



# Treatment-free remission after discontinuation of imatinib, dasatinib, and nilotinib in patients with chronic myeloid leukemia

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p-ISSN 2287-979X / e-ISSN 2288-0011  
<https://doi.org/10.5045/br.2023.2023035>  
**Blood Res 2023;58:S58-S65.**

Received on February 6, 2023  
Revised on March 28, 2023  
Accepted on March 28, 2023

\*This study was supported by a grant from Kyung Hee University in 2018 (KHU-20182182).

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## Abstract

Patients with chronic myeloid leukemia (CML) in the chronic phase receiving tyrosine kinase inhibitor (TKI) therapy are expected to have long-term survival outcomes comparable to those of the general population. Many clinical trials have confirmed that some patients sustain molecular responses without continuing TKI therapy. Treatment-free remission (TFR) is a new goal in treating chronic CML. The safety and outcome of TFR were studied in clinical trials after discontinuing imatinib or the second-generation TKIs dasatinib or nilotinib. TFR was safe in approximately 50% of patients who achieved a deep molecular response to TKI therapy. Patients who relapsed after discontinuing TKI responded immediately to the reintroduction of TKI. The mechanism by which TFR increases the success rate still needs to be understood. The hypothesis that the modulation of immune function and targeting of leukemic stem cells could improve the TFR is under investigation. Despite the remaining questions, the TFR has become a routine consideration for clinicians in the practice of molecular remission in patients with CML.

**Key Words** Chronic myeloid leukemia, Dasatinib, Nilotinib, Imatinib, Treatment-free remission, Tyrosine kinase inhibitor

## INTRODUCTION

The incidence of myeloid malignancies, including chronic myeloid leukemia (CML), continues to increase in Korea [1]. The prevalence of CML has also increased because tyrosine kinase inhibitors (TKI) prolong overall survival. The life expectancy of patients with CML treated with TKIs is now similar to that of the general population [2]. Therefore, CML is considered a model disease for successful targeted therapy. Historically, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been a treatment option that offers long-term remission without the need for maintenance therapy, owing to the contribution of the graft-versus-leukemia effect [3]. Interestingly, *BCR::ABL1* transcripts were detected at low levels in some patients with CML after allo-HSCT without other signs of disease recurrence [4, 5].

Molecular response (MR) monitors the transcript levels of *BCR::ABL1*. *BCR::ABL1* ≤ 1% is equivalent to complete cytogenetic remission. We can define deeper responses, such as the major molecular response (MMR). This was defined as a 3-log reduction in the *BCR::ABL1* transcript level. In

addition, *BCR::ABL1* transcript levels ≤ 0.01% and < 0.0032% are defined as molecular responses of a 4-log (MR<sup>4</sup>) and 4.5-log (MR<sup>4.5</sup>), respectively [6]. Imatinib induces a complete cytogenetic response (CCyR) in > 85% of patients with CML [7]. In a CML-IV trial, the 5-year cumulative MR<sup>4</sup> and MR<sup>4.5</sup> reductions were 68% and 53%, respectively [8, 9]. The currently approved TKIs for treating CML are imatinib, dasatinib, nilotinib, radotinib, bosutinib, and ponatinib [10-15]. Table 1 summarizes the clinical outcomes in selected studies after treatment with imatinib, nilotinib, and dasatinib. However, various adverse events have been reported during maintenance therapy with TKIs. A multicenter post-marketing surveillance was conducted in 669 Korean adult patients who received nilotinib as first- and second-line treatment. This study reported that adverse events and adverse drug reactions occurred in 61.3% and 40.5% of patients, respectively [16]. Some patients who were intolerant to TKIs wanted to stop treatment to improve their quality of life by reducing adverse events. Other medical indications for physicians to modify TKIs include fluid retention, pulmonary arterial hypertension, pleural effusion, peripheral arterial occlusive disease, liver toxicities, skin rashes, and QT interval

**Table 1.** Clinical outcomes of TKIs.

Study	Ref.	TKI	Dose (mg)	N	Age at diagnosis	5-year MR <sup>4</sup> (%)	10-year MR <sup>4</sup> (%)	5-year MR <sup>4,5</sup> (%)	10-year MR <sup>4,5</sup> (%)	5-year survival (%)	10-year survival (%)
CML-IV	[8, 9]	Imatinib	400–800	1,536	53 y	68	81	53	72	90	82
IRIS	[6, 10]	Imatinib	400	553	50 y	NA	NA	NA	NA	89	83.3
ENESTnd	[12]	Imatinib	400	283	46 y	42	56	35	45	92	88.3
		Nilotinib	600	282	47 y	66	73	54	64	94	87.6
DASISION	[11]	Imatinib	400	260	49 y	NA	NA	33	NA	90	NA
		Dasatinib	100	259	46 y	NA	NA	42	NA	91	NA

MR<sup>4</sup>, *BCR::ABL1* ≤ 0.01%; MR<sup>4,5</sup>, *BCR::ABL1* ≤ 0.0032%.

Abbreviations: NA, not available; Ref., reference; TKI, tyrosine kinase inhibitor; y, years.

prolongation.

There have been few initial reports on discontinuing TKI treatment in patients with CML. In 2004, imatinib was discontinued in 23 patients treated with CCyR for 10 months (range, 1–22 mo). The study found that patients had a cytogenetic relapse in 53% of cases [17]. However, the French group published a pilot trial of 12 patients with CML who stopped imatinib after 24–46 months of negative *BCR::ABL1* transcripts by real-time quantitative polymerase chain reaction (RTQ-PCR). After a median follow-up of 18 months, 50% of patients remained at an undetectable level of *BCR::ABL1* transcripts for more than 2 years. This pilot study showed that imatinib discontinuation is feasible [18]. There have been many additional clinical trials of TKI discontinuation; a new goal in CML treatment is to achieve treatment-free remission (TFR) for selected patients with a deep molecular response (DMR) [6, 19]. This review summarizes the clinical outcomes of TFR, patient selection, and issues after stopping TKIs based on the results of published studies and current guidelines.

## CLINICAL TRIALS OF IMATINIB DISCONTINUATION

In the Stop Imatinib (STIM) prospective multicenter trial, inclusion criteria were CML in the chronic or accelerated phase, treated with imatinib at any dose for at least 3 years, and sustained complete molecular response (CMR, >5-log reduction in *BCR::ABL1* and *ABL1* levels, and undetectable transcripts on RTQ-PCR) for at least 2 years [20]. One hundred patients from 19 institutions in France were enrolled between 2007 and 2009. The overall probability of CMR at 12 months in the 69 patients with at least 12 months of follow-up was 41%. Forty-two patients experienced molecular relapse primarily within 6 months of stopping imatinib therapy. However, all the patients responded to imatinib treatment.

The final results of the STIM trial were published 6 years after the interim analysis. The median follow-up period after imatinib discontinuation was 77 months (range, 9–95 mo) [21]. Of the 100 patients who discontinued imatinib, 61 lost undetectable minimal residual disease (UMRD) after

a median of 2.5 months (range, 1–22 mo). The molecular recurrence-free survival rates were 43% at 6 months and 38% at 60 months. Treatment was restarted in 57 of the 61 patients, and 55 patients achieved UMRD. The Sokal risk score and imatinib treatment duration were significant factors associated with the probability of molecular recurrence.

Independent studies from the Australasian Leukaemia & Lymphoma Group (ALLG), Japanese, and Korean groups showed comparable results to the STIM trial [22–24]. Forty patients were enrolled in this ALLG study that started in 2006 (TWISTER) [21]. Patients who had UMRD on imatinib for at least 2 years were included. The estimated rate of TFR at 2 years was 47.1%, and most relapses occurred within 4 months of imatinib discontinuation. Unexpectedly, patients in the TFR group had detectable genomic DNA for *BCR::ABL1* several years after stopping imatinib treatment. A total of 90 patients were analyzed for TFR after a median follow-up of 26.6 months after imatinib discontinuation in the KID study [25]. The probability of a sustained MMR at 24 months was 58.5%. In the KID study, 30% of patients developed or had worsening musculoskeletal pain and pruritus after imatinib discontinuation.

Half of the participants in both the STIM and TWISTER trials received interferon. The second STIM trial (STIM2) was conducted in 23 French centers to test imatinib cessation in a homogenous cohort of patients [26]. One hundred twenty-four patients treated only with imatinib were included in the STIM2 prospective trial from 2011 to 2013. Molecular relapse occurred after the discontinuation of imatinib in 48 patients during a median follow-up of 12 months (range, 1–25 mo). Among the 76 imatinib-free patients, 41 experienced fluctuations in *BCR::ABL1* transcript levels without apparent molecular relapse. This fluctuation suggests that *BCR::ABL1* reappearance does not indicate clinical relapse. Therefore, treatment cessation may not require completely eradicating residual leukemic stem cells. The data were updated after a median follow-up of 23.5 months. One patient died from an unrelated cause, and 107 experienced MMR loss. The molecular recurrence-free survival rates were 52% at 6 months and 50% at 24 months [27].

Therefore, the definition of molecular relapse was revised based on the STIM (A-STIM) trial. The inclusion criteria

were the same as those for the STIM trial, except for patients with confirmed CMR. Molecular relapse was defined as the loss of MMR ( $>0.1\%$  BC-ABL). Eighty patients were enrolled between 2006 and 2012. After imatinib discontinuation, the patients were followed up for 31 months (range, 8–92 mo). The cumulative MMR loss was estimated to be 35% at 12 months and 36% at 24 months. The median time to the second CMR was 7.3 months in retreated patients. No adverse events were associated with disease progression [28].

### CLINICAL TRIALS OF SECOND-GENERATION TKI DISCONTINUATION

The DASFREE study assessed TFR after dasatinib discontinuation in 84 patients with CML. Patients received dasatinib as first- or subsequent-line therapy for at least 2 years and had confirmed MR [4, 5] for at least 1 year. TFR at 2 years was 46% in all study patients [29]. In the Japanese D-STOP trial, dasatinib was discontinued in 65 patients who maintained DMR for over 2 years. The estimated overall treatment-free survival was 62.9% at 12 months [30]. Another dasatinib discontinuation trial in Japan (DADI) evaluated the TFR in 63 patients who maintained MR<sup>4.0</sup> for at least 1 year. The estimated overall TFR rate at 36 months was 44.4% after a median follow-up of 44.0 months [31]. A prospective multicenter study in Canada is ongoing to evaluate TFR during 3 phases: imatinib discontinuation, dasatinib rechallenge, and dasatinib discontinuation (TRAD) [32]. The study was started in March 2015, and 118 patients were enrolled in the imatinib discontinuation phase. The relapse-free survival rate at 12 months after imatinib discontinuation was estimated to be

56.8%, with an MR<sup>4</sup> of 0 defined as molecular relapse. The TFR rate, using MMR loss as an event, was 66.6% at 12 months. Seven of 40 patients treated with dasatinib at molecular relapse have attained an MR<sup>4.5</sup> or deeper response over 12 months. These 7 patients underwent a second TKI discontinuation, and 5 remained in the TFR without losing their MR.

The trial assessed the TFR in patients who received consolidation nilotinib for up to 24 months after achieving MR<sup>4.5</sup> with imatinib or nilotinib. The TFR rate was 60.9% at 1 year among the 87 patients who discontinued nilotinib and were followed for 50.1 months (range, 10.9–57.0 mo) [33]. The single-arm, phase 2 ENESTfreedom trial assessed the TFR following front-line nilotinib in 190 chronic phase CML patients who achieved MR<sup>4.5</sup> for over 2 years [34–36]. The 5-year update reported 81 patients (42.6%) who sustained TFR, with 76 patients (40.0%) in MR<sup>4.5</sup> [34]. The ENESTop trial evaluated TFR in patients who achieved MR<sup>4.5</sup> while on nilotinib for at least 2 years. One hundred twenty-six patients were consolidated with nilotinib for 1 year before attempting TFR. The TFR rate at 5 years was 42.9%. The overall number of adverse events decreased from 86.0% in the first 12 months to 49.1% during the last 5 months of TFR. However, patients retreated with nilotinib showed a cumulative increase in cardiovascular events [37].

The STOP 2G TKI study assessed TFR in patients who achieved MR<sup>4.5</sup> for at least 2 years with nilotinib or dasatinib treatment [38]. An interim analysis of 60 patients reported a 43.3% loss of an MMR after a minimum follow-up of 12 months (range, 12–65 mo). In a univariate analysis, an initial suboptimal response or TKI resistance was the baseline factor associated with worse TFR outcomes. The EURO-SKI is the largest prospective trial, with 61 European centers

**Table 2.** TKI discontinuation studies.

Study	TKI	N	Eligibility criteria			Molecular recurrence-free survival
			Depth of MR	Minimum Tx. (y)	Minimum MR (y)	
STIM1 [20, 21]	Imatinib	100	MR <sup>5.0</sup>	3	2	38% at 5 years
STIM2 [26, 27]	Imatinib	200	MR <sup>4.5</sup>	2	2	50% at 2 years
A-STIM [28]	Imatinib	80	MR <sup>5.0</sup>	3	2	64% at 2 years
TWISTER [22]	Imatinib	40	MR <sup>4.5</sup>	3	2	45% at 42 months
KID study [25]	Imatinib	90	MR <sup>4.5</sup>	3	2	58.5% at 2 years
TRAD [32]	Imatinib	108	MR <sup>4.5</sup>	3	2	56.8% at 12 months
DASFREE [29]	Dasatinib	84	MR <sup>4.5</sup>	2	1	46% at 2 years
D-STOP [30]	Dasatinib	54	MR <sup>4.0</sup>	2	2	62.9% at 12 months
DADI [31]	Dasatinib	63	MR <sup>4.0</sup>	1	1	49% at 6 months
NILST [33]	Nilotinib	90	MR <sup>4.5</sup>	2	2	58.9% at 1 year
ENESTfreedom [34–37]	Nilotinib	190	MR <sup>4.5</sup>	2	2	48.2% at 5 years
ENESTop [38]	Nilotinib	126	MR <sup>4.5</sup>	3	1	42.9% at 5 years
STOP 2G-TKI [39]	Dasatinib/nilotinib	60	MR <sup>4.5</sup>	3	2	53.6% at 4 years
EURO-SKI [40]	Any TKI	755	MR <sup>4.0</sup>	3	1	49% at 2 years
Summary		2,040	$\geq$ MR <sup>4.0</sup>	1–3	1–2	38–64%

MR<sup>4</sup>, BCR::ABL1 $\leq 0.01\%$ ; MR<sup>4.5</sup>, BCR::ABL1 $\leq 0.0032\%$ ; MR<sup>5.0</sup>, BCR::ABL1 $\leq 0.001\%$ .

Abbreviations: INF- $\alpha$ , interferon- $\alpha$ ; MR, molecular response; TKI, tyrosine kinase inhibitor; Tx., treatment; y, year(s).

in 11 countries [39]. Patients were eligible if they had a confirmed DMR for at least 1 year with any TKIs. After a median follow-up period of 27 months, 755 patients were evaluated for molecular responses. The molecular relapse-free survival rates of these patients were 61% at 6 months and 50% at 24 months, respectively. Prolonged treatment and DMR duration predicted a better probability of MMR maintenance at 6 months in 405 patients who received imatinib as the first-line treatment.

### CURRENT GUIDELINES

We can safely stop TKI treatment in some patients with chronic phase CML if we achieve sustained DMR with an adequate duration of TKIs. The clinical studies tried discontinuing TKIs after 1 or 2 years of DMR ( $\geq \text{MR}^{4.0}$ ), and the estimated TFR rate was 38–64% (Table 2). The recently published European LeukemiaNet (ELN) 2020 recommendations and the National Comprehensive Cancer Network (NCCN) [40] describe the guidelines for TFR eligibility in clinical practice. They suggest stopping TKI in patients who have sustained DMR for 2 years (Table 3) [6]. However, the ELN recommends TKI treatment for more than 5 years, and DMR duration  $>3$  years if  $\text{MR}^{4.0}$  or  $>2$  years if  $\text{MR}^{4.5}$ . Both guidelines agree with the mandatory condition that patients in the chronic phase without a prior history of accelerated or blast phase CML are motivated to stop TKIs. In addition, patients require close monitoring after TKI discontinuation using the *BCR::ABL1* test with high-quality and rapid turnaround time quantitative PCR. The feasibility of TFR following the discontinuation of TKIs has been evaluated in clinical studies, chiefly with dasatinib, imatinib, or nilotinib. According to the EURO-SKI study,

NCCN assumes that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained DMR [40].

### PREDICTIVE FACTORS ASSOCIATED WITH TFR

Several characteristics that could predict success have been analyzed in clinical trials (Table 4). Age at discontinuation was a patient-related factor. The DASFREE trial reported that age over 65 years was a prognostic factor for a 2-year TFR [29]. In addition, an inverse relationship between age and risk of relapse was reported in the Imatinib Suspension and Validation (ISAV) multinational trial (95% of patients  $<45$  yr relapsed versus 42% in the class  $\geq 45$  to  $<65$  yr and 33% of patients  $\geq 65$  yr) [41]. The Sokal risk score reflects the overall survival according to age, spleen size, platelet count, and blast count at the diagnosis. The STIM trial showed that the Sokal risk score was significantly associated with the molecular recurrence of the disease by 6 months after imatinib discontinuation [21]. The Sokal risk score identified molecular relapse in another study by Yhim *et al.* [42]. In contrast, Takahashi *et al.* [23] analyzed 43 patients and found that the Sokal risk score was not a significant factor in predicting a molecular recurrence by 12 months. A high Sokal risk score could suggest a high burden and aggressive feature of the disease at diagnosis. The relationships between age, Sokal risk scoring, and TFR showed discrepancies between studies. However, the number of patients included in these studies was too small to draw definitive conclusions.

In the STIM trial, a longer duration of imatinib treatment was identified as an independent factor for molecular recurrence after imatinib cessation [21]. The depth of response

**Table 3.** Criteria for TKI discontinuation in guidelines with modifications.

Criteria	European LeukemiaNet 2020	NCCN V1. 2023
I. Mandatory		
Disease status	Chronic phase only	Same
Patient communication	Motivated patient	Same
<i>BCR::ABL1</i> test	High-quality quantitative PCR using the international scale with a rapid turnaround of test results	Same
Monitoring	Monthly for the first 6 months, every 2 months for 7–12, and every 3 months thereafter	Same
II. Stop allowed		
Line of therapy	First-line, second-line if intolerance was the reason for the change	NS
Type of transcript	Typical e13a2 or e14a2	Quantifiable
Duration of TKI	$>5$ years ( $>4$ yr for 2G TKI)	$>3$ years
Duration of DMR	$>2$ years	Same
III. Stop recommended for consideration		
Duration of TKI	$>5$ years	$>6$ years
Duration of DMR	$>3$ years if $\text{MR}^4$ $>2$ years if $\text{MR}^{4.5}$	same NS

$\text{MR}^4$ , *BCR::ABL1*  $\leq 0.01\%$ ;  $\text{MR}^{4.5}$ , *BCR::ABL1*  $\leq 0.0032\%$ .

Abbreviations: 2G TKI, second-generation tyrosine kinase inhibitors; DMR, deep molecular response; NCCN, National Comprehensive Cancer Network; NS, not specified.

**Table 4.** Predictive factors associated with treatment-free remission in multivariate analysis.

Study	N	Factors related to TFR rate	Hazard ratio	P
STIM1 [21]	88 vs. 11	Sokal risk score (low+intermediate vs. high)	2.22	0.024
	100	Imatinib duration (<58.8 mo vs. ≥58.8 mo)	0.540	0.024
DASFREE [29]	64 vs. 20	Age (<65 yr vs. ≥65 yr)	0.044	0.0012
	42 vs. 42	Dasatinib duration (<median vs. ≥median)	7.761	0.0051
	37 vs. 47	Prior therapy line (1 <sup>st</sup> vs. 2 <sup>nd</sup> +3 <sup>rd</sup> )	8.804	0.0138
ENESTop [39]	126	Time since 1 <sup>st</sup> MR <sup>4,5</sup> until TFR entry for every month increase	1.033	0.032
EURO-SKI [40]	405	MR <sup>4</sup> duration while under TKI	1.18	0.0007
	405	Duration of TKI treatment before MR <sup>4</sup>	1.12	0.08

MR<sup>4</sup>, BCR::ABL1≤0.01%; MR<sup>4,5</sup>, BCR::ABL1≤0.0032%.

Abbreviations: MR, molecular response; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

before TKI discontinuation and the duration of DMR were also predictive factors for TFR. In the analysis of 405 patients who received imatinib as a first-line treatment as a learning sample, more prolonged treatment and DMR duration were associated with an increased probability of maintaining MMR at 6 months in the EURO-SKI trial [39]. TFR was also significantly associated with the treatment duration of dasatinib in multivariate analysis from the DASFREE trial [29]. In contrast, longer treatment duration was not related to better TFR in other TKI discontinuation studies using second-generation TKIs in the first line, such as the ENESTfreedom and first-line DADI trials [34, 43]. These results suggest that the effect of treatment duration on TFR is different between imatinib and second-generation TKIs. Takahashi *et al.* [23] showed that the estimated relapse-free survival rates at 5 years were 78% and 15% among patients who did and did not sustain a CMR for >24 months before therapy cessation, respectively ( $P=0.0002$ ). Michor *et al.* [44] described the dynamics of MR to imatinib in CML patients as a model of the biphasic exponential decline of leukemic cells. Interestingly, the mathematical models based on the biphasic decline of leukemic cells prognosticated that 31% of the patients would remain in DMR (MR<sup>5.0</sup>) after treatment cessation after a fixed period of 2 years [45].

The number of immune cells changes with TKI treatment [46]. In addition, a high number of subsets of T cells and natural killer (NK) cells affect the maintenance of the TFR [47, 48]. A total of 132 consecutive patients with the chronic phase who participated in the clinical EURO-SKI trial were recruited to analyze the function and phenotype of T and NK cells and their relation to successful TKI cessation. The NK cell phenotype was mature in non-relapse patients, whereas patients with more naïve CD56bright NK cells had decreased relapse-free survival [47]. The DADI trial showed that high NK cells and low  $\gamma\delta$ + T-cell and CD4+ regulatory T-cell counts before discontinuation correlated significantly with successful therapy discontinuation [31, 48]. Therefore, immunity is one of the essential factors for a durable TFR. However, the mechanism is not entirely understood. Recently, a hypothesis that ropeginterferone-induced Th1 immunity might improve TFR outcomes was tested in a multicenter,

international phase III trial [49]. Patients with MR<sup>4.0</sup> or better for at least 12 months and at least 3 years of TKI exposure were enrolled. A total of 203 evaluable patients received ropeginterferon (N=95) or no treatment (N=108) after TKI discontinuation. After a median observation of 36 months, the hazard ratio of molecular relapse for the ropeginterferone cohort versus the no-treatment cohort was 1.03 (95% CI, 0.68–0.155; log-rank  $P=0.89$ ). In this trial, ropeginterferon did not increase TFR outcomes. Currently, the German CML-V trial (TIGER study, NCT01657604) has explored interferon treatment in combination with TKI before TKI discontinuation.

## SECOND TREATMENT-FREE REMISSION

Patients whose first TFR attempt failed resumed treatment with the same TKI at the same dose. Fortunately, a significant proportion of patients (88–96.5%) regained DMR after re-treatment [21, 34, 48]. RE-STIM is a multicenter French study that evaluated the second TFR in 70 patients whose first attempt failed. The median time from TKI resumption to second discontinuation was 32 months, and the median duration of the second DMR was 25 months. After a median follow-up of 38.3 months, 64.3% of patients lost an MMR; TFR rates at 12, 24, and 36 months were 48%, 42%, and 35%, respectively [50]. From the single-center Japanese study, Ureshino *et al.* [51] reported retrospective data of the first, second, and third attempts to stop TKIs. At the first TFR attempt, 28 of 53 patients (53.4%) achieved TFR. The remaining 25 patients subsequently attempted a second TFR procedure. Four of the 10 patients (37.5%) had a second TFR at 1-year follow-up. The median time to the second molecular relapse (loss of DMR) was 3.2 months [51]. The data from the second TFR is still small and not recommended in the current guidelines. These studies showed that a second TFR was possible; however, the relapse pattern differed from that of the first TFR. Interestingly, a mathematical model of the patient-specific dynamics of molecular responses predicted the possibility of relapse during the second TFR. In this model, the high-risk group relapsed at a median of 3.25



months compared with 28.2 months in the low-risk group [52].

## CONCLUSION

Currently, TKI discontinuation is safe for select patients with sustained DMR. However, the TFR attempt was successful in approximately 50% of patients. The underlying mechanism explaining why some patients retain TFR while others relapse remains unclear. Immune activities have been speculated to suppress the growth of leukemic clones and stem cells. The approach of mathematical modeling of the kinetics of molecular clones in the STIM trial has led to the possibility that imatinib may increase the frequency of leukemic stem cell clones. Further trials modulating immunity or targeting leukemic stem cells are required to increase the number of patients available for TFR attempts and the success rate of TFR. Despite the remaining questions, TFR attempts have become a real-world practice.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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