) |
| CBA or FISH (peripheral blood) | 54 (21) | 45 (22) | 9 (17) | 9 (18) |
| Both CBA/FISH and RQ-PCR | 139 (54) | 117 (58) | 22 (41) | 20 (40) |
| Treatment for CML prior to first-line TKI, n (%) |  |  |  |  |
| Yes | 126 (49) | 97 (48) | 29 (54) | 26 (52) |
| Prior treatmenta,b |  |  |  |  |
| Hydroxycarbamide | 116 (92) | 89 (92) | 27 (93) | 24 (92) |
| Leukopheresis | 2 (2) | 2 (2) | 0 | 0 |
| Anagrelide | 1 (1) | 1 (1) | 0 | 0 |
| Interferon | 1 (1) | 1 (1) | 0 | 0 |
| Aspirin | 1 (1) | 0 | 1 (3) | 1 (4) |
| No | 128 (50) | 104 (51) | 24 (44) | 23 (46) |
| Unknown | 3 (1) | 2 (1) | 1 (2) | 1 (2) |
| Ph chromosome at baseline |  |  |  |  |
| Yes | 212 (82) | 175 (86) | 37 (69) | 35 (70) |
| No | 3 (1) | 1 (<1) | 2 (4) | 2 (4) |
| Unknown | 42 (16) | 27 (13) | 15 (28) | 13 (26) |
| Clinical characteristics |  |  |  |  |
| WBC count, median (IQR), 109/l | 82.4 (31.2-177.3) | 77.0 (31.2-158.0) | 92.9 (32.3-201.4) | 92.1 (32.5-198.9) |
| Unknown, n (%)c | 4 (2) | 1 (<1) | 3 (6) | 2 (4) |
| Platelet count, median (IQR), 109/l | 404.0 (252.5-603.0) | 393.5 (244.8-603.0) | 439.0 (339.0-578.0) | 441.0 (342.8-589.3) |
| Unknown, n (%)c | 14 (5) | 11 (5) | 3 (6) | 2 (4) |
| Basophils, median (IQR), % | 3.9 (2.0-7.0) | 3.3 (2.0-6.0) | 5.0 (2.3-8.0) | 4.0 (2.3-8.3) |
| Unknown, n (%)c | 59 (23) | 46 (23) | 13 (24) | 13 (26) |
| Eosinophils, median (IQR), % | 2.0 (1.1-3.7) | 2.0 (1.1-3.5) | 2.0 (1.3-3.7) | 2.0 (1.3-3.0) |
| Unknown, n (%)c | 58 (23) | 45 (22) | 13 (24) | 13 (26) |
| Blasts, median (IQR) (%) | 2.0 (1.0-4.8) | 2.0 (1.0-3.4) | 3.0 (1.6-8.4) | 3.0 (1.5-6.0) |
| Unknown, n (%)c | 101 (39) | 77 (38) | 24 (44) | 23 (46) |
| Spleen size below costal margin, median (IQR), cmd | 1.3 (0.0-10.1) | 1.0 (0.0-10.1) | 4.0 (0.0-10.3) | 2.0 (0.0-10.0) |
| Unknown, n (%)c | 85 (33) | 67 (33) | 18 (33) | 17 (34) |
| Sokal risk score, n (%)e |  |  |  |  |
| Low risk | 52 (20) | 43 (21) | 9 (17) | 8 (16) |
| Intermediate risk | 54 (21) | 41 (20) | 13 (24) | 13 (26) |
| High risk | 42 (16) | 31 (15) | 11 (20) | 9 (18) |
| No score recorded and required components not all recorded | 109 (42) | 88 (43) | 21 (39) | 20 (40) |
| EUTOS score, n (%)f |  |  |  |  |
| Low risk | 110 (43) | 90 (44) | 20 (37) | 19 (38) |
| High risk | 34 (13) | 23 (11) | 11 (20) | 9 (18) |
| No score recorded and required components not all recordedg | 113 (44) | 90 (44) | 23 (43) | 22 (44) |
| Hasford score, n (%)h |  |  |  |  |
| Low risk | 25 (10) | 19 (9) | 6 (11) | 5 (10) |
| Intermediate risk | 35 (14) | 32 (16) | 3 (6) | 3 (6) |
| High risk | 19 (7) | 13 (6) | 6 (11) | 4 (8) |
| No score recorded and required components not all recorded | 178 (69) | 139 (68) | 39 (72) | 38 (76) |
| Comorbidities, n (%) |  |  |  |  |
| None recorded | 108 (42) | 80 (39) | 28 (52) | 26 (52) |
| ≥1 recordedi,j | 149 (58) | 123 (61) | 26 (48) | 24 (48) |
| CV comorbidities | 81 (32) | 74 (36) | 7 (13) | 6 (12) |
| Diabetes | 25 (10) | 21 (10) | 4 (7) | 4 (8) |
| Respiratory disease | 20 (8) | 17 (8) | 3 (6) | 3 (6) |
| Renal disease | 16 (6) | 14 (7) | 2 (4) | 2 (4) |
| Nonhaematological cancer | 9 (4) | 8 (4) | 1 (2) | 1 (2) |
| Hepatic disease | 4 (2) | 3 (1) | 1 (2) | 1 (2) |
| Other | 86 (33) | 70 (34) | 16 (30) | 15 (30) |

2G-TKI, second-generation tyrosine kinase inhibitor; CBA, chromosome banding analysis; CML, chronic myeloid leukaemia; CV, cardiovascular; EUTOS, European Treatment and Outcomes Study; FISH, fluorescence in situ hybridization; IQR, interquartile range; Ph, Philadelphia chromosome; RQ-PCR, real-time quantitative polymerase chain reaction; WBC, white blood cell.

a Patients may have received multiple prior treatments.

b Proportion of patients with each prior treatment was calculated out of the total number of patients who received prior treatment.

c Proportion of patients with unknown clinical characteristics was calculated out of the total number of patients in each column.

d Spleens reported to be “normal” or “nonpalpable” were considered to be 0 cm below the costal margin.

e Among 148 patients who received any first-line TKI and had an available Sokal risk score at diagnosis, the score was documented for 96 (65%) and not documented and instead calculated during this analysis for 52 (35%).

f Among 144 patients who received any first-line TKI and had an available EUTOS risk score at diagnosis, the score was documented for 36 (25%) and not documented and instead calculated during this analysis for 108 (75%).

g Includes patients who had a risk category recorded but no score recorded.

h Hasford scores were not collected in case report forms and were calculated if required data were available.

i Patients may have had multiple comorbidities.

j Proportion of patients with each comorbidity was calculated out of the total number of patients in each column.

**Table II. Baseline CV comorbidities and risk factors**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| n (%) | All patients  (N=257) | First-line imatinib  (n=203) | First-line 2G-TKI  (n=54) | First-line nilotinib  (n=50) |
| Diabetes | 25 (10) | 21 (10) | 4 (7) | 4 (8) |
| Smoking |  |  |  |  |
| Documenteda | 174 (68) | 140 (69) | 34 (63) | 32 (64) |
| Current smoker | 38 (22) | 35 (25) | 3 (9) | 3 (9) |
| Ex-smoker | 46 (26) | 39 (28) | 7 (21) | 6 (19) |
| Never smoked | 88 (51) | 65 (46) | 23 (68) | 22 (69) |
| Unclear | 2 (1)b | 1 (1)b | 1 (3)b | 1 (3)b |
| BMI >30 documented | 16 (6) | 14 (7) | 2 (4) | 2 (4) |
| CV comorbidities |  |  |  |  |
| None recorded | 176 (68) | 129 (64) | 47 (87) | 44 (88) |
| ≥1 recordedc,d | 81 (32) | 74 (36) | 7 (13) | 6 (12) |
| Hypertension | 58 (23) | 52 (26) | 6 (11) | 5 (10) |
| Hyperlipidaemia | 28 (11) | 26 (13) | 2 (4) | 2 (4) |
| Coronary artery disease | 14 (5) | 12 (6) | 2 (4) | 2 (4) |
| Myocardial infarction | 11 (4) | 10 (5) | 1 (2) | 1 (2) |
| Coronary artery bypass graft | 9 (4) | 8 (4) | 1 (2) | 1 (2) |
| Arrhythmias | 8 (3) | 7 (3) | 1 (2) | 1 (2) |
| Cerebrovascular accident | 4 (2) | 4 (2) | 0 | 0 |
| Transient ischemic attack | 4 (2) | 3 (1) | 1 (2) | 1 (2) |
| Congestive heart failure | 3 (1) | 2 (1) | 1 (2) | 1 (2) |
| Unstable angina | 2 (1) | 2 (1) | 0 | 0 |
| Percutaneous coronary intervention | 2 (1) | 2 (1) | 0 | 0 |
| Peripheral vascular disease | 2 (1) | 2 (1) | 0 | 0 |
| History of CV disease |  |  |  |  |
| Not documented | 101 (39) | 80 (39) | 21 (39) | 20 (40) |
| Documentation unknowne | 1 (<1) | 1 (<1) | 0 | 0 |
| Documentedf | 155 (60) | 122 (60) | 33 (61) | 30 (60) |
| No history | 26 (17) | 23 (19) | 3 (9) | 3 (10) |
| Details of history not provided | 104 (67) | 76 (62) | 28 (85) | 25 (83) |
| Details of history provided | 25 (16) | 23 (19) | 2 (6) | 2 (7) |
| Family history of CV disease |  |  |  |  |
| Not documented | 159 (62) | 128 (63) | 31 (57) | 29 (58) |
| Documentation unknowne | 1 (<1) | 1 (<1) | 0 | 0 |
| Documented | 97 (38) | 74 (36) | 23 (43) | 21 (42) |

2G-TKI, second-generation tyrosine kinase inhibitor; BMI, body mass index; CV, cardiovascular.

a Proportion of patients in each smoking category was calculated based on the number of patients with documented smoking status.

b Two patients were recorded as "does not smoke"; it was unclear whether they were ex-smokers or never smoked.

c Patients could be listed as having >1 CV comorbidity.

d Proportion of patients with CV comorbidities was calculated based on total number of patients in each column.

e One patient was transferred from another hospital prior to TKI treatment; it was unclear if this patient’s personal or family history of vascular disease had been documented prior to TKI treatment.

f Proportion of patients within each category was calculated based on the number of patients who had documented CV disease history.

**Table III. Frequency of molecular and cytogenetic assessments at ELN milestones for patients on first and second TKI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | All patients  n (%) | Imatinib  first line    n (%) | Second-generation first line  n (%) | Nilotinib first line  n (%) |
| **First TKI** |  |  |  |  |
| **RQ-PCR** |  |  |  |  |
| 3 monthsa | 180/223 (81) | 143/173 (83) | 37/50 (74) | 35/47 (74) |
| 6 monthsb | 141/199 (71) | 105/154 (68) | 36/45 (80) | 34/42 (81) |
| 12 monthsc | 117/170 (69) | 95/132 (72) | 22/38 (58) | 21/35 (60) |
| **CBA/FISH** |  |  |  |  |
| 3 monthsa | 15/223 (7) | 15/173 (9) | 0/50 (0) | 0/47 (0) |
| 6 monthsb | 9/199 (5) | 8/154 (5) | 1/45 (2) | 1/42 (2) |
| 12 monthsc | 2/170 (1) | 2/132 (2) | 0/38 (0) | 0/35 (0) |
| **CBA/FISH and/or RQ-PCR** |  |  |  |  |
| 3 monthsa | 186/223 (83) | 148/173 (86) | 38/50 (76) | 36/47 (77) |
| 6 monthsb | 151/199 (76) | 114/154 (74) | 37/45 (82) | 35/42 (83) |
| 12 monthsc | 117/170 (69) | 95/132 (72) | 22/38 (58) | 21/35 (60) |
| **Second TKI** |  |  |  |  |
| **RQ-PCR** |  |  |  |  |
| 3 monthsa | 63/82 (77) | 8/10 (80) | 55/72 (76) | 43/54 (80) |
| 6 monthsb | 44/66 (67) | 4/8 (50) | 40/58 (69) | 31/46 (67) |
| 12 monthsc | 27/52 (52) | 4/8 (50) | 23/44 (52) | 19/39 (49) |
| **CBA or FISH** |  |  |  |  |
| 3 monthsa | 12/82 (15) | 2/10 (20) | 10/72 (14) | 9/54 (17) |
| 6 monthsb | 4/66 (6) | 0/8 (0) | 4/58 (7) | 4/46 (9) |
| 12 monthsc | 1/52 (2) | 0/8 (0) | 1/44 (2) | 1/39 (3) |
| **CBA/FISH and/or RQ-PCR** |  |  |  |  |
| 3 monthsa | 65/82 (79) | 8/10 (80) | 57/72 (79) | 45/54 (83) |
| 6 monthsb | 45/66 (68) | 4/8 (50) | 41/58 (71) | 32/46 (70) |
| 12 monthsc | 27/52 (52) | 4/8 (50) | 23/44 (52) | 19/39 (49) |
| ≥1 assessment at an ELN milestone (first- or second-line TKI)a | 239/257 (93) | 189/203 (93) | 50/54 (93) | 48/50 (96) |

CBA, chromosome banding analysis; ELN, European LeukemiaNet; FISH, fluorescence in situ hybridization; RQ-PCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

a Denominator included patients with ≥4 months’ follow-up on that TKI.

b Denominator included patients with ≥7 months’ follow-upon that TKI.

c Denominator included patients with ≥13 months’ follow-upon that TKI.

**Table IV. Summary of molecular responses to first-line TKI therapya**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Overall responses | | | First-line TKI | | | |
| First-line imatinib  (n=203) | First-line  2G-TKI  (n=54)b | All patients (N=257) | First-line imatinib  (n=203) | First-line  2G-TKI  (n=54)b | First-line nilotinib  (n=50) | All patients (N=257) |
| Median follow-up durationc on each TKI (range), months | 33.3 (12.6-58.6) | 30.0 (13.2-56.8) | 32.9 (12.6-58.6) | 16.7 (0.5-54.8) | 20.8 (0.5-55.3) | 21.3 (0.5-55.3) | 17.5 (0.5-55.3) |
| EMR at 3 months (±1 months), in patients with 3-month molecular response assessments, n (%) | 88/163 (54) | 29/41 (71) | 117/204 (57) | 88/156 (56) | 28/38 (74) | 26/36 (72) | 116/194 (60) |
| MMR by 12 months (±1 months), n (%) | 84 (41) | 28 (52) | 112 (44) | 71 (35) | 26 (48) | 25 (50) | 97 (38) |
| MMR at any time, n (%) | 156 (77) | 42 (78) | 198 (77) | 102 (50) | 34 (63) | 32 (64) | 136 (53) |
| DMR at any time, n (%) | 95 (47) | 35 (65) | 130 (51) | 58 (29) | 29 (54) | 27 (54) | 87 (34) |

2G-TKI, second-generation tyrosine kinase inhibitor; DMR, deep molecular response; EMR, early molecular response; MMR, major molecular response.

a Patients could appear in multiple molecular response categories. Molecular responses were assessed as early molecular response (EMR; *BCR-ABL1*IS ≤10% at 3 months), MMR (*BCR-ABL1*IS ≤0.1%) by 12 months, MMR at any time and DMR (*BCR-ABL1*IS ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used.

b Fifty patients received first-line nilotinib, and 4 received first-line dasatinib.

c The columns for overall response reported the duration of follow-up for all TKI therapy, including later-line TKIs in patients who switched from their first-line TKI (from start of first-line TKI to most recent data collection). The columns for first-line TKI therapy reported the duration of follow-up for only first-line TKI therapy (from start of first-line TKI to most recent data collection or death in patients who remained on first-line TKI or to end of first-line TKI for patients who switched to a second-line TKI).

**Table V. Summary of molecular responses after switching to second-line TKI therapya**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | All switched patients  (n=113) | Second-line imatinib  (n=13) | Second-line 2G-TKI  (n=100)b | Second-line nilotinib  (n=68) | Switched to second line for resistance  (n=73) | Switched to second line for intolerance or other reason  (n=40)c |
| Median follow-up post first switch (range), monthsd | 23.7 (1.2-54.1) | 22.5 (4.9-43.0) | 23.9 (1.2-54.1) | 29.7 (1.2-52.4) | 27.4 (1.2-51.4) | 20.1 (2.8-54.1) |
| Median follow-up on second-line TKI (range), monthse | 23.9 (13.6 to 50.2) | 19.2 (13.6 to 43.0) | 28.6 (13.9 to 50.2) | 27.3 (13.9 to 50.2) | 25.6 (13.9 to 46.5) | 20.3 (13.6 to 50.2) |
| EMR at 3 months (±1 month) in patients with BCR-ABL1 at 3 months, n (%) | 75/85 (88) | 11/11 (100) | 64/74 (86) | 48/53 (91) | 47/55 (85) | 28/30 (93) |
| EMR at 3 months (±1 month) on second TKI in patients with 3-month molecular response assessments, n (%)f | 59/70 (84) | 10/10 (100) | 49/60 (82) | 38/45 (84) | 39/47 (83) | 20/23 (87) |
| MMR by 12 months (±1 month) on second TKI, n (%)g | 30/50 (60) | 4/7 (57) | 26/43 (60) | 24/38 (63) | 21/35 (60) | 9/15 (60) |
| MMR at any time on second TKI, n (%)g | 37/51 (73) | 4/8 (50) | 33/43 (77) | 29/38 (76) | 27/36 (75) | 10/15 (67) |
| DMR at any time on second TKI, n (%)g | 21/51 (41) | 2/8 (25) | 19/43 (44) | 17/38 (45) | 15/36 (42) | 6/15 (40) |

2G-TKI, second-generation tyrosine kinase inhibitor; DMR, deep molecular response; EMR, early molecular response; MMR, major molecular response.

a Patients could appear in multiple molecular response categories. Molecular responses were assessed as early molecular response (EMR; *BCR-ABL1*IS ≤10% at 3 months), MMR (*BCR-ABL1*IS ≤0.1%) by 12 months, MMR at any time, and DMR (*BCR-ABL1*IS ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used.

b Switched to 2G-TKI; n=68 nilotinib, n=20 dasatinib, n=11 bosutinib, n=1 ponatinib).

c Switched for intolerance (n=38) or switched for another reason (n=2).

d Duration from start of second-line TKI to last data collection or death (included patients with ≥1 switch).

e Duration from start of second-line TKI to last data collection, date of switch to a third-line TKI, or death.

f EMR defined as *BCR-ABL1IS* ≤10% at 3 months (±1 month); only those patients with *BCR-ABL1* available at 3 months were included.

g MMR (≤0.1% *BCR-ABL1*); DMR (≤0.01% *BCR-ABL1*); only those patients with ≥13 months’ follow-up were included.

**Fig 1. Kaplan-Meier curve: time to discontinuation of first-line TKI**

A screenshot of a cell phone

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Patients who had not switched from first TKI at point of data collection were censored at date of data collection or death.

Months on first TKI were unknown for 10 patients on imatinib.

**Fig 2. TKI treatment pathways and molecular responses for patients with ELN optimal, warning (at single vs multiple ELN milestones), or failure responses while on first-line TKI**

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a In patients with multiple test results available; any patient with a failure response to first-line TKI at an ELN milestone (regardless of other responses achieved at earlier milestones) was classified as having a failure response. Patients in the optimal category had only optimal responses at an ELN milestone (3, 6, or 12 months) with either molecular or cytogenetic assessments (where a molecular test was not available). Patients in the warning category had a warning at any milestone with either assessment but had no failure at any milestone with either assessment. Patients without assessments at any ELN milestone could not be categorized. Thirty-four patients had no evaluable test at any ELN milestone by either molecular or cytogenetic test

b Response may have been observed at any time. Duration of follow up varied; patient may have had ≥1 subsequent TKI switch.

Forty-eight patients had ≥1 failure; 11 (23%) remained on first-line TKI (median follow-up, 13.8 months [IQR, 12.8-25.9 months]), and 37 (77%) switched TKIs (median follow-up, 25.1 months [IQR, 14.3-32.6 months]). Of those who switched, 22 had their first failure at 6 months (*BCR-ABL1*IS range, 10.1%-60.1%; 2 patients had a failure according to FISH), and 15 had their first failure at 12 months (*BCR-ABL1*IS range, 1.2%-12.7%). Among these patients with a failure who switched TKI, 17 (46%) and 10 (27%) achieved MMR and DMR at any time, respectively, vs 4 (36%) and 0 patients who did not switch TKI.

Of 81 patients with warning but no failure, 52 (64%) remained on first-line TKI (median follow-up 28.4 months [IQR, 13.7-40.4 months]), and 29 (36%) switched TKIs (median follow-up 30.9 months [IQR, 20.3-38.3 months]). Of those who switched TKI, 19/29 had ≥1 additional RQ-PCR assessment between the initial warning and TKI switch. Of 34 patients without any quantifiable assessment at any ELN milestone, 27 (79%) switched TKIs.

**Fig 3. Disease progressiona**

A close up of a map

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a Eight patients (7 on imatinib, 1 on a second-generation TKI) progressed to accelerated phase (AP) during the course of the study. The median time to progression was 16.5 months (range, 2.1-31.1; IQR, 7.5-26.4; time to progression was unknown for one patient on first-line imatinib).

Three patients had a prior warning response at an ELN milestone (all 3 patients received imatinib as first TKI), and 3 patients had a failure response at an ELN milestone (2 patients received imatinib first line and 1 patient received nilotinib). The other 2 patients who progressed to AP had no prior evaluable response at an ELN milestone (both patients received imatinib 1L). Treatments for progression to AP were TKIs in 3 patients, chemotherapy in 4 patients, and allogenic haematopoietic stem cell transplant (HSCT) in 5 patients

Six patients progressed to BP (all received first-line imatinib), including 4 who were previously recorded as progressing to AP. Median time from start of first-line TKI to progression to BP was 22.7 months (range 1.2- 32.1; IQR, 17.2-30.1). Treatments for progression to BP were TKIs in 4 patients, chemotherapy in 4 patients, allogenic HSCT in 2 patients and haploidentical allogenic HSCT in one patient

Among 4 patients who progressed to AP only, 2 received 1 TKI prior to progression, 1 received 3 TKIs prior to progression, and 1 had an unknown date of disease progression. Among 4 patients who progressed to AP and BP, 2 each received 1 or 2 TKIs prior to their earliest progression, respectively. Among 2 patients who progressed to BP only, 1 each received 1 or 2 TKIs prior to progression, respectively. None of the patients who progressed were observed to have only ELN-optimal responses to first-line TKI; 3 patients had ≥1 failure, 4 had ≥1 warning and 2 had no available assessments at ELN milestones.

In the 10 patients who progressed to AP and/or BP, baseline Sokal score was recorded as high for 4, intermediate for 2, low for 1 and unknown for 3.

b A total of 15/257 patients died during the study observation period; 5 of these patients had progressed to AP and/or BP prior to death (n=4 had blast crisis prior to death). Another 5 patients had progressed but were still alive at data collection (n=2 had blast crisis); all had received alternative treatment with 4 of 5 receiving both transplant and chemotherapy after progressing (n=1 after alternative TKI); the other patient received a transplant only.

**Supplementary Tables/Figures**

**Supplementary Table I. Reasons for choice of first-line TKI recorded for ≥2% of all patients**

|  |  |  |  |
| --- | --- | --- | --- |
| Recorded reason, n (%)a | All patients  (N=257) | First-line imatinib  (n=203) | First-line 2G-TKI  (n=54) |
| Known reasonsb | 113 (44%) | 92 (45) | 21 (39) |
| Clinician preference | 26 (10) | 18 (9) | 8 (15) |
| Standard first-line choice | 20 (8) | 17 (8) | 3 (6) |
| Good results expected | 17 (7) | 15 (7) | 2 (4) |
| Ease of administration | 9 (4) | 9 (4) | 0 |
| Ineligibility for clinical trial/no trial available | 9 (4) | 9 (4) | 0 |
| Cardiovascular comorbidities | 9 (4) | 9 (4) | 0 |
| Low risk | 7 (3) | 7 (3) | 0 |
| Tolerability/side effect profile | 7 (3) | 6 (3) | 1 (2) |
| Perceived as better option compared with others | 7 (3) | 6 (3) | 1 (2) |
| Patient choice | 7 (3) | 5 (2) | 2 (4) |
| Local or network guidance | 7 (3) | 7 (3) | 0 |
| Smoker | 6 (2) | 6 (3) | 0 |
| Patient age | 3 (1) | 3 (1) | 0 |
| Diabetes | 3 (1) | 3 (1) | 0 |
| High Sokal risk score | 3 (1) | 1 (<1) | 2 (4) |
| Renal comorbidities | 2 (1) | 2 (1) | 0 |
| Started treatment in another country (and moved to United Kingdom) | 2 (1) | 0 | 2 (4) |
| Intermediate Sokal risk | 1 (<1) | 0 | 1 (2) |
| Low QRISK | 1 (<1) | 0 | 1 (2) |
| Reasons unknown | 144 (56) | 111 (55) | 33 (61) |

2G-TKI, second-generation tyrosine kinase inhibitor.

a Percentages were calculated out of total number of patients in each column.

b Some patients had multiple reasons recorded.

**Supplementary Table II. Baseline blood pressure (Whelton*, et al* 2018)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| n (%) | All patients  (N=257) | First-line imatinib  (n=203) | First-line 2G-TKI  (n=54) | First-line nilotinib  (n=50) |
| Documenteda | 74 (29) | 62 (31) | 12 (22) | 11 (22) |
| Normal  (SBP <120 mm Hg and DBP <80 mm Hg) | 14 (19) | 11 (18) | 3 (25) | 3 (27) |
| Elevated  (SBP 120-129 mm Hg and DBP <80 mm Hg) | 15 (20) | 13 (21) | 2 (17) | 1 (9) |
| Stage 1 hypertension  (SBP 130-139 mm Hg or DBP 80-89 mm Hg) | 12 (16) | 8 (13) | 4 (33) | 4 (36) |
| Stage 2 hypertension  (SBP ≥140 mm Hg or DBP ≥90 mm Hg) | 30 (41) | 27 (44) | 3 (25) | 3 (27) |
| Hypertensive crisis  (SBP >180 mm Hg and/or DBP >120 mm Hg) | 3 (4) | 3 (5) | 0 | 0 |
| Not documented | 182 (71) | 140 (69) | 42 (78) | 39 (78) |
| Not known whether documented | 1 (<1)b | 1 (<1)b | 0 | 0 |

2G-TKI, second-generation tyrosine kinase inhibitor; DBP, diastolic blood pressure; SBP, systolic blood pressure.

a Proportion of patients in each blood pressure category is calculated out of the number of patients with documented blood pressure.

b One patient was transferred from another hospital prior to TKI treatment; it was unclear if this patient’s blood pressure had been documented prior to TKI treatment.

**Supplementary Table III. Reasons for switch from first-line TKI**

|  |  |
| --- | --- |
| n (%)a | Patients who switched from first-line TKI  (n=113)b |
| Resistancec | 73 (65) |
| Intolerance or other reasons | 40 (35) |
| Intolerance | 38 (34) |
| Other reasonsd | 2 (2) |

TKI, tyrosine kinase inhibitor.

a Proportions were calculated based on the total number of patients who switched from first-line TKI.

b Among these patients, 40% (45 of 113) had mutation detection done at any time before or after switching, and 19% (21 of 113) had mutation analysis done after the first switch; of those, 16 patients were switched due to resistance, and 5 patients were switched due to intolerance or other reasons.

c Included patients who switched due to both resistance and intolerance.

d Other reasons for switch were listed as they were recorded.

**Supplementary Table IV. Overall TKI pathways**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Total TKIs, n | Patients, n | TKIs received | | | | | Patients, n | % (n=257) |
| First line | Second line | Third line | Fourth line | Fifth line |
| 1 | 144 | Imatinib |  |  |  |  | 112 | 43.6% |
| Nilotinib |  |  |  |  | 29 | 11.3% |
| Dasatinib |  |  |  |  | 3 | 1.2% |
| 2 | 59 | Imatinib | Nilotinib |  |  |  | 37 | 14.4% |
| Imatinib | Dasatinib |  |  |  | 5 | 1.9% |
| Imatinib | Bosutinib |  |  |  | 5 | 1.9% |
| Nilotinib | Imatinib |  |  |  | 6 | 2.3% |
| Nilotinib | Dasatinib |  |  |  | 2 | 0.8% |
| Nilotinib | Bosutinib |  |  |  | 3 | 1.2% |
| Nilotinib | Ponatanib |  |  |  | 1 | 0.4% |
| 3 | 35 | Imatinib | Nilotinib | Dasatinib |  |  | 12 | 4.7% |
| Imatinib | Nilotinib | Bosutinib |  |  | 8 | 3.1% |
| Imatinib | Nilotinib | Imatinib |  |  | 1 | 0.4% |
| Imatinib | Dasatinib | Bosutinib |  |  | 3 | 1.2% |
| Imatinib | Dasatinib | Nilotinib |  |  | 2 | 0.8% |
| Imatinib | Dasatinib | Ponatanib |  |  | 2 | 0.8% |
| Imatinib | Dasatinib | Imatinib |  |  | 1 | 0.4% |
| Imatinib | Bosutinib | Nilotinib |  |  | 1 | 0.4% |
| Nilotinib | Imatinib | Dasatinib |  |  | 2 | 0.8% |
| Nilotinib | Imatinib | Bosutinib |  |  | 2 | 0.8% |
| Nilotinib | Imatinib | Nilotinib |  |  | 1 | 0.4% |
| 4 | 16 | Imatinib | Nilotinib | Dasatinib | Bosutinib |  | 3 | 1.2% |
| Imatinib | Nilotinib | Dasatinib | Ponatinib |  | 3 | 1.2% |
| Imatinib | Nilotinib | Bosutinib | Ponatinib |  | 1 | 0.4% |
| Imatinib | Nilotinib | Imatinib | Nilotinib |  | 1 | 0.4% |
| Imatinib | Nilotinib | Dasatinib | Imatinib |  | 1 | 0.4% |
| Imatinib | Dasatinib | Nilotinib | Imatinib |  | 1 | 0.4% |
| Imatinib | Bosutinib | Dasatinib | Imatinib |  | 1 | 0.4% |
| Nilotinib | Imatinib | Dasatinib | Bosutinib |  | 1 | 0.4% |
| Nilotinib | Imatinib | Bosutinib | Nilotinib |  | 1 | 0.4% |
| Nilotinib | Dasatinib | Bosutinib | Ponatinib |  | 1 | 0.4% |
| Nilotinib | Dasatinib | Bosutinib | Imatinib |  | 1 | 0.4% |
| Dasatinib | Bosutinib | Nilotinib | Imatinib |  | 1 | 0.4% |
| 5 | 3 | Imatinib | Dasatinib | Bosutinib | Ponatinib | Imatinib | 1 | 0.4% |
| Imatinib | Dasatinib | Bosutinib | Dasatinib | Bosutinib | 1 | 0.4% |
| Imatinib | Nilotinib | Dasatinib | Nilotinib | Ponatinib | 1 | 0.4% |

TKI, tyrosine kinase inhibitor.

**Supplementary Table V. Summary of molecular responses to second-line TKI therapy in patientsa**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | All patients  (n=113) | Imatinib 2L  (n=13) | 2G-TKI 2L  (n=100) | Nilotinib 2L  (n=68) | Switched to 2L for resistance  (n=73) | Switched to 2L for intolerance/other reason  (n=40) |
| Median follow-up on TKI (range), months | 11.1 (0.2-50.2) | 15.9 (0.9-43.0) | 10.9 (0.2-50.2) | 14.5 (0.2-50.2) | 27.4 (1.2-51.4) | 20.1 (2.8-54.1) |
| EMR at 3 months (±1 month) in patients with *BCR-ABL1* at 3 months, n (%) | 59/70 (84) | 10/10 (100) | 49/60 (82) | 38/45 (84) | 39/47 (83) | 20/23 (87) |
| MMR by 12 months (±1 month),  n (%) | 41/92 (45) | 7/12 (58) | 34/80 (43) | 26/57 (46) | 26/61 (43) | 15/31 (48) |
| MMR at any time, n (%) | 48/94 (51) | 7/13 (54) | 41/81 (51) | 31/58 (53) | 32/62 (52) | 16/32 (50) |
| DMR at any time, n (%) | 28/94 (30) | 4/13 (31) | 24/81 (30) | 18/58 (31) | 19/62 (31) | 9/32 (28) |
| 2G-TKI, second-generation tyrosine kinase inhibitor; 2L, second line; DMR, deep molecular response; EMR, early molecular response; MMR, major molecular response; RQ-PCR, real-time quantitative polymerase chain reaction.  For EMR, patient was required to have RQ-PCR at 3 months (±1 month). | | | | | | |
| Molecular response categories were not mutually exclusive; the same patient could appear in multiple response categories. | | | | | | |
| For MMR/DMR responses, denominator included only those patients with ≥1 RQ-PCR on second line (and by 12 months [±1 month] on second line for the MMR by 12-month responses).  a Follow-up period was months from second TKI until switch in patients who switched to third TKI or, in those who did not switch, to data collection or death. Molecular responses were assessed as early molecular response (EMR; *BCR-ABL1*IS ≤10% at 3 months), MMR (*BCR-ABL1*IS ≤0.1%) by 12 months, MMR at any time, and DMR (*BCR-ABL1*IS ≤0.01%) at any time. To account for variations in real-world appointment scheduling, a window of ±1 month was applied to ELN-defined time points; if multiple assessments were available within the window, the one closest to the time point was used. | | | | | | |

**Supplementary Fig 1. TKI treatment pathways and molecular responses for patients with ELN-defined optimal, warning, or failure responses while on second-line TKI**

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Both patients with a warning response switched after a warning at a single ELN-defined milestone. MMR or DMR response may have been observed at any time; duration of follow up varied; patient may have had ≥1 subsequent TKI switch.