**MOVE BEYOND THE THRESHOLD**

As an extended half-life recombinant FVIII, Esperoct offers a simple way to reach higher trough FVIII activity levels compared to standard half-life treatments.1-4,10

**Mode of Action Video**

*40°C storage for up to 3 months before reconstitution**

*Esperoct® is licenced for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency)*

This advertisement is intended for Healthcare Professionals

---

**Prescribing Information**

**Esperoct®**

Esperoct 500 IU Esperoct 1000 IU Esperoct 1500 IU Esperoct 2000 IU Esperoct 3000 IU Powder for solvent for solution for injection Turoctocog alfa pegol Human factor VIII, produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line, and no additives of human or animal origin are used in the cell culture, purification, conjugation or formulation. Indication: Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency). Pharmacology and administration: Treatment includes the correct diagnosis and treatment of bleeding episodes. Required dose: IU = body weight (kg) x desired factor VIII rise (IU/d) x 0.5 (IU/kg per IU/d). Mild haemarthrosis: early haemarthrosis, mild muscle bleeding or mild oral bleeding. Factor VII level required (IU/d): 0-20. Frequency of doses: 1-2x daily, until resolution of haemarthrosis. Haemarthrosis: Factor VII level required (IU/d): 0-30. Frequency of doses: 1-2x daily, until resolution. Severe or life-threatening haemarthroses: Factor VII level required (IU/d): 0-60. Frequency of doses: 1-2x daily, until resolution. Minor surgery: Factor VII level required (IU/d): 0-60. Frequency of doses: 1-2x daily, until resolution. Moderate or major surgery: Factor VII level required (IU/d): 0-30. Frequency of doses: 1-2x daily, until resolution.

---

of insufficient clinical response than high titre inhibitors. Patients treated with coagulation factor VIII products should be monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Cardiovascular events: In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk. Cataract-related complications: If a central venous access device (CVA) is required, the risk of CVA-related complications including local infections, bacteremia and catheter site thrombosis should be considered. Pneumococcal vaccination: Patients with a history of severe reactions to pneumococcal vaccine should receive the quadrivalent pneumococcal vaccine (107 CFU in 0.5 ml) before administration of the first dose of Esperoct. A booster dose is recommended after 1 year. In patients with a history of transient febrile reactions to pneumococcal vaccine, the recommended dose and frequency of administration should be used. In patients with a history of adverse reactions to pneumococcal vaccine, the recommended dose and frequency of administration should be used. In patients with a history of severe reactions to pneumococcal vaccine, the recommended dose and frequency of administration should be used. In patients with a history of severe reactions to pneumococcal vaccine, the recommended dose and frequency of administration should be used. ABBR, annualised bleed rate; EHL, extended half-life; FVIII, factor VIII; FVIII; recombinant factor VIII; SHL, standard half-life.

---

Novo Nordisk Ltd., 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA. Novo Nordisk Customer Care Line Tel: 0845 600 5055. Calls may be monitored for training purposes.

Novo Nordisk® is a trademark owned by Novo Nordisk A/S. Esperoct® is a trademark owned by Novo Nordisk Health Care AG. Date of preparation: May 2020 UK20E5900004.
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

Dragana Milojkovic,1 Nicholas C. P. Cross,2 Sahra Ali,3 Jenny Byrne,4 Gavin Campbell,5 Fiona L. Dignan,6 Mark Drummond,7 Brian Huntly,8 Scott Marshall,9 Mary Frances McMullin,10 Pratap Neelakantan,11 Manoj Raghavan,12 Muttuswamy Sivakumaran,13 Jane Tighe,14 Farooq Wandroo,15 Fenella Willis,16 Fiona Glen,17 Louise Fildes,18 Sarah J. Collington,18 Jacqueline Ryan,18 Richard E. Clark19 and Adam J. Mead20

1Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, 2University of Southampton, Southampton, 3Castle Hill Hospital, Hall and East Yorkshire Hospitals NHS Trust, Cottingham,4Nottingham City Hospital, Nottingham University Hospitals NHS Trust, Nottingham, 5Colchester Hospital University NHS Foundation Trust, Colchester, 6Manchester Royal Infirmary, Manchester University Hospitals Foundation Trust, Manchester, 7Beatson Cancer Centre, Glasgow, 8Addenbrookes, Cambridge University Hospitals NHS Foundation Trust, Cambridge, 9Sunderland Royal Hospital, City Hospitals Sunderland NHS Foundation Trust, Sunderland, 10Belfast City Hospital, Belfast Health and Social Care Trust, Belfast, 11Royal Berkshire, Royal Berkshire NHS Foundation Trust, Belfast, 12Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, 13Peterborough City Hospital, Northwest Anglia NHS Foundation Trust, Peterborough, 14Aberdeen Royal Infirmary, NHS

Summary

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 who had been 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 revealed 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%, respectively, 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, CML 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.1–3 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,4 it is increasingly evident that 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.4 This is the principal purpose of the 2013 European LeukemiaNet (ELN) recommendations, which increased focus on molecular responses at three, six and 12 months, with patients’ responses categorised as optimal, warning or failure.4 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.4

While the ELN 2013 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,4 deeper levels of response, including MR4 (BCR-ABL1IS ≤0·01%) and MR4.5 (BCR-ABL1IS ≤0·0032%), are also recognised as important milestones.5–7 Some patients with a sustained deep molecular response (DMR, MR4 or better) may be eligible to attempt treatment-free remission (TFR).8–11 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, but achievement of responses in real-world practice is less well studied, particularly in the second-line setting.12–14 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 receiving 2G- or third-generation-TKIs compared with imatinib, especially in patients with pre-existing CV risk factors.13–17 Given the excellent long-term outcomes in CML, comorbidities are now a major consideration.18,19 However, in routine UK 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.4

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 the start of first-line TKI, aged ≥18 years and at ≥6 months of follow-up from the 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, recorded reasons for stopping/changing TKIs, adherence to ELN 2013 recommendations and disease progression frequency and management. AE data were not collected.

Data were analysed using descriptive statistics, with a cut-off date of 6 June 2018, using Microsoft Excel and STATA (version 13; StataCorp LLC, College Station, TX, USA). 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.

For comparison with ELN, where data were available, responses were categorised as optimal, warning or failure according to ELN 2013 recommendations. If 

\[ \text{BCR-ABL1} \]

transcript levels were not available on the IS, unconverted 

\[ \text{BCR-ABL1/ABL1} \]

percentages were used to reflect real-world practices at that centre (all centres used \text{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

Between November 2015 and September 2017, 257 patients (186 from 14 tertiary centres and 71 from seven general hospitals) were enrolled. Median follow-up by the data cut-off was 32.9 months (range, 12.6–58.6). Baseline characteristics are shown in Table I. Clinical characteristics (other than white blood cell 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; the clinician preference of ‘standard first-line choice’ and ‘good results expected’ were the most frequently cited reasons Table SI. 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, respectively. Patients receiving a first-line 2G-TKI were younger [median, 46 years (95% CI, 41–53 years)] than those receiving first-line imatinib [median, 55 years (95% CI, 52–59 years); Mann-Whitney U test, \( P = 0.0128 \)].

CV risk factors and other documented comorbidities at baseline

Among all patients, 149 (58%) had \( \geq 1 \) recorded comorbidity at baseline (Table I). Seventy-four patients (36%) receiving imatinib had CV comorbidities at baseline vs. seven (13%) receiving a 2G-TKI (Table II). Only 74 patients (29%) had baseline blood pressure documented; 33 (45%) had stage \( \geq 2 \) hypertension Table II.20

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, respectively. CV risk assessment tool use was documented for 10 patients (4%), with the validated QRISK2 tool used in three (1%).

Response monitoring practices

Within 12 months of starting first-line TKI, 250 patients (97%) had \( \geq 1 \) real-time quantitative polymerase chain reaction (RQ-PCR) assessment and 221 patients (86%) had \( \geq 3 \) RQ-PCR assessments. Two-hundred and four (79%), 177 (69%), and 162 (63%) patients had assessments at the three-, six-, or 12-month ELN milestones (regardless of TKI line), respectively. Cytogenetic testing (chromosome banding analysis or fluorescence in situ hybridisation) 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, while 24/203 (12%) and 8/50 (16%) had dose reductions, and 14% and 12% had dose interruptions, respectively.

Quantifiable molecular or cytogenetic assessments were performed at \( \geq 1 \) ELN milestone during first-line TKI in 223 patients (87%) (Fig 2). Forty-eight patients had \( \geq 1 \) failure, 11 (23%) remained on first-line TKI [median follow-up, 13.8 months [interquartile range (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 two (2%) (Table SIII). Thirteen patients (12%) switched to imatinib, 68 (60%) to nilotinib, 20 (18%) to dasatinib, 11 (10%) to bosutinib and one (1%) to ponatinib (Table SIV). 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.
Table I. Patient demographics and baseline characteristics.

| Sex, n (%) | All patients (n = 257) | First-line imatinib (n = 203) | First-line 2G-TKI (n = 54) | First-line nilotinib (n = 50) |
|------------|------------------------|-------------------------------|--------------------------|-----------------------------|
| 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] | 55.4 [18.4–92.4] | 45.8 [20.3–79.5] | 45.1 [20.3–79.5] |
| Time from CML diagnosis to start of first-line 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) |
| 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)                     |
| Sokal risk score, n (%) |                      |                              |                          |                             |
| 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 |                      |                              |                          |                             |
| EUTOS score, n (%)** |                      |                              |                          |                             |
| Low risk   | 110 (43)               | 90 (44)                       | 20 (37)                  | 19 (38)                     |
| High risk  | 34 (13)                | 23 (11)                       | 11 (20)                  | 9 (18)                      |

*TKI = tyrosine kinase inhibitors. **The authors. British Journal of Haematology published by British Society for Haematology and John Wiley & Sons Ltd.
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, respectively, 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 Table V.

Of the 113 patients who switched TKI at least once, 18 (16%) had failure on second-line TKI (Figure S1), seven (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)].

**Kinase domain mutation analysis**

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 four (10%) who switched due to intolerance or other reasons. Clinically actionable mutations were identified in six patients (Table SVI).

**Overall TKI pathways**

Among all patients, 144 (56%) received only a first-line TKI, and 59 (23%), 35 (14%), 16 (6%) and three (1%) received two, three, four and five TKIs, respectively; sequences of TKI received are described in Table SIV. 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 five after progression). Survival outcomes and treatments to manage progression are summarised in Fig 3.
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 (i) TKI treatment pathways, (ii) implementation of ELN recommendations for molecular-based patient management, (iii) attainment of DMR with first- and second-line TKI in real-world practice and (iv) assessment of baseline CV risk factors.

Despite a relatively short median follow-up (<33 months), almost half of the 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 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                    |                        |                               |                             |                               |
| Documented*                | 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)†                 | 1 (1)†                        | 1 (3)†                      | 1 (3)†                        |
| BMI > 30 documented        | 16 (6)                 | 14 (7)                        | 2 (4)                       | 2 (4)                         |
| CV comorbidities           |                        |                               |                             |                               |
| None recorded              | 176 (68)               | 129 (64)                      | 47 (87)                     | 44 (88)                       |
| ≥1 recorded‡§              | 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 unknown§     | 1 (<1)                 | 1 (<1)                        | 0                           | 0                             |
| Documented**               | 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 unknown§     | 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.

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

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

§Patients could be listed as having ≥1 CV comorbidity.

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

§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.

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

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 (i) TKI treatment pathways, (ii) implementation of ELN recommendations for molecular-based patient management, (iii) attainment of DMR with first- and second-line TKI in real-world practice and (iv) assessment of baseline CV risk factors.

Despite a relatively short median follow-up (<33 months), almost half of the 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 six years of follow-up, although no other alternative TKI was available at the time of IRIS recruitment. In IRIS long-term follow-up (median, 10 years), imatinib discontinuation was most frequently attributed to unsatisfactory therapeutic effect (15%), withdrawal of consent (10%), or AEs (6%). 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 five-year data cut-off among patients allocated to nilotinib 300 mg twice daily). 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, although prognostic scores were better documented (98%) in the Swedish CML registry. CV events have been reported to be increased with 2G-TKIs, 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 factors should therefore be carefully considered when choosing a TKI.

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

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

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

*Denominator included patients with ≥4 months’ follow-up on that TKI.
†Denominator included patients with ≥7 months’ follow-up on that TKI.
‡Denominator included patients with ≥13 months’ follow-up on that TKI.
Table IV. Summary of molecular responses to first-line TKI therapy.*

|                                | Overall responses | First-line TKI |
|--------------------------------|-------------------|----------------|
|                                | First-line imatinib | First-line 2G-TKI | All patients |
| (n = 203)                      |                   |                | (n = 203) |
| Median follow-up duration† 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 month), 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 month), 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; IS, International Scale; MMR, major molecular response.

*Patients could appear in multiple molecular response categories. Molecular responses were assessed as EMR (BCR-ABL1 ≤10% at three months), MMR (BCR-ABL1 ≤0-1% by 12 months, MMR at any time and DMR (BCR-ABL1 ≤0-01% at any time. To account for variations in real-world appointment scheduling, a window of ± one 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.

†Fifty patients received first-line nilotinib, and four received first-line dasatinib.

‡The columns for overall response reported the duration of follow-up for all TKI therapies, including later-line TKIs in patients who switched from their first-line TKI (from start of first-line TKI to most recent data collection, akin to an intention-to-treat analysis). 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 continued receiving first-line TKI or to end of first-line TKI for patients who switched to a second-line TKI).

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.25 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 tools, such as QRISK2, was rarely documented. Baseline blood pressure was documented in fewer than one-third of patients, and when baseline blood pressure was recorded, it was often elevated, with three 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.
Fig 2. TKI treatment pathways and molecular responses for patients with ELN optimal, warning (at single versus multiple ELN milestones) or failure responses while on first-line TKI. *To account for variations in real-world appointment scheduling, a window of ± one month was applied to ELN-defined time points (three, six and 12 months). 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 (three, six or 12 months) with either molecular or cytogenetic assessment (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 categorised. Thirty-four patients had no evaluable test at any ELN milestone by either molecular or cytogenetic test. bResponse may have been observed at any time. Duration of follow-up varied; patient may have had ≥ one subsequent TKI switch. Forty-eight patients had ≥ one 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 six months (BCR-ABL1 range, 10–1%–60–1%; two patients had a failure according to FISH), and 15 had their first failure at 12 months (BCR-ABL1 range, 1–2–12–7%). Among these patients with a failure who switched TKIs, 17 (46%) and 10 (27%) achieved MMR and DMR at any time, respectively, vs. four (36%) and no patients, who did not switch TKIs. Of 81 patients with warning but no failure, 52 (64%) remained on first-line TKI [median follow-up 24–8 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 TKIs, 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. 48 patients with ELN-defined failure responses; 39 were treated with imatinib as first-line therapy and nine with a 2G-TKI; 38 patients (79%) also had an ELN-defined warning at a prior ELN time point (with either a molecular or cytogenetic test). DMR, deep molecular response; ELN, European LeukemiaNet; EMR, early molecular response; FISH, fluorescence in situ hybridisation; IQR, interquartile range; IS, International Scale; MMR, major molecular response; RQ-PCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.

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, although with higher frequency in Europe than the United States. This finding is important because a previous study showed that patients without frequent molecular monitoring
indicating rapid adoption of molecular monitoring at early three months (81%) compared with SIMPLICITY (32%), high level of testing for early molecular response (EMR) at associated with greater TKI treatment adherence in patients with frequent molecular monitoring (3 assessments were available within the window, the one closest to the time point was used.

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

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

|                          | All switched patients (n = 113) | Second-line imatinib (n = 13) | Second-line 2G-TKI (n = 100)† | Second-line nilotinib (n = 68) | Switched to second line for intolerance or other reason (n = 40)² |
|--------------------------|---------------------------------|-------------------------------|-------------------------------|-------------------------------|---------------------------------------------------------------|
| Median follow-up post first switch (range), months³ | 23-7 (1–25–94–1) | 22-5 (4–9–43–0) | 23-9 (1–25–94–1) | 29-7 (1–25–52–4) | 27-4 (1–25–51–4) |
| Median follow-up on second-line TKI (range), months⁴ | 23-9 (13–6–50–2) | 19-2 (13–6–43–0) | 28-6 (13–9–50–2) | 27-3 (13–9–50–2) | 25-6 (13–9–46–5) |
| EMR at 3 months (±1 month) on second TKI in patients with 3-month molecular response assessments, n (%)** | 59/70 (84) | 10/10 (100) | 49/60 (82) | 38/45 (84) | 39/47 (83) |
| MMR by 12 months (±1 month) on second TKI, n (%)†† | 30/50 (60) | 4/7 (57) | 26/43 (60) | 24/38 (63) | 21/35 (60) |
| MMR at any time on second TKI, n (%)‡‡ | 37/51 (73) | 4/8 (50) | 33/43 (77) | 29/38 (76) | 27/36 (75) |
| DMR at any time on second TKI, n (%)¶¶ | 21/51 (41) | 2/8 (25) | 19/43 (44) | 17/38 (45) | 15/36 (42) |

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

*Patients could appear in multiple molecular response categories. Molecular responses after switch to second TKI were assessed as EMR (BCR-ABL1 ≥10% at three months), MMR (BCR-ABL1 <0-1%) by 12 months, MMR at any time and DMR (BCR-ABL1 <0-0%) 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.

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

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

³Duration from start of second-line TKI to last data collection or death (included patients with ≥1 switch).

⁴Duration from start of second-line TKI to last data collection, date of switch to a third-line TKI, or death.

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

††MMR (≥0-1% BCR-ABL1); DMR (≥0-01% BCR-ABL1); only those patients with ≥13 months’ follow-up were included.

were at higher risk of disease progression. In addition, frequent molecular monitoring (3–4 times per year) was associated with greater TKI treatment adherence in patients with CML.

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, a finding which 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 three months (81%) compared with SIMPLICITY (32%), indicating rapid adoption of molecular monitoring at early milestones in the UK.

However, despite a generous one-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. In
A Study on Tyrosine Kinase Inhibitor Use in the Real World

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, treatment goals are evolving to include deeper responses and TFR. Studies have shown that deeper molecular responses were associated with improved outcomes compared with complete cytogenetic response and a sustained DMR is a prerequisite for attempting TFR in both clinical practice guidelines and clinical trials. Clinical studies have demonstrated that 2G-TKIs can also lead to improved rates of DMR in the second line. Results from our study showed that patients switching from first-line treatment may achieve...

Fig 3. Disease progression. Eight patients (seven on imatinib, one 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 to 31-1; IQR, 7-5 to 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 three received imatinib as first TKI), and three patients had a failure response at an ELN milestone (two received imatinib first-line and one received nilotinib). The other two patients who progressed to AP had no prior evaluable response at an ELN milestone (both patients received first-line imatinib). Treatments for progression to AP were TKIs in three patients, chemotherapy in four patients and allogeneic haematopoietic stem cell transplant (HSCT) in five patients. Six patients progressed to BP (all received first-line imatinib), including four 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 to 32-1; IQR, 17-2 to 30-1). Treatments for progression to BP were TKIs in four patients, chemotherapy in four patients, allogeneic HSCT in two patients and haploidentical allogeneic HSCT in one patient. Among four patients who progressed to AP only, two received one TKI prior to progression, one received three TKIs prior to progression, and one had an unknown date of disease progression. Among four patients who progressed to AP and BP, two each received one or two TKIs prior to their earliest progression, respectively. Among two patients who progressed to BP only, one each received one or two TKIs prior to progression, respectively. None of the patients who progressed were observed to have only ELN-optimal responses to first-line TKI; three patients had ≥ one failure, four had ≥ one warning and two had no available assessments at ELN milestones. In the 10 patients who progressed to AP and/or BP, the baseline Sokal score was recorded as high for four, intermediate for two, low for one and unknown for three. A total of 15/257 patients died during the study observation period; five of these patients had progressed to AP and/or BP prior to death (n = 4 had blast crisis prior to death). Another five patients had progressed but were still alive at data collection (n = 2 had blast crisis); all had received alternative treatment with four of five receiving both transplant and chemotherapy after progressing (n = 1 after alternative TKI); the other patient received a transplant only. AP, accelerated phase; BP, blast phase; ELN, European LeukemiaNet; TKI, tyrosine kinase inhibitor.

Tyrosine kinase inhibitor use in the real world

© 2020 The Authors. British Journal of Haematology published by British Society for Haematology and John Wiley & Sons Ltd
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 randomised 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 a 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, including very recent updates to the ELN recommendations, is warranted.

Acknowledgements

We are grateful to the principal investigators and research teams at each of the 21 UK participating sites who made this study possible. Most importantly, we extend our gratitude to all the patients who consented to be part of this research. We thank OPEN VIE (formerly pH Associates) for their support in the conduct of this research study. We also thank Silvia Sanz, Fiona Read, Michelle Murchie and Rozinder Bains of the Novartis Pharmaceutical UK Ltd haematology medical team for their ongoing input and support in the conduct of this study. We thank Christopher Edwards, PhD, and Karen Kaluza Smith, PhD, of ArticulateScience LLC for their medical editorial assistance with this manuscript. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. This study was sponsored and funded by Novartis Pharmaceuticals UK Ltd. The authors had full control of the content and made the final decision for all aspects of this article.

Author contributions

AIM and DM designed the research study, performed the research, analysed the data and wrote the paper. REC and PN designed the research study, performed the research and analysed the data. JR and FG designed the research study, analysed the data and wrote the paper. NCPC, LF and SJC designed the research and analysed the data. FWa, JB, FLD, SA, MD, JT, MFM, GC, BH, FWi, MS, MR and SM performed the research and analysed the data.

Conflict of interests

AIM participated in advisory boards for Novartis, Bristol-Myers Squibb (BMS) and Pfizer, and received honoraria, research funding, travel, accommodations and expenses from Novartis. REC participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis, BMS and Pfizer. NCPC participated in advisory boards for Novartis, BMS and Pfizer; received honoraria from Novartis, BMS, Pfizer and Ariad/Icyte; and received research funding from Novartis, BMS and Pfizer. FLD received honoraria, travel, accommodations and expenses from Novartis and Pfizer. MFM participated in advisory boards for Novartis and received honoraria from Novartis, Pfizer and BMS. SM participated in advisory boards for Novartis, BMS and Pfizer and received honoraria, research funding, travel, accommodations and expenses from Novartis. FWa received educational grants from Pfizer and Novartis. MR participated in advisory boards and received honoraria from Novartis. JR participated in advisory boards and received honoraria from Novartis, Pfizer and Incyte. SA participated in advisory boards and received honorarium, travel and accommodations from Novartis. MD received honoraria from Novartis and Pfizer and research funding from Novartis. JT received support for conference attendance from Novartis. BH participated in advisory boards for Novartis, Pfizer and BMS. FWi received honoraria, travel, accommodation and expenses from Novartis. DM 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, MS and GC declared no conflict of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Material.

References

1. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016;34:2851–7.
2. Höglund M, Sandin F, Hellström K, Björeman M, Björkholm M, Brune M, et al. Tyrosine kinase inhibitor usage, treatment outcome and prognostic scores in CML: report from the population-based Swedish CML registry. Blood. 2013;122:1284–92.
3. Sasaki K, Strom SS, O’Brien S, Jabbour E, Ravandi F, Konopleva M, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. Lancet Haematol. 2015;2:e186–e193.
4. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122:872–84.
5. Cross NCP, White HE, Muller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia. 2012;26:2172–5.
6. Etienne G, Dulucq S, Nicolini FE, Morisset S, Fort MP, Schmitt A, et al. Achieving deeper molecular response is associated with a better clinical
outcome in chronic myeloid leukemia patients on imatinib front-line therapy. Haematologica. 2014;99:458–64.

7. Hehlmann R, Müller MC, Lauseker M, Hanfstein B, Fabarius A, Schreiber A, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-Study IV. J Clin Oncol. 2014;32:415–23.

8. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JJWM, Hjorth-Hansen H, et al. Chronic myeloid leukemia: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2017;28:viv41–iv51.

9. Mahon FX. Treatment-free remission in CML: who, how, and why? Hematol. American Society of Hematology. Education Program. 2017;10:102–9.

10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia Version 3.2020. Fort Washington, PA: National Comprehensive Cancer Network; 2020.

11. Rea, D, Ame, S, Berger, M, Cayuela, JM, Charbonnier, A, Coiteux, V, et al. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia: recommendations for clinical practice from the French Chronic Myeloid Leukemia Study Group. Cancer. 2018;124:2956–63.

12. Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim DW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J Clin Oncol. 2018a;36:231–7.

13. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boque C, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. J Clin Oncol. 2016;34:2333–40.

14. Hochhaus A, Saglio G, Hughes TP, Larson RA, Issaragrisil S, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30:1044–54.

15. Chai-Adisaksopha C, Lam W, Hillis C. Major arterial events in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a meta-analysis. Leukemia Lymphoma. 2016;57:1300–10.

16. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre PD, Faqquette R, Chuah C, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive myeloid leukaemia: final 5-year results of the phase 2 PACE trial. Blood. 2018b;132:393–404.

17. Lipton JH, Chuah C, Guerci-Bresler A, Rosti G, Simpson D, Assouline S, et al. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17:e62–12.

18. Jabbour E, Makenbaeva D, Lingohr-Smith M, Lin J. Evaluation of comorbidities relevant to tyrosine kinase inhibitor treatment among patients with chronic myelogenous leukemia in the U.S. managed care setting. Blood. 2014;124:4550.

19. Saussele, S, Krauss, MP, Hehlmann, R, Lauseker, M, Proetel, U, Kalmanti, L, et al. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML-Study IV. Blood. 2015;126:42–9.

20. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;71:e127–e248.

21. Hochhaus A, O’Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia. 2009;23:1054–61.

22. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med. 2017a;376:917–27.

23. Goldberg SL, Cortes JE, Gambacorti-Passerini C, Hehlmann R, Khoury HJ, Michallet M, et al. First-line treatment selection and early monitoring patterns in chronic phase-chronic myeloid leukemia in routine clinical practice: SIMPLICITY. Ann Hematol. 2017;92:1214–23.

24. Nesi GNG, Sydlto R, Braithwaite B, Frackleton S, Apperley J, Milejkovic D, et al. First report from the UK National Registry for chronic myeloid leukaemia: analysis of baseline characteristics of 435 patients. Br J Haematol. 2018;181:BSH18-PO-016.

25. NICE National Institute for Health and Care Excellence. Myeloid Leukaemia. 2018. Available from: https://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers#path=view%3Apathways/blood-and-bone-mar-row-cancers/myeloid-leukaemia.xml&content=view-node%3AAnodes ponatinib [cited 2018 October 22].

26. Goldberg SL, Chen L, Guerin A, Macalalad AR, Liu N, Kaminsky M, et al. Association between molecular monitoring and long-term outcomes in chronic mylogenues leukemia patients treated with first line imatinib. Curr Med Res Opin. 2018;32:1075–82.

27. Guérin A, Chen L, Dea K, Wu EQ, Goldberg SL. Association between regular molecular monitoring and tyrosine kinase inhibitor therapy adherence in chronic myelogenous leukemia in the chronic phase. Curr Med Res Opin. 2014;30:1345–52.

28. Mahon FX, Boquistepani C, Kim DW, Benyamini N, Clementino NCD, Shuvaev V, et al. Treatment-free remission after second-line nilotinib treatment in patients with chronic myeloid leukemia in chronic phase: results from a single-group, phase 2, open-label study. Ann Intern Med. 2018;168:461–70.

29. Ross DM, Masszi T, Gómez-Casares MT, Hellmann A, Stentoft J, Connolly E, et al. Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENESTfreedom study. J Cancer Res Clin Oncol. 2018;144:945–54.

30. Hughes TP, Leber B, Cervantes F, Spector N, Pasquini R, Clementino NCD, et al. Sustained deep molecular responses in patients switched to nilotinib due to persistent BCR-ABL1 on imatinib: final ENESTcmr randomized trial results. Leukemia. 2017;31:2529–31.

31. Hochhaus A, Baccarani M, Silver RT, Apperley JF, Cervantes F, et al. European LeukaemiaNet 2020 recommendations for treating chronic myeloid leukaemia. Leukemia. 2020;34:966–84.