Treatment Free Remission (TFR) in Chronic Phase-Chronic Myeloid Leukemia (CP-CML): Analysis of Predictive Factors and Novel Scoring Systems For Molecular Recurrence

A. LAGANA'[1], E. SCALZULLI[1], I. CARMOSINO[1], M.L. BISEGNA[1], C. IELO[1], D. DIVERIO[1], M. MARTELLI[1] and M. BRECCIA[1]

1. Hematology, Department of Translational and Precision Medicine, Policlinico Umberto I-Sapienza University, Rome, Italy

Background

Treatment free remission (TFR) is a key treatment goal in **chronic-phase chronic myeloid leukemia (CP-CML)** patients with sustained deep molecular response (DMR). While clinical trials report that approximately 40%–50% of such patients can discontinue tyrosine kinase inhibitors (TKIs) without presenting a **molecular relapse (MRec)**, real-world data remain limited. Optimizing patient selection prior to TKI discontinuation and enabling early identification of patients at high risk of MRec is crucial for effective CML management and resource allocation.

Objectives

The primary objective of this study was to evaluate the **success rate and duration of TFR** following TKI discontinuation. Additionally, we aimed to identify **clinical and molecular factors predictive of MRec** in a real-world setting.

Secondary objectives included:

- Characterizing the **timing of MRec**
- Assessing the overall **feasibility** of TFR
- Developing a practical, point-based **baseline prognostic score** to support patient selection prior to TKI discontinuation
- Exploring the **utility of early molecular monitoring** to enhance risk stratification for MRec.

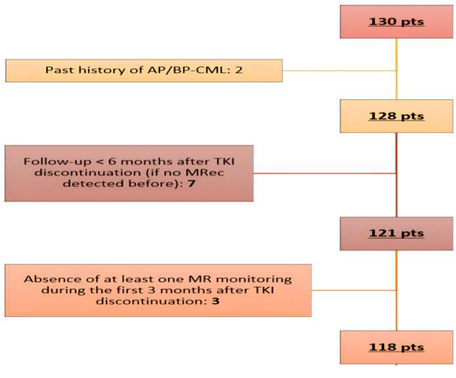
Methods

We conducted a single-center, retrospective observational study on adult CP-CML patients who discontinued TKI for any reason.

Eligibility criteria include all the following:

- **Prior treatment** with one or more TKIs (either as first-line or subsequent-line) for an overall duration **≥ 3 years**
- **Interruption** of TKI treatment for any reason lasting **≥ 1 month**
- **Serial monitoring** of BCR:ABL1 levels during TFR
- Molecular response (MR) at the time of discontinuation **at least MR4.0** (BCR::ABL1 transcript level ≤ 0.01%) on International Scale (IS)

Exclusion criteria and patient disposition flowchart:



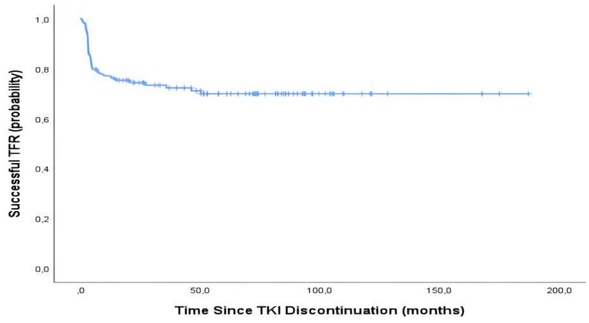
Molecular monitoring was performed by **RT-qPCR** for BCR::ABL1 following the schedule indicated by international guidelines.

MRec was defined as **loss of MR3.0** (BCR::ABL1 ≥ 0.1%^{IS}) and **unstable DMR** was defined as at least one episode of **confirmed DMR loss** (in ≥2 consecutive tests at least one month apart) prior to achieving a final stable DMR.

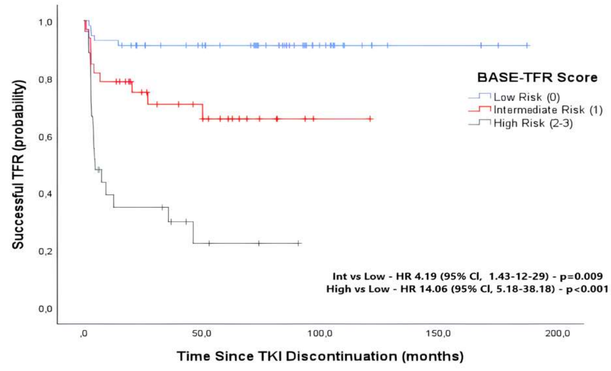
MRec-free survival was defined as the time from TKI stop to MRec or last follow-up.

Results

Among the **118 CP-CML patients**, 60.2% were on imatinib and 39.8% on second-generation TKIs at the time of treatment interruption. Reasons for TKI discontinuation were: shared decision (78%), toxicity (20.3%) and patient own choice (1.7%). The median **TKI therapy duration** was **10.6 years**, while the median **stable DMR duration** prior to discontinuation was **6.1 years**. After a *median follow-up of 72.5 months*, 34 patients (**28.8%**) experienced **MRec**, with most relapses (70.6%) occurring within the first 6 months. The estimated **MRec-free survival rate** was 79.7% at 6 months and **69.9%** at last follow-up.



Multivariate analysis identified three independent baseline factors significantly associated with shorter TFR duration: a **high Sokal risk score** at diagnosis (HR 2.93, p=0.018), a **stable DMR duration < 5 years** (HR 3.63, p=0.002), and a history of **unstable DMR** (HR 2.47, p=0.019). Based on these variables, we developed the **BASE-TFR score**, a simple 3-point system that stratifies patients according to their baseline risk of MRec. The score demonstrated an **AUC of 0.806** for its association with MRec (p<0.001).

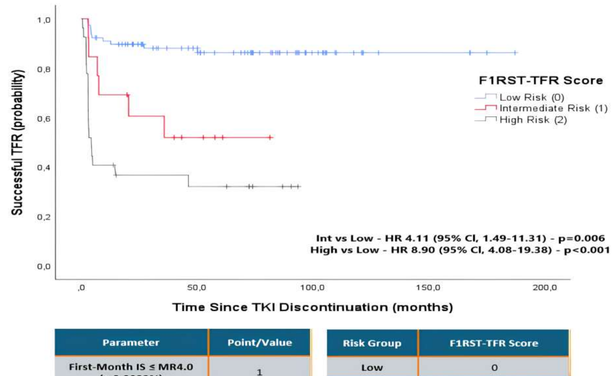


Parameter	Point/Value
Sokal Score – High Risk	1
Stable DMR < 5 years	1
Prior Unstable DMR	1

Risk Group	BASE-TFR Score
Low	0
Intermediate	1
High	≥ 2

BASE-TFR - Baseline Assessment for Successful Ending of Treatment-Free Remission

Univariate analysis showed that MR assessment one-month post-discontinuation provided two parameters associated with a shorter TFR period: a **one-month MR > 0.0032%^{IS}** (HR 5.82, p<0.001) and a **difference ≥ 0.0017%** between the last available response before discontinuation and first-month MR (HR 9.66, p<0.001). A score called **F1RST-TFR** was developed by assigning one point for each of these parameters, which showed an **AUC of 0.759** for its association with MRec (p<0.001).



Parameter	Point/Value
First-Month IS ≤ MR4.0 (> 0.0032%)	1
First-Month MR Difference ≥ 0.0017%	1

Risk Group	F1RST-TFR Score
Low	0
Intermediate	1
High	2

F1RST-TFR = First-Month ResponSe Threshold for successful Treatment-Free Remission

Conclusions

TFR is a **feasible objective** in real-world clinical practice when patients are carefully selected and adequately monitored. The **BASE-TFR** and **F1RST-TFR** scores offer practical tools to stratify relapse risk both at baseline, allowing a better patient selection, and during early follow-up, potentially guiding clinical decisions about TFR. While our results are promising, prospective validation in larger, independent cohorts is essential before these scores can be implemented in routine practice.

Correspondence: Massimo Breccia - breccia@bce.uniroma1.it
First Author: Alessandro Laganà - lagana@bce.uniroma1.it

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