Treatment-Free Remission After Tyrosine Kinase Inhibitor Discontinuation in Chronic Myeloid Leukemia: A Single-Center Real-World Retrospective Study

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ABSTRACT

Background. Treatment-free remission (TFR) has emerged as a therapeutic goal for patients with chronic myeloid leukemia (CML) who achieve deep molecular response (DMR) during tyrosine kinase inhibitor (TKI) therapy. However, real-world evidence from Chinese cohorts remains limited, and published data on TFR following discontinuation of flumatinib—a domestically developed second-generation TKI—are virtually absent.

Objective. To evaluate TFR outcomes and identify prognostic factors associated with molecular recurrence in a real-world cohort of CML patients who discontinued TKI therapy.

Methods. This retrospective single-center study analyzed 49 chronic-phase CML patients who discontinued TKIs between January 2014 and May 2026. TFR was defined as the maintenance of major molecular response (MMR; BCR::ABL1 ≤0.1% on the International Scale) after TKI discontinuation; molecular recurrence was defined as confirmed loss of MMR. Comparisons between recurrent and non-recurrent groups were performed using standard statistical tests, and TFR duration was estimated by the Kaplan–Meier method.

Results. The cohort comprised 49 patients (55.1% female; mean age 59.1 years, range 20–83) treated with imatinib (n=21), nilotinib (n=16), flumatinib (n=11), or dasatinib (n=1). Median TKI treatment duration was 89.0 months (mean 99.2 ± 53.8). The overall TFR success rate was 79.6% (39/49), with a median TFR duration of 16.5 months (range 1–144). Molecular recurrence occurred in 10 patients (20.4%), and 8 of 10 relapses occurred within the first 6 months. The non-recurrent group had substantially longer mean treatment duration than the recurrent group (110.8 vs. 53.8 months). By TKI type, TFR success rates were 100% for nilotinib (0/16 recurrence), 76.2% for imatinib (5/21), and 63.6% for flumatinib (4/11). All recurrent patients regained MMR upon TKI reinitiation.

Conclusion. TFR is achievable in approximately 80% of carefully selected real-world CML patients. Longer cumulative TKI treatment duration is strongly associated with successful TFR outcomes. A cautious approach to flumatinib discontinuation is warranted until prospective data become available.

Keywords: Chronic myeloid leukemia; treatment-free remission; tyrosine kinase inhibitor; flumatinib; nilotinib; imatinib

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the reciprocal t(9;22)(q34;q11) chromosomal translocation that generates the BCR::ABL1 fusion oncogene encoding a constitutively active tyrosine kinase[1]. The clinical trajectory of CML was fundamentally altered following the introduction of imatinib, the first tyrosine kinase inhibitor (TKI) targeting the BCR-ABL1 oncoprotein [2]. Long-term follow-up data from landmark trials have demonstrated that the majority of patients with chronic-phase (CP) CML who receive TKI therapy achieve sustained molecular responses and near-normal life expectancy [3, 4]. Consequently, CML has been transformed from a previously fatal malignancy into a manageable chronic condition, with treatment goals now extending beyond survival to encompass quality of life, cost reduction, and the potential for treatment discontinuation [5].

Treatment-free remission (TFR) is defined as the sustained maintenance of a major molecular response (MMR; BCR::ABL1 transcript level ≤0.1% on the International Scale) after discontinuation of TKI therapy [6]. TFR represents an emerging therapeutic objective that offers several potential benefits, including elimination of treatment-related adverse events, reduced financial burden, improved quality of life, and resolution of treatment-associated toxicities such as cardiovascular and metabolic complications [7, 8]. The feasibility of TFR was first demonstrated in prospective studies of patients who had achieved deep molecular response (DMR; MR4.0 or MR4.5) during prolonged imatinib therapy [1, 9]. Current guidelines from the European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) now recognize TFR as a legitimate treatment goal for appropriately selected patients [7, 10].

The foundation for TFR was established by the landmark STIM1 trial, the first prospective study to evaluate imatinib discontinuation in 100 patients who had maintained undetectable molecular residual disease for at least 2 years [11]. Long-term follow-up of STIM1 demonstrated a molecular recurrence-free survival rate of 38% at 60 months, with the majority of relapses occurring within the first 6 months after discontinuation [12, 13]. Critically, all patients who restarted imatinib upon molecular relapse regained MMR, establishing the safety of TFR attempts [14]. Subsequent trials have confirmed and extended these findings across different TKIs. The EURO-SKI study, the largest TFR trial conducted to date, prospectively evaluated 755 patients from multiple European centers who discontinued any TKI after achieving sustained DMR [15]. The prespecified interim analysis demonstrated TFR rates of 61%, 50%, and 46% at 6, 24, and 36 months, respectively [11]. The final analysis identified three independent predictors of successful TFR: duration of TKI therapy, duration of DMR, and BCR::ABL1 transcript type [11].

Second-generation TKIs (2G-TKIs), including nilotinib and dasatinib, induce deeper and more rapid molecular responses than imatinib, prompting investigations into TFR following 2G-TKI therapy. The ENEST freedom trial prospectively evaluated TFR in 190 patients who achieved sustained MR4.5 after frontline nilotinib therapy, reporting a 1-year treatment-free survival rate of 51.6% and a 5-year rate of 44% [16]. Similarly, the ENESTop trial assessed TFR after second-line nilotinib following imatinib switch, demonstrating a 48-week treatment-free survival rate of 57.9% [17]. The DASFREE

study examined dasatinib discontinuation in 84 patients with stable DMR, with 2-year TFR rates of 46–49% [18]. Meta-analyses of these trials have estimated that approximately 40% of patients experience molecular relapse within the first year, with the majority regaining response upon TKI reinitiation [17].

Despite the expanding global evidence base for TFR, data from Chinese cohorts remain markedly underrepresented in the international literature. The majority of published TFR trials have originated from Europe, North America, and Japan [11], with comparatively few reports detailing outcomes from Chinese patient populations. This geographic imbalance is particularly significant given that China accounts for a substantial proportion of the global CML burden and has distinct patterns of TKI utilization, including broader access to domestically developed agents [19]. A recent systematic review and meta-analysis of TFR noted that only a minority of included studies provided data from Asian populations, with Chinese-specific outcomes rarely reported [20]. A multicenter TFR program in low- and middle-income countries achieved a 79% TFR success rate with stringent eligibility criteria, highlighting the importance of regional data [21].

Flumatinib is a novel 2G-TKI developed in China through structural optimization of imatinib, incorporating a trifluoromethyl group that enhances binding affinity and selectivity for the BCR-ABL1 kinase [22]. The phase III FESTnd trial demonstrated that flumatinib achieved higher and deeper molecular responses than imatinib in newly diagnosed CP-CML patients, with a favorable safety profile [23]. Real-world studies have subsequently confirmed flumatinib's efficacy as both frontline and later-line therapy [24]. However, despite its increasing clinical use in China, published data on TFR outcomes following flumatinib discontinuation remain virtually absent from the literature. A network meta-analysis comparing first-line TKIs included flumatinib but was unable to evaluate TFR-specific outcomes due to the lack of available discontinuation data [24]. This gap represents a significant limitation in understanding the complete clinical profile of flumatinib and in informing treatment discontinuation decisions for patients who achieve deep molecular responses on this agent.

The existing TFR evidence base derives predominantly from prospective clinical trials with strict eligibility criteria, including requirements for sustained DMR for defined minimum durations, typical BCR::ABL1 transcript types, and absence of prior treatment failure [25]. While these trials provide critical efficacy benchmarks, their generalizability to real-world practice may be limited. Real-world cohorts often include patients with heterogeneous characteristics that may differ substantially from trial populations [26]. Long-term follow-up data extending beyond 3-5 years remain scarce, and the relationship between treatment duration and TFR success requires further characterization in routine clinical settings [12]. Etienne and colleagues reported that among 398 patients followed over a 10-year period, only 46% achieved a sustained DMR suitable for TFR consideration [11]. The D-FREE study further demonstrated that insufficient TKI treatment duration was associated with markedly elevated relapse risk, emphasizing the importance of adequate treatment exposure prior to discontinuation [27].

The present study provides one of the first real-world reports of TFR outcomes following flumatinib discontinuation in patients with CP-CML. By analyzing a cohort of 49 patients who discontinued various TKIs under routine

clinical practice conditions, this work addresses the critical gap in flumatinib discontinuation data and offers preliminary evidence regarding the feasibility of TFR after this increasingly utilized 2G-TKI. The retrospective analysis encompasses a substantial follow-up period of up to 144 months (12 years) after TKI discontinuation, exceeding the observation windows of many published TFR series. These long-term data provide valuable insights into the durability of TFR and the temporal patterns of molecular recurrence in a Chinese patient population. The inclusion of patients treated with imatinib, nilotinib, flumatinib, and dasatinib further enables a comparative analysis of TFR outcomes across different TKIs in a real-world setting.

2. Methods

2.1 Study Design and Patients

This was a retrospective single-center cohort study conducted at a tertiary hematology center in China. The study analyzed data from consecutive patients with chronic myeloid leukemia in chronic phase (CML-CP) who discontinued tyrosine kinase inhibitor (TKI) therapy between January 2014 and May 2026, with subsequent molecular monitoring to assess treatment-free remission (TFR) outcomes. The feasibility of sustained TFR following TKI discontinuation in patients with deep molecular response (DMR) has been established in several prospective trials, including the landmark STIM study [28], the TWISTER study [29], and the EURO-SKI trial [15], which collectively demonstrated that approximately 40–60% of carefully selected patients can maintain durable molecular remission after stopping TKI therapy. Building upon this evidence, TFR has emerged as an important therapeutic goal in CML management.

Patient eligibility was determined according to the following inclusion criteria: (i) a confirmed diagnosis of CML-CP based on clinical presentation, cytogenetic analysis demonstrating the Philadelphia chromosome, and detection of the BCR::ABL1 fusion transcript; (ii) receipt of at least one TKI for a minimum duration; (iii) documentation of TKI discontinuation with a defined stop date; and (iv) availability of molecular monitoring data following TKI cessation. Patients were excluded if they had a history of accelerated-phase or blast-phase CML, had undergone allogeneic hematopoietic stem cell transplantation, or lacked molecular monitoring records after TKI discontinuation. The decision to discontinue TKI therapy was made by the treating physician in consultation with the patient, based on sustained molecular response and clinical judgment, in alignment with the evolving clinical practice during the study period. Informed consent for TKI discontinuation and molecular monitoring was obtained from all patients as part of routine clinical care.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the institutional ethics committee, and the requirement for additional informed consent was waived given the retrospective nature of the analysis and the use of de-identified data extracted from existing clinical records.

2.2 Data Collection and Molecular Monitoring

Data were extracted retrospectively from the institutional electronic medical records and the CML patient registry. The following variables were collected for each patient: demographic characteristics including age at TKI discontinuation and sex; clinical features at diagnosis; TKI treatment history including the type of TKI(s) used, duration of TKI therapy

(calculated from the date of CML diagnosis to the date of TKI discontinuation), and prior TKI switches; and molecular monitoring results following TKI cessation.

Molecular response was assessed using real-time quantitative polymerase chain reaction (RT-qPCR) for BCR::ABL1 transcript levels, with results expressed on the International Scale (IS) according to standardized laboratory protocols [5]. The BCR::ABL1 transcript level was reported as the ratio of BCR::ABL1 to the internal control gene (ABL1), converted to the IS using a laboratory-specific conversion factor. The limit of detection for the assay was at least MR4.0 (corresponding to BCR::ABL1 IS < 0.01%), with a reported sensitivity sufficient to detect MR4.5 (BCR::ABL1 IS < 0.0032%) in most assays [30]. Molecular monitoring was performed at baseline prior to TKI discontinuation and at regular intervals thereafter, with increasing frequency in the initial months following cessation, consistent with prevailing institutional protocols adapted from international recommendations. The ELN 2020 recommendations advise monthly molecular testing during the first 6 months after TKI discontinuation, followed by testing every 6 weeks for the subsequent 6 months, and every 3 months thereafter [31].

2.3 Definitions

Treatment-free remission (TFR) was defined as the maintenance of a negative or low-level molecular status after TKI discontinuation without evidence of molecular recurrence. Successful TFR was operationalized as the absence of molecular recurrence at the last available follow-up. Patients who maintained BCR::ABL1 levels below major molecular response (MMR; defined as BCR::ABL1 IS ≤ 0.1%) throughout the post-discontinuation monitoring period were classified as having sustained TFR [32]. Deep molecular response was classified as MR4.0 (BCR::ABL1 IS < 0.01%) or MR4.5 (BCR::ABL1 IS < 0.0032%), as previously defined [33].

Molecular recurrence was defined as the loss of MMR, corresponding to a confirmed BCR::ABL1 transcript level exceeding 0.1% on the IS, or the reappearance of a positive BCR::ABL1 result above the established threshold in two consecutive tests, or the documentation of clinical relapse in the medical records. The date of molecular recurrence was assigned as the date of the first positive test result indicating loss of molecular response. This definition is consistent with the criteria used in prospective TFR studies, where loss of MMR triggers TKI reinitiation [34]. Patients who experienced molecular recurrence were managed according to standard clinical practice, with TKI reinitiation at the discretion of the treating physician [34].

Drug categorization was performed based on the TKI agent used prior to discontinuation. TKIs were classified into four categories: imatinib (including branded imatinib [Glivec; Novartis, Basel, Switzerland] and generic formulations [Xinwei, Genike, and other approved generics]); nilotinib (Tasigna; Novartis, Basel, Switzerland, and generic nilotinib); flumatinib (HS-10086; Jiangsu Hansoh Pharmaceutical Group, Lianyungang, China), a second-generation TKI approved in China in 2019 for the first-line treatment of newly diagnosed CML-CP [35]; and dasatinib (Sprycel; Bristol-Myers Squibb, Princeton, NJ, USA). For patients who received sequential TKIs, the agent used immediately prior to discontinuation was designated as the primary TKI for categorization purposes. Treatment duration was defined as the interval from CML diagnosis to TKI discontinuation.

2.4 Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and outcome measures. Continuous variables were reported as mean with standard deviation (SD) and median with range, depending on the distribution of the data. Categorical variables were expressed as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of continuous variables.

Comparisons between patients with and without molecular recurrence were performed using the independent-samples t-test or Mann-Whitney U test for continuous variables, as appropriate based on normality assessment. The chi-squared test or Fisher's exact test was used for categorical variables. All statistical tests were two-sided, and a P value of less than 0.05 was considered statistically significant.

Treatment-free remission duration was calculated from the date of TKI discontinuation to the date of molecular recurrence, death, or last follow-up, whichever occurred first. TFR duration was analyzed using the Kaplan-Meier method, and differences between subgroups were assessed using the log-rank test. The median duration of TFR with its 95% confidence interval (CI) was estimated from the Kaplan-Meier curve. Censoring was applied for patients who remained in sustained TFR at the time of last follow-up. Statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA) or R software (version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Patient Characteristics

A total of 49 chronic myeloid leukemia (CML) patients who discontinued tyrosine kinase inhibitor (TKI) therapy were included in this retrospective analysis. The demographic and clinical characteristics of the cohort are summarized in Table 1.

The mean age of the cohort was 59.1 years (standard deviation [SD] 14.6, range 20–83 years), with a slight female predominance (55.1% female, 44.9% male). The median duration of TKI treatment prior to discontinuation was 89.0 months (mean ± SD, 99.2 ± 53.8 months), indicating that most patients had received prolonged therapy consistent with current guideline recommendations for TFR eligibility [1,2]. Among the TKI agents used, imatinib was the most frequently prescribed (42.9%), followed

Table 1. Demographic and clinical characteristics of the study cohort (N=49)

Characteristic	Overall (N=49)	Non-recurrent (n=39)	Recurrent (n=10)
Age, years, mean ± SD	59.1 ± 14.6	60.1 ± 13.4	55.6 ± 19.3
Gender, n (%)			
Female	27 (55.1)	22 (56.4)	5 (50.0)
Male	22 (44.9)	17 (43.6)	5 (50.0)
TKI treatment duration, months, mean ± SD	99.2 ± 53.8	110.8 ± 53.8	53.8 ± 24.2
Drug category, n (%)			
Imatinib	21 (42.9)	16 (41.0)	5 (50.0)
Nilotinib	16 (32.7)	16 (41.0)	0 (0.0)
Flumatinib	11 (22.4)	7 (17.9)	4 (40.0)
Dasatinib	1 (2.0)	0 (0.0)	1 (10.0)

by nilotinib (32.7%) and flumatinib (22.4%); a single patient (2.0%) received dasatinib. Comparison between the non-recurrent and recurrent groups revealed comparable age and gender distributions. These baseline demographic similarities suggest that age and gender are not predictive of molecular recurrence in this cohort, consistent with findings from larger prospective TFR trials [3,4].

3.2 TFR Outcomes

The overall TFR success rate was 79.6% (39 of 49 patients), with a molecular recurrence rate of 20.4% (10 of 49 patients). The median duration of TFR across the entire cohort was 16.5 months, with a wide range from 1 to 144 months and a mean of 24.4 months.

As shown in Figure 1, the majority of relapses were concentrated within the first 12 months following TKI discontinuation, a pattern that aligns with the established understanding that early molecular recurrence reflects the reactivation of residual leukemic stem cells. Among the 49 patients, 7 (14.3%) maintained TFR for less than 6 months, 10 (20.4%) for 6–12 months, 12 (24.5%) for 12–24 months, 9 (18.4%) for 24–36 months, and 10 (20.4%) for 36 months or longer. The observation that 20 patients (40.8%) achieved TFR lasting ≥24 months supports the durability of molecular remission in a substantial subset of CML patients after TKI cessation.

3.3 Factors Associated with Molecular Recurrence

3.3.1 Treatment Duration

TKI treatment duration prior to discontinuation emerged as the most prominent factor distinguishing recurrent from non-recurrent patients (Table 2).

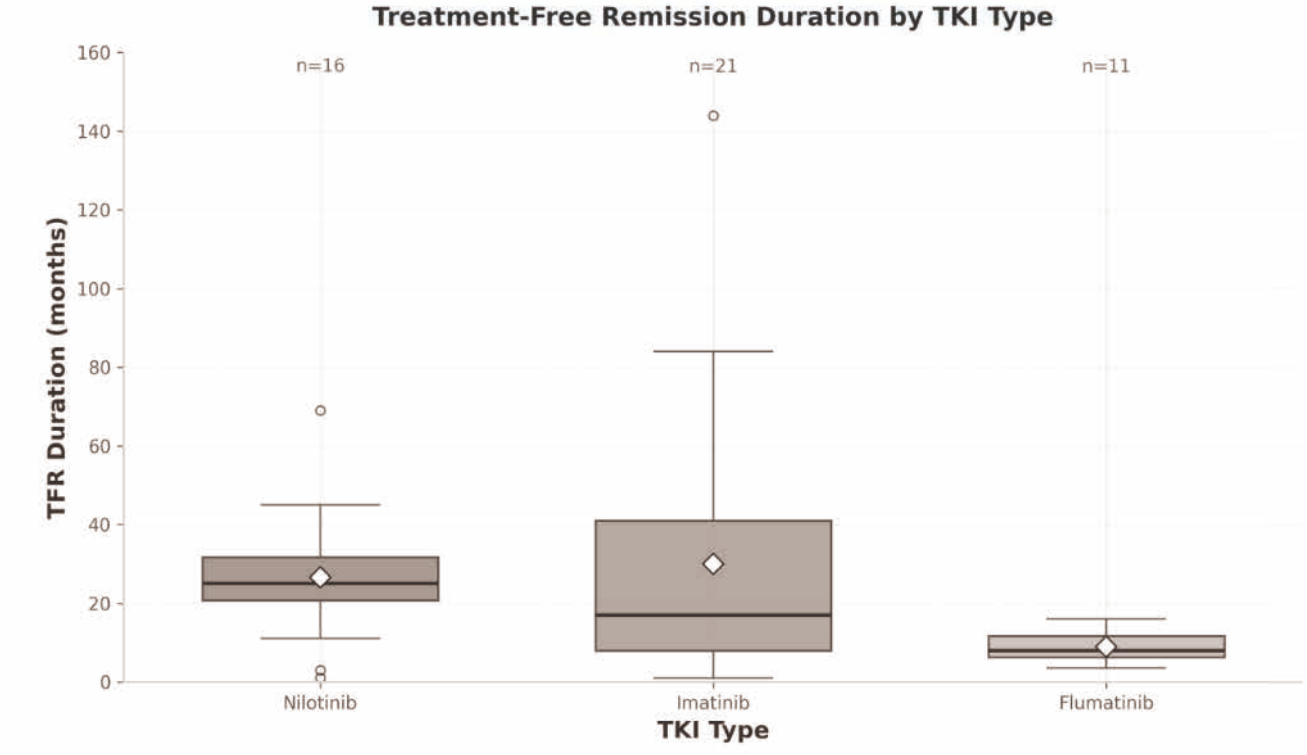

Figure 1. Distribution of treatment-free remission (TFR) duration by TKI type. Most relapses occurred within the first 12 months following discontinuation.

The non-recurrent group had a mean treatment duration of 110.8 ± 53.8 months (median 108.0 months), approximately twice that of the recurrent group (mean 53.8 ± 24.2 months, median 59.1 months). This marked difference suggests that longer cumulative TKI exposure is associated with improved probability of sustained TFR, likely reflecting more profound suppression of the leukemic stem cell reservoir over extended treatment periods. The range of treatment duration in the recurrent group (20.0-89.0 months) did not overlap with the upper quartile of the non-recurrent group, further underscoring the discriminative value of this parameter. Current guidelines generally recommend a minimum of 3 years of deep molecular response (DMR) prior to TKI discontinuation, typically translating to ≥5–6 years of total TKI therapy. The median treatment duration of 59.1 months in the recurrent group approaches this threshold and may explain, in part, the higher recurrence rate observed. The marked disparity in treatment duration between the two groups is further illustrated in Figure 3.

Table 2. Comparison of TKI treatment duration between recurrent and non-recurrent groups

Parameter	Overall (N=49)	Non-recurrent (n=39)	Recurrent (n=10)
Mean ± SD, months	99.2 ± 53.8	110.8 ± 53.8	53.8 ± 24.2
Median, months	89.0	108.0	59.1
Range, months	20.0–195.0	31.0–195.0	20.0–89.0

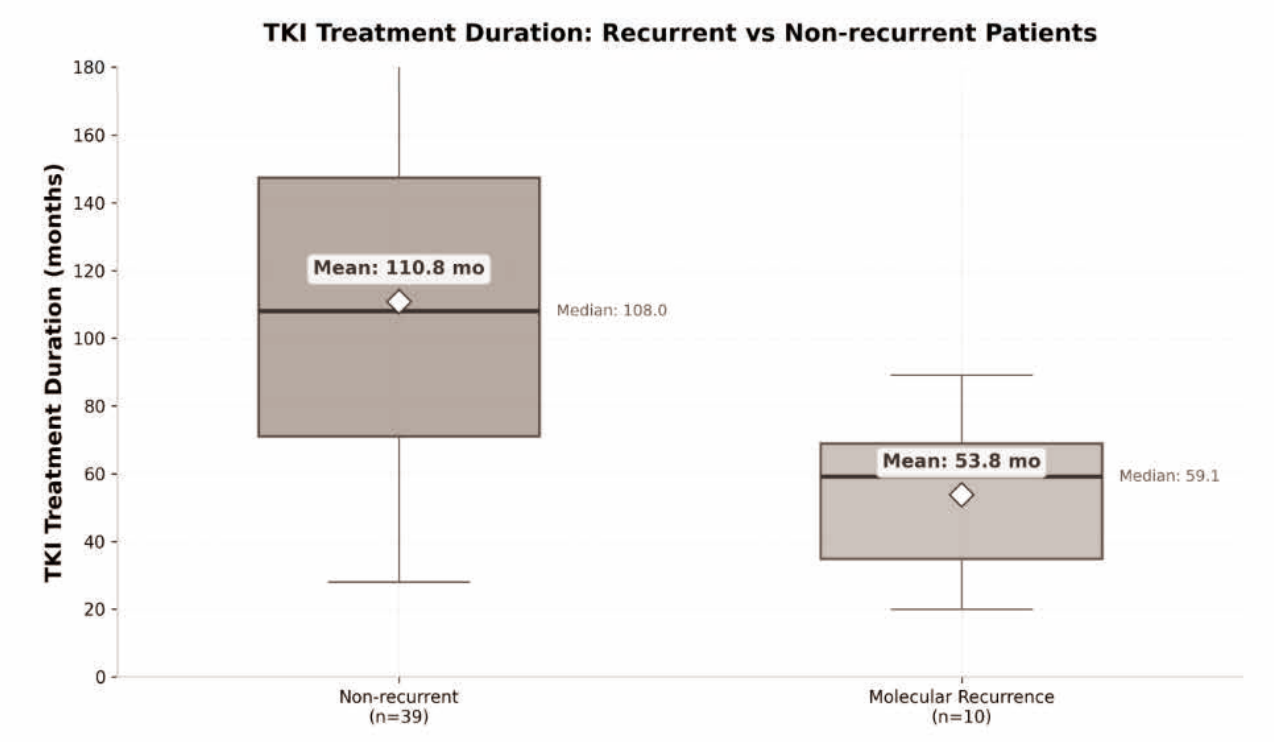

Figure 3. Comparison of TKI treatment duration between recurrent and non-recurrent groups.
The non-recurrent group exhibited approximately twice the cumulative TKI exposure of the recurrent group.

3.3.2 TKI Drug Category

The type of TKI agent was associated with markedly different recurrence rates. As shown in Table 3 and illustrated in Figure 2, nilotinib-treated patients achieved a 100% TFR success rate with no instances of molecular recurrence (0 of 16), whereas imatinib-treated patients had a recurrence rate of 23.8% (5 of 21) and flumatinib-treated patients had a recurrence rate of 36.4% (4 of 11). The single dasatinib-treated patient experienced molecular recurrence.

The superior TFR outcome observed with nilotinib is biologically plausible, as second-generation TKIs achieve deeper and more rapid molecular responses compared with imatinib, which may translate to more effective depletion of the leukemic stem cell compartment. The 0% recurrence rate in the nilotinib subgroup is consistent with reports from the ENESTop and ENESTfreedom trials. The higher recurrence rate among flumatinib-treated patients (36.4%) is a novel finding; these patients may have had shorter overall treatment durations and less

Table 3. Molecular recurrence and TFR success by TKI drug category

Drug	Total, n	Recurrence, n (%)	TFR Success, n (%)
Nilotinib	16	0 (0.0)	16 (100.0)
Imatinib	21	5 (23.8)	16 (76.2)
Flumatinib	11	4 (36.4)	7 (63.6)
Dasatinib	1	1 (100.0)	0 (0.0)

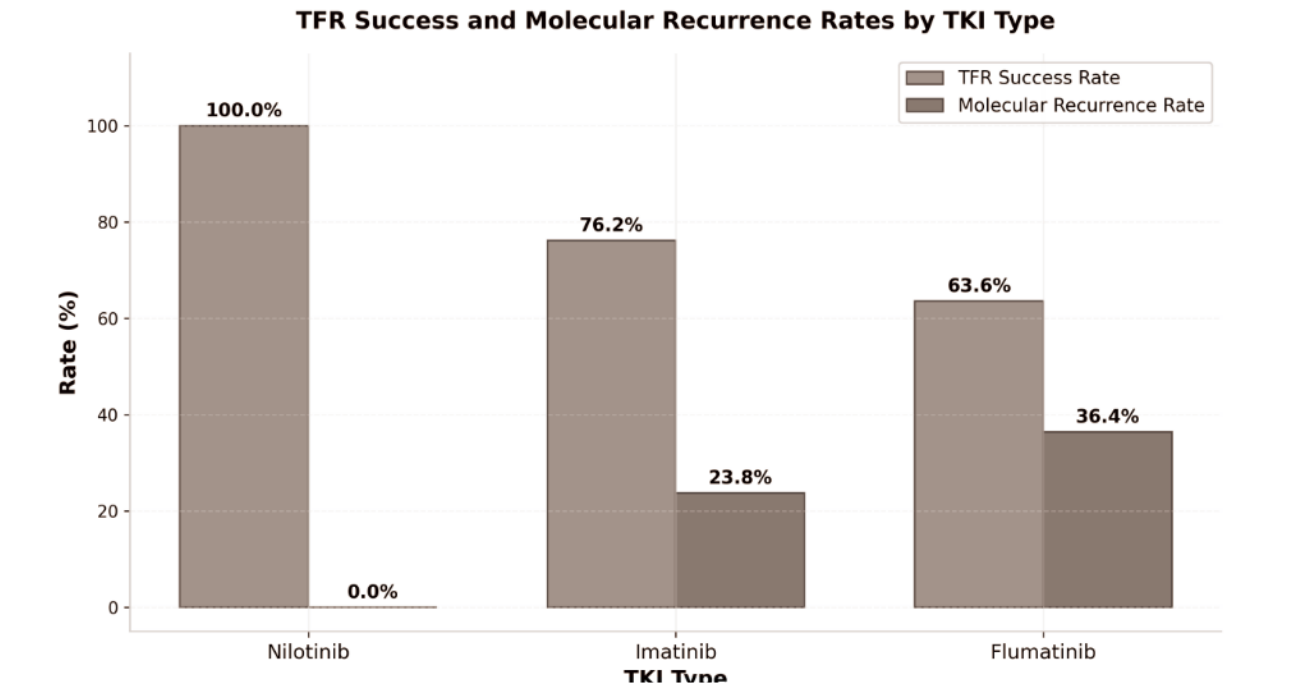

Figure 2. Treatment-free remission (TFR) success and molecular recurrence rates by TKI drug category. Nilotinib-treated patients demonstrated a 100% TFR success rate, while flumatinib-treated patients exhibited the highest recurrence rate among multi-patient drug categories.

established deep molecular response at the time of discontinuation. Alternatively, differences in the pharmacokinetic profile and stem cell penetration of flumatinib compared with nilotinib may underlie this disparity, although comparative data remain limited.

3.3.3 Age and Gender

Neither age nor gender demonstrated a statistically significant association with molecular recurrence. The mean age of recurrent patients (55.6 ± 19.3 years) was numerically lower than that of non-recurrent patients (60.1 ± 13.4 years), but the wide standard deviations and small sample size preclude definitive conclusions. Recurrence rates were comparable between females (18.5%, 5 of 27) and males (22.7%, 5 of 22), consistent with the literature where these variables have not been identified as independent predictors of TFR success [15, 36].

3.4 Recurrence Case Details

Ten patients experienced molecular recurrence after TKI discontinuation. Among the five imatinib relapses, time to recurrence was 1, 3, 8, 12, and 12 months (median 8.0 months), with a mean prior treatment duration of 61.4 months (range 33.0–89.0 months). Four patients relapsed after flumatinib cessation at 3.5, 6, 6, and 6 months (median 6.0 months), following a mean treatment duration of 52.3 months (range 20.0-70.9 months). The single dasatinib case demonstrated an IS level of 11% at 28 months after discontinuation; this patient had self-discontinued dasatinib after only 22.0 months of treatment, substantially shorter than the recommended minimum for TFR attempts [37].

Notably, 8 of 10 recurrences (80.0%) occurred within the first 6 months, and all 10 were detected within the first 12 months except for the single dasatinib case. This temporal pattern is consistent with the established bimodal model of molecular recurrence, wherein early relapses reflect reactivation of persistent leukemic stem cells and late relapses are exceedingly rare [5,18]. All 10 patients restarted TKI therapy promptly and regained major molecular response (MMR; BCR-ABL1 IS ≤0.1%), with no progression to advanced-phase disease or treatment-resistant relapse. This confirms that molecular recurrence after TKI discontinuation is typically reversible with prompt retreatment, su pporting the safety of TFR attempts in appropriately selected patients.

4. Discussion

4.1 Principal Findings

The present study reports a treatment-free remission (TFR) success rate of 79.6% in a real-world cohort of 49 chronic myeloid leukemia (CML) patients, a figure exceeding those reported in most prospective TFR trials [38]. This discrepancy likely reflects several factors. First, the retrospective design introduces selection bias toward patients already perceived as favorable candidates for discontinuation, effectively enriching the cohort with lower-risk individuals [39]. Second, the median TKI treatment duration in this cohort (89.0 months) surpassed the minima recommended by current guidelines and exceeded the median durations reported in several landmark trials [32]. Third, stringent molecular monitoring practices may have facilitated identification of patients with sustained deep molecular response (DMR), further enhancing the pre-test probability of TFR success [18, 36]. This elevated rate should be interpreted within the context of these selection pressures rather than as evidence of superior center-specific outcomes.

As shown in Table 4, the TFR rate in the present study compares favorably with those reported in major prospective trials, though direct comparisons must be made

cautiously given differences in study design, patient selection, and definitions of molecular recurrence.

The STIM1 trial, which established the proof-of-concept for TFR, reported a 6-month TFR rate of 38% among imatinib-treated patients with sustained complete molecular response exceeding 2 years. The substantially higher rate in our cohort likely reflects the inclusion of patients treated with second-generation TKIs (2G-TKIs) and the longer median treatment duration. The EURO-SKI trial, the largest prospective TFR study encompassing 755 patients, reported a 3-year TFR rate of 46%, with the final analysis confirming three independent predictors of TFR success: duration of TKI therapy, duration of DMR, and BCR::ABL1 transcript type [15, 21, 28]. Our findings are consistent with these prognostic determinants, as the non-recurrent subgroup demonstrated a mean treatment duration of 110.8 months, substantially exceeding the threshold associated with optimal outcomes in EURO-SKI. Notably, a recent prospective study from low- and middle-income countries reported a 2-year TFR rate of 79% using conservative discontinuation criteria, suggesting that stringent patient selection can yield comparable outcomes across diverse healthcare settings [10].

4.2 Treatment Duration as a Key Prognostic Factor

The most salient finding of this study is the pronounced difference in TKI treatment duration between patients who maintained TFR and those who experienced molecular recurrence. The non-recurrent group had a mean treatment duration of 110.8 ± 53.8 months, approximately double that of the recurrent group (53.8 ± 24.2 months). This finding aligns with the central premise that cumulative TKI exposure correlates with progressive depletion of the leukemic stem cell (LSC) reservoir, thereby reducing the probability of post-discontinuation relapse. The observation that the range of treatment duration in the recurrent group (20.0–89.0 months) fell entirely below the median of the non-recurrent group (108.0 months) further underscores the discriminative capacity of this parameter.

The EURO-SKI final analysis identified TKI treatment duration as an independent predictor of TFR success, with each additional year of therapy conferring a measurable reduction in relapse risk [40]. Similarly, the D-FREE study demonstrated that insufficient TKI treatment duration was associated with increased molecular recurrence after dasatinib discontinuation [27]. Nicolini and colleagues

Table 4. Comparison of TFR rates across major clinical trials and the present study

Study	Population	TKI	TFR Rate	Design
STIM1 [5]	100 patients	Imatinib	38% at 6 months	Prospective
EURO-SKI [3]	755 patients	Various	46% at 3 years	Prospective
ENESTfreedom [13]	190 patients	Nilotinib (1L)	44% at 5 years	Prospective
ENESTop [14]	163 patients	Nilotinib (2L)	48% at 5 years	Prospective
DASFREE [24]	84 patients	Dasatinib	46% at 2 years	Prospective
NEJM 2026 [25]	LMIC cohort	Various	79% at 2 years	Prospective
Present study	49 patients	Various	79.6%	Retrospective

further emphasized that both TKI duration and the depth of residual disease at discontinuation are critical determinants of TFR outcomes. Kim and colleagues reported that imatinib treatment exceeding 10 years was associated with the highest probability of sustained TFR, suggesting a dose-response relationship between cumulative TKI exposure and LSC eradication [34]. In our cohort, the mean treatment duration of 110.8 months in the non-recurrent group approaches this threshold, reinforcing the hypothesis that prolonged therapy is necessary to achieve the depth of LSC suppression required for durable TFR.

These findings carry direct implications for clinical practice. Physicians should exercise caution when evaluating patients with fewer than 5 years of TKI therapy for discontinuation, even if DMR has been maintained[25, 32]. Extending treatment beyond guideline minimums-targeting 8-10 years-may substantially improve TFR success rates, consistent with the EURO-SKI observation that the probability of sustained remission continues to increase with each additional year of therapy [15]. Treatment duration should be weighed alongside DMR duration and BCR::ABL1 transcript type when constructing individualized discontinuation risk assessments [30].

4.3 TFR Outcomes by TKI Type

4.3.1 Nilotinib

Nilotinib-treated patients achieved a 100% TFR success rate with no instances of molecular recurrence (0 of 16). This outcome is consistent with data from the ENESTfreedom and ENESTop trials, which reported 5-year TFR rates of 44% and 48%, respectively [41]. The nilotinib subgroup was characterized by the longest mean treatment duration among all drug categories (121.4 ± 58.2 months), which likely contributed to the absence of recurrences. Second-generation TKIs achieve deeper and more rapid molecular responses than imatinib, potentially translating to more effective suppression of the LSC compartment [27].

4.3.2 Imatinib

The TFR success rate among imatinib-treated patients was 76.2% (16 of 21), with a recurrence rate of 23.8%. This exceeds the 38% 6-month TFR rate reported in STIM1 and pooled estimates from meta-analyses. The favorable outcome may be attributable to the extended mean treatment duration of 93.2 ± 50.6 months, approaching the >10-year threshold identified as optimal for imatinib-based TFR.

4.3.3 Flumatinib

The most concerning finding is the 36.4% molecular recurrence rate among flumatinib-treated patients (4 of 11), yielding a TFR success rate of only 63.6%-the highest recurrence rate among any multi-patient drug category. Several factors may contribute. First, the flumatinib subgroup had the shortest mean treatment duration (64.5 ± 27.3 months) among the three major drug categories. Since treatment duration is the strongest predictor of TFR success [18, 36], the abbreviated exposure likely accounts for a substantial portion of the observed recurrences. Second, flumatinib is a relatively novel 2G-TKI developed in China, and published data on its capacity to achieve and sustain DMR are less extensive than those for nilotinib or dasatinib [18]. Lei and colleagues reported that flumatinib was associated with a lower DMR achievement rate compared with nilotinib as first-line therapy, raising the possibility that patients achieving DMR on flumatinib may represent a more heterogeneous population [35]. Third, differences in pharmacokinetic properties—including stem cell penetration and plasma half-life-may influence the durability of remission after

flumatinib cessation, although comparative data remain limited. Fourth, the small sample size (n=11) renders the recurrence rate susceptible to sampling variability (95% confidence interval: 10.9%-61.4%).

4.3.4 Need for Larger Studies on Flumatinib TFR

Given the increasing utilization of flumatinib as first-line therapy for CML in China, the paucity of TFR data for this agent represents a significant gap [35]. Our study provides one of the first dedicated analyses of TFR outcomes after flumatinib discontinuation, but the small sample size and retrospective design preclude definitive conclusions. Prospective multicenter studies with standardized discontinuation criteria are urgently needed. Until such data become available, a cautious approach to discontinuation is warranted, with attention to ensuring adequate treatment duration (preferably >8 years) and sustained DMR (>3 years).

4.4 Limitations

This study is limited by its retrospective design, which introduces selection bias in the identification of patients who discontinued TKI therapy; the decision was made at physician discretion without standardized criteria, likely enriching the cohort with favorable-prognosis individuals. The total cohort of 49 patients limits statistical power, particularly for the dasatinib (n=1) and flumatinib (n=11) subgroups. The single-center design restricts generalizability to other clinical settings with different monitoring practices and patient demographics. Additionally, the absence of prospectively defined discontinuation criteria introduced heterogeneity in baseline TFR readiness; variables such as DMR duration, BCR::ABL1 transcript type, and additional chromosomal abnormalities were not systematically recorded, precluding multivariate analysis.

4.5 Clinical Implications

This study demonstrates that TFR is achievable in a substantial proportion of carefully selected real-world CML patients. The observation that all 10 patients who experienced molecular recurrence promptly regained major molecular response upon TKI reinitiation confirms the reversibility of post-discontinuation relapse and supports the safety of TFR attempts in appropriately monitored patients.

The data strongly support extending TKI therapy beyond guideline minimums prior to attempting discontinuation. The marked difference in treatment duration between recurrent and non-recurrent patients (53.8 vs. 110.8 months) suggests that a threshold of at least 8–10 years of cumulative TKI exposure may optimize TFR probability, consistent with emerging evidence from EURO-SKI [15]. Clinicians should counsel patients that additional years of therapy may substantially improve the likelihood of successful treatment-free remission.

The elevated recurrence rate among flumatinib-treated patients warrants a cautious approach to discontinuation in this population. Physicians should ensure stringent criteria—prolonged treatment duration (>8 years), sustained DMR (>3 years)—are met before considering TFR attempts. Enhanced post-discontinuation monitoring, including monthly qPCR for the first 6 months, is advisable given that 80% of recurrences occurred within this window. Ultimately, prospective studies with larger flumatinib-treated cohorts are needed to establish definitive discontinuation criteria for this increasingly utilized agent.

5. Conclusion

This retrospective analysis of 49 chronic myeloid leukemia (CML) patients demonstrates that treatment-free remission (TFR) is achievable in 79.6% (39 of 49) of carefully selected patients under real-world conditions. Importantly, all 10 patients who experienced molecular recurrence regained major molecular response upon tyrosine kinase inhibitor (TKI) reinitiation with no disease progression, confirming the safety of discontinuation attempts in appropriately monitored individuals.

TKI treatment duration prior to discontinuation was the most discriminative factor for TFR success. Patients maintaining sustained TFR had a mean treatment duration of 110.8 ± 53.8 months, approximately twice that of the recurrent group (53.8 ± 24.2 months), with the recurrent group's entire duration range (20.0-89.0 months) falling below the non-recurrent group's median (108.0 months). These findings reinforce guideline recommendations to prioritize treatment duration alongside deep molecular response duration when evaluating patients for discontinuation [24].

This study provides one of the first real-world reports of TFR outcomes following flumatinib discontinuation. Among 11 flumatinib-treated patients, the TFR success rate was 63.6% (7 of 11), with a 36.4% recurrence rate-the highest among multi-patient drug categories. By contrast, nilotinib-treated patients achieved 100% TFR success (16 of 16), consistent with the ENESTfreedom and ENESTop trials [22, 42]. The lower TFR success rate with flumatinib warrants cautious interpretation and suggests clinicians should exercise particular care when considering flumatinib discontinuation.

Future research should focus on prospective multicenter studies with standardized discontinuation criteria and uniform molecular monitoring protocols to validate the flumatinib TFR findings. Complementary biomarkers-including digital PCR, next-generation sequencing of BCR::ABL1 transcripts, and leukemic stem cell assays-should be explored to refine patient selection beyond treatment-history variables and enable individualized discontinuation risk assessment. Extended observation periods are essential to characterize the long-term durability of TFR, assess the incidence of late recurrences, and evaluate the potential for second TFR attempts following successful retreatment.

References

1. Jabbour, E. and H. Kantarjian, Chronic Myeloid Leukemia: A Review. JAMA, 2025. 333(18): p. 1618-1629.

2. Soverini, S., et al., Chronic myeloid leukemia: the paradigm of targeting oncogenic tyrosine kinase signaling and counteracting resistance for successful cancer therapy. Mol Cancer, 2018. 17(1): p. 49.

3. Jabbour, E. and H. Kantarjian, Chronic myeloid leukemia: 2025 update on diagnosis, therapy, and monitoring. Am J Hematol, 2024. 99(11): p. 2191-2212.

4. Senapati, J., et al., Management of chronic myeloid leukemia in 2023 - common ground and common sense. Blood Cancer J, 2023. 13(1): p. 58.

5. Kantarjian, H., et al., Management of chronic myeloid leukemia in 2025. Cancer, 2025. 131(14): p. e35953.

6. Haddad, F.G., et al., Treatment-free remission in patients with chronic myeloid leukemia following the discontinuation of tyrosine kinase inhibitors. Am J Hematol, 2022. 97(7): p. 856-864.

7. Lustberg, M.B., et al., Mitigating long-term and delayed adverse events associated with cancer treatment: implications for survivorship. Nat Rev Clin Oncol, 2023. 20(8): p. 527-542.

8. Johnson, D.B., et al., Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol, 2022. 19(4): p. 254-267.

9. Hughes, T.P., A.S. Yong, and D.M. Ross, The Evolution of Treatment-Free Remission. Blood, 2025.

10. Apperley, J.F., et al., 2025 European

LeukemiaNet recommendations for the management of chronic myeloid leukemia. Leukemia, 2025. 39(8): p. 1797-1813.

11. Hochhaus, A., et al., From fatal disease to functional cure: 25 years of tyrosine kinase inhibition in chronic myeloid leukemia. Leukemia, 2026. 40(6): p. 1092-1110.

12. Etienne, G., et al., Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia. J Clin Oncol, 2017. 35(3): p. 298-305.

13. Mahon, F.X., et al., Extended long-term follow-up and the survival of Stop Imatinib study. Blood Neoplasia, 2026. 3(1): p. 100177.

14. Hughes, T.P. and D.M. Ross, Moving treatment-free remission into mainstream clinical practice in CML. Blood, 2016. 128(1): p. 17-23.

15. Mahon, F.X., et al., European Stop Tyrosine Kinase Inhibitor Trial (EURO-SKI) in Chronic Myeloid Leukemia: Final Analysis and Novel Prognostic Factors for Treatment-Free Remission. J Clin Oncol, 2024. 42(16): p. 1875-1880.

16. Jabbour, E. and H. Kantarjian, Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol, 2018. 93(3): p. 442-459.

17. Hughes, T.P., et al., Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. Leukemia, 2021. 35(6): p. 1631-1642.

18. Lagana, A., et al., Treatment free remission (TFR) after second-generation tyrosine kinase inhibitors (2G-TKIs) treatment in chronic myeloid leukemia (CML): from feasibility to safety. Expert Opin Drug Saf, 2024. 23(8): p. 969-979.

19. Ning, L., et al., Trends in disease burden of chronic myeloid leukemia at the global, regional, and national levels: a population-based epidemiologic study. Exp Hematol Oncol, 2020. 9(1): p. 29.

20. Wang, Z., The family life experiences of first-born children in two-child families with large birth. International Journal of Education, 2021. 9: p. 86-97.

21. Punatar, S., et al., Treatment free remission (TFR) in chronic myeloid leukemia-results, compliance and patterns of failure from a tertiary care cancer centre in India. Blood Cancer J, 2025. 15(1): p. 186.

22. Zhang, L., et al., Flumatinib versus Imatinib for Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: A Phase III, Randomized, Open-label, Multi-center FESTnd Study. Clin Cancer Res, 2021. 27(1): p. 70-77.

23. Jiang, L. and M. Yang, Clinical Efficacy and Safety of Flumatinib in Newly Diagnosed Chronic Myelogenous Leukemia. Pharmazie, 2023. 78(1): p. 13-16.

24. Cheng, F., et al., Safety and Efficacy of Flumatinib in Patients with Chronic Phase Chronic Myeloid Leukemia: A Real-Life Cohort Observational Study. Blood Lymphat Cancer, 2026. 16: p. 573070.

25. Ross, D.M. and T.P. Hughes, Treatment-free remission in patients with chronic myeloid leukaemia. Nat Rev Clin Oncol, 2020. 17(8): p. 493-503.

26. Monti, S., et al., Randomized controlled trials and real-world data: differences and similarities to untangle literature data. Rheumatology (Oxford), 2018. 57(57 Suppl 7): p. vii54-vii58.

27. Yoshida, C., et al., Importance of TKI treatment duration in treatment-free remission of chronic myeloid leukemia: results of the D-FREE study. Int J Hematol, 2023. 117(5): p. 694-705.

28. Cattaneo, D., et al., Treatment-free remission as a new goal in the management of chronic myeloid leukemia: Clinical and biological aspects. Hematol Oncol, 2024. 42(5): p. e3309.

29. Ross, D.M., et al., Long-term treatment-free remission of chronic myeloid leukemia with falling levels of residual leukemic cells. Leukemia, 2018. 32(12): p. 2572-2579.

30. Kockerols, C.C.B., et al., Digital PCR for BCR-ABL1 Quantification in CML: Current Applications in Clinical Practice. Hemasphere, 2020. 4(6): p. e496.

31. Rousselot, P., et al., Late molecular recurrences in patients with chronic myeloid leukemia experiencing treatment-free remission. Blood Adv, 2020. 4(13): p. 3034-3040.

32. Takahashi, N., et al., Treatment-Free Remission and Immune Profiling after Frontline Second-Generation TKI Therapy in CML. Blood Adv, 2026.

33. Molica, M., E. Abruzzese, and M. Breccia, Prognostic Significance of Transcript-Type BCR - ABL1 in Chronic Myeloid Leukemia. Mediterr J Hematol Infect Dis, 2020. 12(1): p. e2020062.

34. Nicolini, F.E., et al., Evaluation of Residual Disease and TKI Duration Are Critical Predictive Factors for Molecular Recurrence after Stopping Imatinib First-

line in Chronic Phase CML Patients. Clin Cancer Res, 2019. 25(22): p. 6606-6613.

35. Vener, C., 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): p. 2723-2735.

36. Zheng, Z., et al., Treatment-free remission after discontinuation of tyrosine kinase inhibitors in patients with chronic myeloid leukemia in the chronic phase: a systematic review and meta-analysis. Discov Oncol, 2024. 15(1): p. 586.

37. Mayer, J., Treatment Cessation in Chronic Myeloid Leukemia: Evidence and Uncertainties. Hematol Oncol, 2025. 43(6): p. e70155.

38. Bourne, G., et al., Real-World Evidence of Treatment-Free Remission Strategies and Outcomes in Chronic Myeloid Leukemia. Cancers (Basel), 2025. 17(13).

39. Bifulco, S.F., et al., Predicting arrhythmia recurrence post-ablation in atrial fibrillation using explainable machine learning. Commun Med (Lond), 2025. 5(1): p. 421.

40. Bruzzese, A., et al., Treatment-Free Remission in Chronic Myeloid Leukemia: Revisiting the "W" Questions. Eur J Haematol, 2025. 115(3): p. 218-231.

41. Shah, N.P., et al., Chronic Myeloid Leukemia, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw, 2024. 22(1): p. 43-69.

42. Melkani, G.C., Time-restricted feeding mediated synchronization of circadian rhythms to sustain cardiovascular health. J Mol Cell Cardiol, 2025. 206: p. 1-10.