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Real-world Management of CML: Outcomes and Treatment Patterns

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Abstract

Purpose of Review Chronic myeloid leukemia (CML) is a disease that previously signified a poor prognosis, but treatment options and outcomes have improved over the last several decades. Despite this, challenges remain in optimal management in clinical practice, as the characteristics in trial populations differ from patients who are treated in a real-world setting. This review describes recent updates in real-world treatment patterns and outcomes in patients with CML.

Recent Findings Several analyses describing real-world practice patterns show that tyrosine kinase inhibitors (TKIs) are the most commonly prescribed agents in multiple lines of therapy. First-generation (1G) and second-generation (2G) TKIs are the most commonly prescribed, even in the third line and beyond. Third-generation (3G) TKIs are typically utilized in patients with resistant disease who are younger with fewer comorbidities. Hematopoietic stem cell transplant (HSCT) is utilized significantly less, given other treatment options available. The goals of treatment with CML have shifted to quality of life, cost savings, and treatment-free response (TFR). Despite clear guidelines for attempting TFR, discontinuation practice patterns remain inconsistent.

Summary TKIs are the mainstay of CML treatment, including those in later lines of therapy. In real-world practice, several challenges still remain with regard to optimal management. Specifically, ideal sequencing of treatments, side effect profiles of tyrosine kinase inhibitors (TKIs), current role and timing of transplant, and adherence to recommendations for attempting to achieve a treatment-free response (TFR). A national registry could characterize these practice patterns in order to find ways to optimize care for CML patients.

Keywords Chronic myelogenous leukemia · Review · Treatment · Real world

Background

Since 2001, *BCR::ABL1* tyrosine kinase inhibitors (TKIs) have greatly improved the survival of patients with chronic-phase chronic myeloid leukemia (CML), with prevalence in the USA predicted to rise from 70,000 in 2010 to 180,000 in 2050 [1]. There are currently 6 TKIs approved for CML in the USA: 1st generation (1G) imatinib [2]; 2nd generation (2G) dasatanib [3], nilotinib [4], and bosutinib [5]; and 3rd generation (3G) ponatinib [6] and asciminib [7, 8]. TKIs are now the mainstay of treatment in CML unless there is a specific contraindication [9, 10]. As progression-free survival (PFS) and overall survival (OS) have improved over the years related to deep molecular responses with TKIs, one of the main goals of treatment has shifted to focus on treatment-free remission (TFR) [11]. Most of what is known about both TKI treatment responses and TFR rates comes from clinical trials in which patient populations differ significantly from the general CML population. The goal of this review is to provide an update on real-world data on CML outcomes and current treatment patterns.

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Differences Between Patient Outcomes and Characteristics in Clinical Trials Versus Routine Medical Practice

Box 1: Trial participants are different from other patients

- Younger age
- Fewer comorbidities
- Race/ethnicity not reflective of the US population

Clinical guidelines for first-line treatment of CML with TKIs are based mainly on data from 3 randomized controlled trials (RCTs) [3–5]. However, patients enrolled in these trials differed from the general CML population in multiple ways that may affect expected outcomes (Box 1, Table 1). First, the median age in the RCTs was 46–52 years, while the median age for CML diagnosis in the USA is 65 years. This is especially important since the population aged 65 and over is projected to double by 2050 compared to 2012 [12]. Second, patients enrolled in the trials had minimal comorbidities, especially low cardiac risk. About 20% of patients with CML would have been excluded from the RCTs due to stringent eligibility criteria, e.g., absence of chronic obstructive pulmonary disease, uncontrolled diabetes, drug abuse, arrythmia, or myocardial infarction (MI) <6 months before CML diagnosis, chronic pancreatitis, and peripheral arterial obstructive disease [13]. RCTs also excluded patients on specific concomitant medications, including medications leading to QT prolongation or proton pump inhibitors, which are commonly used in the general population [14, 15] and may affect the efficacy or toxicity of TKIs. Third, these were international RCTs with patients from North America, Asia, Europe, and South America. They do not reflect the race/ethnicity of the US CML population, overrepresenting Asian patients and underrepresenting Black patients. CML outcomes can differ considerably among countries. A study from the Swedish national cancer registry found survival of patients with CML to be similar to the general population [16], while two studies suggest a 2-fold higher risk of death in CML patients compared to controls in the USA [17, 18]. The reasons for these differences are unknown. Finally, 2 of the pivotal trials followed patients for only 5 years, so information on longer-term outcomes is limited. The differences between trial patients and other patients make extrapolation of results and treatment recommendations from trials to routine practice challenging [13], leading several countries to evaluate population-based data in patients with CML. These assessments are primarily retrospective and have several limitations; however, important data have emerged.

First-line Treatment

Four of the six TKIs are approved by the US Food and Drug Administration (FDA) for use in the first-line treatment of CML: imatinib (1G), dasatinib (2G), nilotinib (2G), and bosutinib (2G). Various guidelines such as the NCCN or ELN suggest that the choice of first-line treatment should be based on several factors, including disease risk, side effect profile, cost, and patient comorbidities [10, 23]. Although imatinib remains the most commonly prescribed first-line agent, the use of 2G TKI has been increasing and makes up approximately 20–40% of TKIs used in the first line, with the most common 2G TKIs used being dasatinib and nolotinib [24•], [25–27]. Physician survey data suggests that reasons for selecting 2G TKI over imatinib include a high Sokal risk score or if TFR is a high priority for the patient [25]. Imatinib tends to remain the choice of first-line agent in older adults with comorbidities, as shown in a study evaluating dosing patterns in patients 70 years or older [28], and the

Table 1 Patient characteristics in trials compared to SEER/US population data

	Nilotinib [4] 300 mg	Imatinib [4] 400 mg	Dasatinib [3] 100 mg	Imatinib [3] 400 mg	Bosutinib [5] 400 mg	Imatinib [5] 400 mg	SEER/ US CML [19–22]
Age (median)	47	46	46	49	52	53	65
Male (%)	56	56	56	63	57.7	56	60
Race (%)							
Asian	27	25	-	-	12	13	6
Black	4	2	-	-	4	4	12
White	60	66	-	-	78	77	63
Other	9	6	-	-	6	6	19
Cardiac risk (%)	14[a]	11.6[a]	3.5[b]	5.0[b]	11.4[c]	12[c]	25[a,d]

[a]Framingham general risk of CVE >20%

[b]Preexisting ischemic heart disease

[c]Per case report forms collected at screening if the patient had a history of coronary disease

[d]Age 60–69

median age for first-line imatinib use in the SIMPLICITY cohort was 59 years vs. 56 years and 54 years for dasatinib and nilotinib, respectively [29••]. Bosutinib was initially approved in 2012 for the treatment of CML in later lines of therapy and received approval in newly diagnosed CML in 2017 based on data from the phase 3 BFORE trial [5]. Likely related to its later approval in the first-line setting compared to other TKIs, it remains the least prescribed in the first-line setting among approved agents [24•], [25, 26].

Regardless of first-line TKI choice, the rate of discontinuation or switching is common, with approximately one-third of patients switching TKIs across most real-world studies [24•], [25, 26], [30•], [31•]. For example, a recent real-world study of 1168 chronic-phase CML patients showed that by 36 months, approximately one-third of patients had permanently discontinued treatment, with a cumulative incidence at 12 months, 24 months, and 36 months being 19.6%, 29.7%, and 34.2%, respectively [31•]. More patients with TKI discontinuation were in the imatinib group, and in univariate analysis, factors associated with a higher rate of TKI discontinuation included older age, higher white blood cell (WBC) count, spleen enlargement, and high Sokal risk [31•]. The Japanese Hokkaido Hematology Study group evaluated 450 patients and found 66% required modifications of 1st line therapy for TKI-related adverse events (AEs, 48%) or treatment failure (18%) [32]. They also found that patients with even a single comorbidity, age >60 years, a grade 3 or 4 toxicity, or on a lower dose TKI had worse survival [32]. An important clinical conclusion of this study was to recommend early TKI switching for patients with grade 3 or 4 toxicities. Changes in TKI therapy most frequently happen in the first year, with intolerance being the most common reason for switching, followed by non-response or disease progression [30•]. In the prospective SIMPLICITY observational study, treatment discontinuation was reported in 21.8% of patients in the first year of follow-up, with a higher portion in the imatinib group, with the greatest discontinuation occurring in the first three months [30•]. The most common reason for discontinuation was intolerance, followed by resistance, particularly in the imatinib group. Interruptions were reported in 16% of patients with a quarter of patients having more than one interruption, most commonly due to hematologic toxicity [30•]. In the second year, treatment discontinuations and interruptions occurred at a decreased rate, in 10% and 4% of patients, respectively [30•].

Several systematic reviews and meta-analyses have shown 2G TKIs to have a shorter time to respond and deeper response when compared to imatinib, but have not shown a significant difference in overall survival [33–36]. Additionally, they carry risks of increased adverse events compared to imatinib. A large meta-analysis of 1st line treatment in CML found no overall survival benefit to 2G TKIs, and their use was associated with an increased risk of arterial occlusive events [37]. In an Italian study, GFR (glomerular filtration rate, a measure of kidney function) decreased significantly in patients on imatinib but not on nilotinib or dasatinib [38]; yet, this finding could be biased because patients were on imatinib longer than the other two TKIs. A review of the US FDA reporting system demonstrated that, compared to other antineoplastic drugs, patients on TKIs had increased cardiac failure, ischemic heart disease, cardiac arrythmias, torsades de pointes/QT prolongation, hypertension, and pulmonary hypertension. All TKIs except imatinib were associated with increased reporting of cardiac failure. Dasatinib and bosutinib were associated with the highest risk of cardiac failure, which is a surprising finding given that increased risk was not found in clinical trials [39, 40]. Nilotinib, ponatinib, and bosutinib were associated with ischemic heart disease; nilotinib was associated with cardiac arrythmias; ponatinib was associated with hypertension; imatinib and dasatinib were associated with pulmonary hypertension [41]. Given that the reporting rate to the FDA is, on average, 6% of actual cases [42, 43], a large clinical study is needed to better define the risk of known and unknown toxicities. A retrospective UK study conducted in several centers demonstrated low adherence to guidelines and little evidence that cardiovascular (CV) history was considered in the choice of therapy [44]. Taken together, these data suggest that the competing risk from CV toxicity should be weighed in treatment decisions due to the higher risk in the general population, yet estimates from clinical trials are currently informing this trade-off.

Second-line Treatment

Among the patients who proceed to second-line therapy, 2G TKIs are the most commonly used. In real-world US data, patients who switch to second-line therapy initiated either dasatinib (58%) or nilotinib (37%), most within approximately 12 months of treatment initiation [27]. An Italian study that included 491 patients receiving second-line therapy found a similar distribution, with ~70% receiving dasatinib or nilotinib, followed by bosutinib (12%), ponatinib (10%), and imatinib (7%) [45••]. On closer evaluation in this cohort, the choice of second-line therapy was heterogenous when looking at patients who received 2G TKI in the first line. Specifically, patients who received dasatinib in the first line were switched more frequently to nilotinib or ponatinib in the second line, whereas those who started on nilotinib switched to dasatinib or imatinib most frequently [45••]. The proportion of patients with baseline hypertension, metabolic, and CV comorbidities was higher in patients treated with bosutinib and imatinib [45••]. In contrast, older adults who received 2G TKI in the first-line setting are more

likely to switch to imatinib in the second line [26]. Furthermore, among older and younger patient populations, there is real-world data to suggest that patients receiving second-line therapy have average daily doses lower than those recommended by the manufacturer, which likely aligns with patients switching related to intolerance [45••], [46, 47].

Among older adults who receive a 2G TKI in the second-line setting, dasatinib and nilotinib are the most common [26], with some data suggesting that nilotinib may have a slight advantage. Specifically, a Medicare database study of over 600 patients showed longer treatment duration, less frequent dose reduction, reduced risk of mortality, and lower healthcare utilization cost among patients >65 treated with nilotinib compared to dasatinib [46]. Notably, half of the patients were started on the lower-than-recommended dose of nilotinib, but of those who discontinued, about half resumed treatment and a quarter switched to another TKI. This is in comparison to dasatinib, where most patients started on the recommended dose, but were more likely to have dose reductions and a shorter time to discontinuation. Of those who discontinued, less than half resumed, a third switched to another TKI, and a higher proportion remained untreated compared to nilotinib (14% vs. 7%) [46].

The majority of patients who switch to second-line therapy are still likely to have some degree of clinical and molecular response, more commonly in those who switched because of intolerance compared to resistance. The Japanese New TARGET (Timely and Appropriate Registration System for GLIVEC Therapy) 2nd-line study evaluated outcomes of CP-CML patients who received a second-line TKI. The majority of patients utilized imatinib (93%) as first-line therapy, and switched related to resistance (60%) or intolerance (38%), and still had good clinical outcomes overall, with an estimated 3-year PFS of 98.7% and probabilities of achieving complete cytogenetic response (CCyR) and major molecular response (MMR) of 89.3% and 87.2%, respectively. Not surprisingly, the chances of achieving CCyR and MMR were better in the group that switched related to imatinib-intolerance compared to resistance [48]. Another study evaluating only patients started on 2G TKI in the first-line setting reported that patients were more likely to switch related to intolerance as compared to resistance. As may be predicted, the 5-year OS was better in the intolerance group (95%) compared to the resistance group (80%) [49]. Of note, the vast majority of patients in the intolerance group had achieved MMR4 or MR 4.5 by the time of the switch. Together, these data suggest that patients who require a switch to second-line treatment after 2G TKI therapy related to resistance may be more likely to require three or more lines of therapy.

Several mechanisms of TKI resistance exist including patient factors (adherence, drug-drug interactions) and disease-related (clonal evolution, genomic amplification of the *BCR::ABL1* gene, and *BCR::ABL1* kinase domain mutations) [50]. Ponatinib is a 3G TKI that is approved for use in patients with resistance or intolerance to at least two prior TKIs or those that harbor the *T315I* kinase domain mutation of *BCR::ABL1* [51]. In various international studies and registries, ponatinib is prescribed as 2nd line therapy in approximately 10–20% of patients [45••], [52–54]. Among patients receiving ponatinib as 2nd line therapy, only about 1% of patients were prescribed imatinib as first-line therapy, with a switch from either dasatinib or nilotinib being far more common [45••], [54]. Notably, patients are much younger in this setting, with the median age across most studies of 54-56, were switched related to previous treatment failure, and tended to have more aggressive disease [45••], [52–54].

Third Line and Beyond

In patients with CML, approximately 10% will proceed to third-line therapy, and 2% will proceed to fourth line or greater [24•], [55]. With so many options for TKI therapy, nearly all patients are treated with these agents in the third-line setting [24•], [45••], [55]. The optimal sequencing is not well defined, and choices in the third line or greater likely depend on the patient's fitness, comorbidities, and mutation profiles [56]. The majority of patients treated with 3 or greater lines tend to cycle between 1G and 2G TKIs, particularly dasatinib, nilotinib, and imatinib [45••], [55]. Among older adults who receive three or more lines of therapy, most commonly receive imatinib, dasatinib, or nilotinib, with only about one-fifth being started on ponatinib or bosutinib [26]. Notably, of those who received imatinib as frontline therapy, nearly half returned to imatinib as the third-line agent [26].

The 3G TKI ponatinib has increasing use in later lines, although it still is not prescribed as commonly as 1G and 2G TKIs. Analyses between the USA and Italy have shown ponatinib use in approximately 10–20% of patients in third or greater lines of therapy [45••], [55]. As a pan *BCR::ABL1* inhibitor, it is able to overcome several resistance mechanisms, particularly the *T315I* mutation which is resistant to all other currently available TKIs [57, 58]. Several real-world observational and retrospective studies have shown clinical efficacy with ponatinib in heavily pre-treated patients or those with resistant disease, with at least half of patients of patients being able to achieve major molecular response (MMR) [52, 58–62]. Patients tend to be younger and adverse events were common, but encouragingly, doses as low as 15 mg were used with efficacy and safety, specifically shown in the retrospective analysis by Binotto et al. [62]. A recent retrospective analysis from MD Anderson

Cancer Center evaluated outcomes when ponatinib versus 2G TKIs were used in the third-line setting, including patients in the PACE and OPTIC trials [63]. In this cohort, ponatinib showed deeper responses compared to 2G TKIs and was associated with an 81% 3-year PFS rate compared to 60% with 2G TKIs; however, it is important to note that the patient population was young with few comorbidities, which may limit its ability to be generalized to the overall population [63].

Novel agents have also been developed over the years to treat resistant CML. Omacetaxine is a semisynthetic purified homoharringtonine (HHT) compound that inhibits protein synthesis and was approved by the FDA in 2012 for patients with refractory CML or intolerant to two or more TKIs [64]. It is most commonly used as a bridge to SCT as its administration can be inconvenient, subcutaneous, and has less duration of response compared to other agents [64]. More recently, Asciminib, the first *BCR::ABL1* inhibitor that Specifically Targets the ABL Myrisoyl Pocket (STAMP), was approved in 2021 based on results from the phase 3 ASCEMBL trial comparing asciminib to bosutinib [7, 65]. With 2 years of median follow-up, a little over half of the patients in the study remain on treatment, and of those who discontinued, only 7% were related to adverse events [66]. Additionally, a recent matching-adjusted indirect comparison of asciminib compared to competing TKIs in the third line or later also suggested promising response outcomes and improved tolerability [67]. At this juncture, the data on asciminib is still maturing, and more head-to-head comparisons are needed.

Although not as commonly performed as previously was done, alloHSCT continues to have a role in the management of CML and remains an effective and curative option, albeit in a small population of young, otherwise fit patients with resistant disease. Per NCCN and ELN guidelines, alloHSCT should be considered for patients who present in accelerated or blast phase, lack of response to treatment (particularly, no response to 3G TKI within 3 months), or progress to more advanced disease while on treatment [10, 23]. Registry data shows that the indication for transplant in 60–75% of patients is failure to achieve deeper remission with non-transplant treatments due to resistance [55, 68, 69]. One major prognostic factor for OS in alloHSCT is disease status at the time of transplant. Several analyses have shown worse outcomes in patients who are transplanted while actively in the advanced phase (AP) or blast crisis (BC) as opposed to the chronic phase (CP) [69–71]. This can make the timing of transplant difficult to determine in those whose initial disease was in the chronic phase and progresses later. Reduced intensity conditioning (RIC) regimens vs. myeloablative conditioning (MAC) regimens were shown to have an association with earlier relapse, lower chronic graft-vs-host-disease (GVHD), but no significant difference in OS, potentially related to TKI or donor lymphocyte infusion (DLI) salvage options that are available [68].

Treatment-free Response

As the survival of patients with CML has improved over the years, there has been a shift in the goal of CML therapy to focus on cost savings, quality of life, and TFR [11]. Several factors have been identified to improve the chances of successful TFR, which can be summarized by the discontinuation criteria in the NCCN guidelines, including (1) age > 18 years, (2) CP-CML without a history of AP-CML or BP-CML, (3) on approved TKI therapy for at least 3 years, (4) prior evidence of quantifiable *BCR::ABL1* transcript, (5) stable molecular response (MR4, *BCR::ABL1* $\leq$ 0.01%IS) for at least 2 years documented on at least 4 tests performed at least 3 months apart, (6) access to reliable qPCR test with a sensitivity of detection of at least MR4.5 and can provide results within 2 weeks, (7) monthly monitoring after discontinuation, and (8) prompt resumption of TKI for loss of MMR [10]. The prospective LAST trial showed that successful TFR could be achieved in approximately 60% of patients with significant improvement in patient-reported outcomes (PROs) [72••]. Some notable influences of resuming or declining to stop TKI therapy include "TKI withdrawal syndrome" of increased musculoskeletal pain, as well as anxiety regarding relapse risk [73, 74].

Despite the availability of clear guidelines for TKI discontinuation, treatment discontinuation patterns remain inconsistent. Current treatment pattern discontinuation was assessed in physician surveys before and after the publication of the NCCN guidelines. Before the guidelines were published, approximately 34% of physicians attempted discontinuation which increased to ~90% after the guidelines were published, of which approximately two-thirds of attempts were performed outside of a clinical trial setting [75], [76••]. Interestingly, despite updated guidelines, only a little over half of physicians were aware of them, and there remained significant heterogeneity with regard to what was considered an adequate response, reasons for treatment discontinuation, access to qPCR testing sensitive enough to detect MR4.5, and definition of relapse [76••]. Those with access to more sensitive testing, practice in an academic or large group setting tended to adhere more closely to the guidelines in terms of the definition of response and length of time on TKI before a trial of discontinuation, although it is notable among the whole cohort that only one-third of patients had monthly molecular monitoring performed after discontinuation [76••]. Approximately one-fifth of patients relapsed, most within the first 12 months, and the rate of relapse was notably lower in the group that defined adequate response in accordance with the published guidelines

(11% vs. 28%) [76••]. These challenges are not isolated to the USA, with physician survey data from other parts of the world showed that 26% of respondents did not have access to a standardized polymerase chain reaction (PCR) test, and half were unaware of when the last standardization occurred [25]. Furthermore, although a majority were aware of recommendations for monitoring every 3 months in the first year, this was only achieved in clinical practice by 51%, with the most common barriers cited including cost and laboratory capability [25]. These data suggest that there is significant room for improvement in access to sensitive testing and education on the definitions of adequate response and appropriate monitoring practices in a real-world setting.

Conclusion

Outcomes in CML have vastly improved in the last half century related to extraordinary advances in treatment options. Despite this, several questions remain regarding how to best implement treatment options in a real-world setting. A national registry is needed to help better characterize treatment patterns and outcomes and find ways to continue to improve care for CML patients.

Compliance with Ethical Standards

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References

Papers of particular interest, published recently, have been highlighted as:
•Of importance
••Of major importance

1. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer. 2012;118(12):3123–7. https://doi.org/10.1002/cncr.26679.
2. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031–7. https://doi.org/10.1056/NEJM200104053441401.
3. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. J Clin Oncol. 2016;34(20):2333–40. https://doi.org/10.1200/jco.2015.64.8899.
4. Kantarjian HM, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre P, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35(2):440–53. https://doi.org/10.1038/s41375-020-01111-2.
5. Brümmendorf TH, Cortes JE, Milojkovic D, Gambacorti-Passerini C, Clark RE, Le Coutre P, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. Leukemia. 2022;36(7):1825–33. https://doi.org/10.1038/s41375-022-01589-y.
6. Cortes J, Apperley J, Lomaia E, Moiraghi B, Undurraga Sutton M, Pavlovsky C, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. Blood. 2021;138(21):2042–50. https://doi.org/10.1182/blood.2021012082.
7. Rea D, Mauro MJ, Boquimpani C, Minami Y, Lomaia E, Voloshin S, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138(21):2031–41. https://doi.org/10.1182/blood.2020009984.
8. Cortes J, Hughes T, Mauro M, Hochhaus A, Rea D, Goh YT, et al. Asciminib, a first-in-class STAMP inhibitor, provides durable molecular response in patients (pts) with chronic myeloid leukemia (CML) harboring the T315I mutation: primary efficacy and safety results from a phase 1 trial. Blood. 2020;136:47–50. https://doi.org/10.1182/blood-2020-139677.
9. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv41–51. https://doi.org/10.1093/annonc/mdx219.
10. National Comprehensive Cancer Network. Chronic myeloid leukemia (version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf
11. Atallah E, Sweet K. Treatment-free remission: the new goal in CML therapy. Curr Hematol Malignancy Rep. 2021;16(5):433–9. https://doi.org/10.1007/s11899-021-00653-1.
12. Ortman J VV, Hogan H. An aging nation: the older population in the United States. https://www.census.gov/prod/2014pubs/p25-1140.pdf.
13. Latagliata R, Carmosino I, Vozella F, Volpicelli P, De Angelis F, Loglisci MG, et al. Impact of exclusion criteria for the DASISION and ENESTnd trials in the front-line treatment of a 'real-life' patient population with chronic myeloid leukaemia. Hematol Oncol. 2017;35(2):232–6. https://doi.org/10.1002/hon.2274.
14. Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and Torsade de Pointes in Germany. Europace. 2014;16(1):101–8. https://doi.org/10.1093/europace/eut214.
15. Halfdanarson OO, Pottegard A, Bjornsson ES, Lund SH, Ogmundsdottir MH, Steingrimsson E, et al. Proton-pump inhibitors among adults: a nationwide drug-utilization study. Therap Adv Gastroenterol. 2018;11:1756284818777943. https://doi.org/10.1177/1756284818777943.
16. Bower H, Bjorkholm M, Dickman PW, Hoglund 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(24):2851–7. https://doi.org/10.1200/JCO.2015.66.2866.

17. Jamy O, Godby R, Sarmad R, Costa LJ. Survival of chronic myeloid leukemia patients in comparison to the general population in the tyrosine kinase inhibitors era: a US population-based study. Am J Hematol. 2021;96(7):E265–E8. https://doi.org/10.1002/ajh.26195.
18. Radivoyevitch T, Weaver D, Hobbs B, Maciejewski JP, Hehlmann R, Jiang Q, et al. Do persons with chronic myeloid leukaemia have normal or near normal survival? Leukemia. 2020;34(2):333–5. https://doi.org/10.1038/s41375-019-0699-y.
19. USA facts. https://usafacts.org/data/topics/people-society/population-and-demographics/population-data/population/.
20. Cancer Stat Facts: Leukemia - chronic myeloid leukemia (CML) 2018. https://seer.cancer.gov/statfacts/html/cmyl.html.
21. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics—2021 Update. Circulation. 2021;143(8):e254–743. https://doi.org/10.1161/CIR.0000000000000950.
22. Ford ES, Giles WH, Mokdad AH. The distribution of 10-Year risk for coronary heart disease among U.S. adults: findings from the National Health and Nutrition Examination Survey III. J Am Coll Cardiol. 2004;43(10):1791–6. https://doi.org/10.1016/j.jacc.2003.11.061.
23. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966–84. https://doi.org/10.1038/s41375-020-0776-2.
24.•• Banegas MP, Rivera DR, O'Keeffe-Rosetti MC, Carroll NM, Pawloski PA, Tabano DC, et al. Long-term patterns of oral anticancer agent adoption, duration, and switching in patients with CML. J Natl Compr Canc Netw. 2019;17(10):1166–72. https://doi.org/10.6004/jnccn.2019.7303. **Large retrospective review of real-world treatment patterns of oral and non-oral therapies for CML dating back to the 2000s including lines of therapy and trends in the use of TKIs**
25. Turkina A, Wang J, Mathews V, Saydam G, Jung CW, Al Hashmi HH, et al. TARGET: a survey of real-world management of chronic myeloid leukaemia across 33 countries. Br J Haematol. 2020;190(6):869–76. https://doi.org/10.1111/bjh.16599.
26. Shallis RM, Wang R, Bewersdorf JP, Zeidan AM, Davidoff AJ, Huntington SF, et al. Contemporary practice patterns of tyrosine kinase inhibitor use among older patients with chronic myeloid leukemia in the United States. Ther Adv Hematol. 2021;12:20406207211043404. https://doi.org/10.1177/20406207211043404.
27. Henk HJ, Woloj M, Shapiro M, Whiteley J. Real-world analysis of tyrosine kinase inhibitor treatment patterns among patients with chronic myeloid leukemia in the United States. Clin Ther. 2015;37(1):124–33. https://doi.org/10.1016/j.clinthera.2014.10.019.
28. Seo HY, Ko TH, Hyun SY, Song H, Lim ST, Shim KY, et al. Tyrosine kinase inhibitor dosing patterns in elderly patients with chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2019;19(11):735–43.e2. https://doi.org/10.1016/j.clml.2019.08.009.
29.•• 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. Am J Hematol. 2017;92(11):1214–23. https://doi.org/10.1002/ajh.24887. **A large prospective observational study which evaluated TKI use and management patterns in the first-line setting for patients with CML. Highlighted gaps in adherence to monitoring recommendations when initiating patients on TKI therapy**
30.• Hehlmann R, Cortes JE, Zyczynski T, Gambacorti-Passerini C, Goldberg SL, Mauro MJ, et al. Tyrosine kinase inhibitor interruptions, discontinuations and switching in patients with chronic-phase chronic myeloid leukemia in routine clinical practice: SIMPLICITY. Am J Hematol. 2019;94(1):46–54. https://doi.org/10.1002/ajh.25306. **Provides prospective observational data on treatment interruptions and switching TKI therapy in routine clinical practice**
31.• Latagliata R, Capodanno I, Miggiano MC, Iurlo A, Cavazzini F, Crescenzi SL, et al. Permanent discontinuation of tyrosine kinase inhibitor frontline therapy in patients with chronic phase chronic myeloid leukemia patients during the first 36 months of treatment: a "Campus CML" study. Blood. 2022;140(Supplement 1):3906–7. https://doi.org/10.1182/blood-2022-170415. **A large retrospective review of ~1000 CML patients showing that nearly one-third of patients permanently discontinue frontline TKI therapy in the first 3 years of treatment due to resistance or toxicity**
32. Ota S, Matsukawa T, Yamamoto S, Ito S, Shindo M, Sato K, et al. Severe adverse events by tyrosine kinase inhibitors decrease survival rates in patients with newly diagnosed chronic-phase chronic myeloid leukemia. Eur J Haematol. 2018;101(1):95–105. https://doi.org/10.1111/ejh.13081.
33.• Vener C, Banzi R, Ambrogi F, Ferrero A, Saglio G, Pravettoni G, et al. First-line imatinib vs second- and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis. Blood Adv. 2020;4(12):2723–35. https://doi.org/10.1182/bloodadvances.2019001329. **A recent systemic review and meta-analysis comparing first-line imatinib to second- and third-generation TKIs, including several major clinical trials (ENEST, DASISION, BFORE, NordCML006)**
34. Gurion R, Raanani P, Vidal L, Leader A, Gafter-Gvili A. First line treatment with newer tyrosine kinase inhibitors in chronic myeloid leukemia associated with deep and durable molecular response – systematic review and meta-analysis. Acta Oncol. 2016;55(9-10):1077–83. https://doi.org/10.1080/0284186x.2016.1201214.
35. Pavey T, Hoyle M, Ciani O, Crathorne L, Jones-Hughes T, Cooper C, et al. Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses. Health Technol Assess. 2012;16(42):iii–v. https://doi.org/10.3310/hta16420.
36. Tang L, Zhang H, Peng YZ, Li CG, Jiang HW, Xu M, et al. Comparative efficacy and tolerability of front-line treatments for newly diagnosed chronic-phase chronic myeloid leukemia: an update network meta-analysis. BMC Cancer. 2019;19(1):849. https://doi.org/10.1186/s12885-019-6039-9.
37. Haguet H, Graux C, Mullier F, Dogne JM, Douxfils J. Long-term survival, vascular occlusive events and efficacy biomarkers of first-line treatment of CML: a meta-analysis. Cancers (Basel). 2020;12(5). https://doi.org/10.3390/cancers12051242.
38. Molica M, Scalzulli E, Colafigli G, Fegatelli DA, Massaro F, Latagliata R, et al. Changes in estimated glomerular filtration rate in chronic myeloid leukemia patients treated front line with available TKIs and correlation with cardiovascular events. Ann Hematol. 2018;97(10):1803–8. https://doi.org/10.1007/s00277-018-3375-9.
39. 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. 2018;36(3):231–7. https://doi.org/10.1200/JCO.2017.74.7162.

40. Hochhaus A, Gambacorti-Passerini C, Abboud C, Gjertsen BT, Brummendorf TH, Smith BD, et al. Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: primary results of the phase 4 BYOND study. Leukemia. 2020;34(8):2125–37. https://doi.org/10.1038/s41375-020-0915-9.
41. Cirmi S, El Abd A, Letinier L, Navarra M, Salvo F. Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: an analysis of the FDA adverse event reporting system database (FAERS). Cancers (Basel). 2020;12(4) https://doi.org/10.3390/cancers12040826.
42. Bégaud B, Martin K, Haramburu F, Moore N. Rates of spontaneous reporting of adverse drug reactions in France. Jama. 2002;288(13):1588. https://doi.org/10.1001/jama.288.13.1588.
43. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96. https://doi.org/10.2165/00002018-200629050-00003.
44. Milojkovic D, Cross NCP, Ali S, Byrne J, Campbell G, Dignan FL, et al. 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. Br J Haematol. 2021;192(1):62–74. https://doi.org/10.1111/bjh.16733.
45.•• Breccia M, Chiodi F, Nardozza AP, Valsecchi D, Perrone V, Sangiorgi D, et al. Real-world analysis of the therapeutic management and disease burden in chronic myeloid leukemia patients with later lines in Italy. J Clin Med. 2022;11(13) https://doi.org/10.3390/jcm11133597. **A real-world retrospective study that focuses on TKI use patterns in 2nd and greater lines of therapy, including a focus on treatment sequencing**
46. Smith BD, Liu J, Latremouille-Viau D, Guerin A, Fernandez D, Chen L. Treatment patterns, overall survival, healthcare resource use and costs in elderly Medicare beneficiaries with chronic myeloid leukemia using second-generation tyrosine kinase inhibitors as second-line therapy. Curr Med Res Opin. 2016;32(5):817–27. https://doi.org/10.1185/03007995.2016.1140030.
47. Perrone V, Giacomini E, Andretta M, Arenare L, Cillo MR, Latini M, et al. Italian real-world analysis of a tyrosine kinase inhibitor administration as first- or second-line of therapy in patients with chronic myeloid leukemia. Ther Clin Risk Manag. 2021;17:617–22. https://doi.org/10.2147/tcrm.S309342.
48. Sakurai M, Okamoto S, Matsumura I, Murakami S, Takizawa M, Waki M, et al. Treatment outcomes of chronic-phase chronic myeloid leukemia with resistance and/or intolerance to a 1st-line tyrosine kinase inhibitor in Japan: the results of the new TARGET study 2nd-line. Int J Hematol. 2020;111(6):812–25. https://doi.org/10.1007/s12185-020-02843-8.
49. Ma CE, Ghosh S, Leyshon C, Blosser N, Dersch-Mills D, Jupp J, et al. Clinical outcome of chronic myeloid leukemia patients who switch from first-line therapy with a second generation tyrosine kinase inhibitor to an alternative TKI. Leuk Res. 2021;111:106674. https://doi.org/10.1016/j.leukres.2021.106674.
50. Lau A, Seiter K. Second-line therapy for patients with chronic myeloid leukemia resistant to first-line imatinib. Clin Lymphoma Myeloma Leuk. 2014;14(3):186–96. https://doi.org/10.1016/j.clml.2013.11.002.
51. Pulte ED, Chen H, Price LSL, Gudi R, Li H, Okusanya OO, et al. FDA approval summary: revised indication and dosing regimen for ponatinib based on the results of the OPTIC trial. Oncologist. 2022;27(2):149–57. https://doi.org/10.1093/oncolo/oyab040.
52. Devos T, Theunissen K, Benghiat FS, Gadisseur A, Meers S, Selleslag D, et al. Efficacy and safety of ponatinib in CML and Ph+ ALL patients in real-world clinical practice: data from a Belgian Registry. Blood. 2018;132(Supplement 1):1744. https://doi.org/10.1182/blood-2018-99-114070.
53. Luciano L, Specchia G, Martino B, Accurso V, Santoro M, Malato A, et al. A real life evaluation of efficacy and safety of ponatinib therapy in CML patients. Blood. 2017;130(Supplement 1):2905. https://doi.org/10.1182/blood.V130.Suppl_1.2905.2905.
54. Breccia M, Abruzzese E, Castagnetti F, Bonifacio M, Gangemi D, Sorà F, et al. Ponatinib as second-line treatment in chronic phase chronic myeloid leukemia patients in real-life practice. Ann Hematol. 2018;97(9):1577–80. https://doi.org/10.1007/s00277-018-3337-2.
55. Atallah EL, Maegawa R, Latremouille-Viau D, Rossi C, Guérin A, Wu EQ, et al. Chronic myeloid leukemia: part I-real-world treatment patterns, healthcare resource utilization, and associated costs in later lines of therapy in the United States. J Health Econ Outcomes Res. 2022;9(2):19–29. https://doi.org/10.36469/001c.36975.
56. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2022 update on diagnosis, therapy, and monitoring. Am J Hematol. 2022;97(9):1236–56. https://doi.org/10.1002/ajh.26642.
57. O'Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, et al. AP24534, a Pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009;16(5):401–12. https://doi.org/10.1016/j.ccr.2009.09.028.
58.• Luciano L, Annunziata M, Attolico I, Di Raimondo F, Maggi A, Malato A, et al. The multi-tyrosine kinase inhibitor ponatinib for chronic myeloid leukemia: real-world data. Eur J Haematol. 2020;105(1):3–15. https://doi.org/10.1111/ejh.13408. **Review article summarizing data including outcomes and adverse events for the use of ponatinib in real-world settings**
59. Shacham-Abulafia A, Raanani P, Lavie D, Volchek Y, Ram R, Helman I, et al. Real-life experience with ponatinib in chronic myeloid leukemia: a multicenter observational study. Clin Lymphoma Myeloma Leuk. 2018;18(7):e295–301. https://doi.org/10.1016/j.clml.2018.05.002.
60. Heiblig M, Rea D, Chrétien M-L, Charbonnier A, Rousselot P, Coiteux V, et al. Ponatinib evaluation and safety in real-life chronic myelogenous leukemia patients failing more than two tyrosine kinase inhibitors: the PEARL observational study. Exp Hematol. 2018;67:41–8. https://doi.org/10.1016/j.exphem.2018.08.006.
61. Devos T, Havelange V, Theunissen K, Meers S, Benghiat FS, Gadisseur A, et al. Clinical outcomes in patients with Philadelphia chromosome-positive leukemia treated with ponatinib in routine clinical practice-data from a Belgian registry. Ann Hematol. 2021;100(7):1723–32. https://doi.org/10.1007/s00277-021-04507-x.
62. Binotto G, Castagnetti F, Gugulotta G, Abruzzese E, Iurlo A, Stagno F, et al. Ponatinib 15mg daily, combining efficacy and tolerability. A retrospective survey in Italy. 23rd Eur Hematol Assoc Congress. 2018;(Abstract PS1122). https://library.ehaweb.org/eha/2018/stockholm/215436/gianni.binotto.ponatinib.15.mg.daily.combining.efficacy.and.tolerability.a.html
63. Jabbour EJ, Sasaki K, Haddad FG, Issa GC, Garcia-Manero G, Kadia TM, et al. The outcomes of patients with chronic myeloid leukemia treated with third-line BCR::ABL1 tyrosine kinase inhibitors. Am J Hematol. 2023;98(4):658–65. https://doi.org/10.1002/ajh.26852.
64. Winer ES, DeAngelo DJ. A review of omacetaxine: a chronic myeloid leukemia treatment resurrected. Oncol Ther. 2018;6(1):9–20. https://doi.org/10.1007/s40487-018-0058-6.
65. FDA approves asciminib for Philadelphia chromosome-positive chronic myeloid leukemia [press release]. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-appro

ves-asciminib-philadelphia-chromosome-positive-chronic-myeloid-leukemia, October 29, 2021 2021.

66. Hochhaus A, Rea D, Boquimpani C, Minami Y, Cortes JE, Hughes TP, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia. 2023;37(3):617–26. https://doi.org/10.1038/s41375-023-01829-9.
67. Atallah E, Mauro MJ, Hochhaus A, Boquimpani C, Minami Y, Maheshwari VK, et al. Matching-adjusted indirect comparison of asciminib versus other treatments in chronic-phase chronic myeloid leukemia after failure of two prior tyrosine kinase inhibitors. J Cancer Res Clin Oncol. 2023. https://doi.org/10.1007/s00432-022-04562-5.
68. Chhabra S, Ahn KW, Hu Z-H, Jain S, Assal A, Cerny J, et al. Myeloablative vs reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chronic myeloid leukemia. Blood Adv. 2018;2(21):2922–36. https://doi.org/10.1182/bloodadvances.2018024844.
69.• Lubking A, Dreimane A, Sandin F, Isaksson C, Markevarn B, Brune M, et al. Allogeneic stem cell transplantation for chronic myeloid leukemia in the TKI era: population-based data from the Swedish CML registry. Bone Marrow Transplant. 2019;54(11):1764–74. https://doi.org/10.1038/s41409-019-0513-5. **Real-world data from a Swedish registry highlighting indications and risk factors for patients with CML undergoing allogeneic hematopoietic stem cell transplant**
70. Khoury HJ, Kukreja M, Goldman JM, Wang T, Halter J, Arora M, et al. Prognostic factors for outcomes in allogeneic transplantation for CML in the imatinib era: a CIBMTR analysis. Bone Marrow Transplant. 2012;47(6):810–6. https://doi.org/10.1038/bmt.2011.194.
71. Niederwieser C, Morozova E, Zubarovskaya L, Zabelina T, Klyuchnikov E, Janson D, et al. Risk factors for outcome after allogeneic stem cell transplantation in patients with advanced phase CML. Bone Marrow Transplant. 2021;56(11):2834–41. https://doi.org/10.1038/s41409-021-01410-x.
72.•• Atallah E, Schiffer CA, Radich JP, Weinfurt KP, Zhang MJ, Pinilla-Ibarz J, et al. Assessment of outcomes after stopping tyrosine kinase inhibitors among patients with chronic myeloid leukemia: a nonrandomized clinical trial. JAMA Oncol. 2021;7(1):42–50. https://doi.org/10.1001/jamaoncol.2020.5774. **LAST trial which evaluated 172 patients prospectively at multiple academic centers in the USA with 3 years of follow-up after discontinuation of TKIs, providing real-world data on TFR by molecular criteria as well as data on patient-reported outcomes (PROs)**
73. Flynn KE, Atallah E, Lin L, Shah NP, Silver RT, Larson RA, et al. Patient- and physician-reported pain after tyrosine kinase inhibitor discontinuation among patients with chronic myeloid leukemia. Haematologica. 2022;107(11):2641–9. https://doi.org/10.3324/haematol.2021.280377.
74. Cutica I, Riva S, Orlandi EM, Iurlo A, Vener C, Elena C, et al. Psychological factors affecting the willingness to accept a possible tyrosine kinase inhibitor (TKI) discontinuation in chronic myeloid leukaemia (CML) patients. Patient Prefer Adherence. 2022;16:2963–75. https://doi.org/10.2147/ppa.S369326.
75. Ritchie EK, Latremouille-Viau D, Guerin A, Pivneva I, Habucky K, Ndife B, et al. Tyrosine kinase inhibitor therapy treatment and discontinuation in patients with chronic myeloid leukemia in chronic phase in the United States: a clinical practice perspective. Leuk Lymphoma. 2019;60(6):1476–84. https://doi.org/10.1080/10428194.2018.1538510.
76.• Atallah EL, Sadek I, Maegawa R, Cao X, Latremouille-Viau D, Pivneva I, et al. Tyrosine kinase inhibitor therapy discontinuation in patients with chronic myeloid leukemia in chronic phase in the United States after clinical practice guideline updates. Leuk Lymphoma. 2021;62(7):1730–9. https://doi.org/10.1080/10428194.2021.1885656. **Data on real-world TKI discontinuation patterns before and after the publication of practice guidelines. Highlights discordance between parameters recommended prior to TKI discontinuation and how this happens in routine clinical practice**