

RESEARCH ARTICLE

Risk of progression in chronic phase-chronic myeloid leukemia patients eligible for tyrosine kinase inhibitor discontinuation: Final analysis of the TFR-PRO study

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Abstract

Disease progression to accelerated/blast phase (AP/BP) in patients with chronic phase chronic myeloid leukemia (CP-CML) after treatment discontinuation (TD) has never been systematically reported in clinical trials. However, recent reports of several such cases has raised concern. To estimate the risk of AP/BP among TD-eligible patients, we conducted TFR-PRO, a cohort retro-prospective study: 870 CP-CML patients eligible for TD formed a discontinuation cohort (505 patients) and a reference one (365 patients). The primary objective was the time adjusted rate (TAR) of progression in relation to TD. Secondary endpoints included the TAR of molecular relapse, that is, loss of major molecular response (MMR). With a median follow up of 5.5 years and 5188.2 person-years available, no events occurred in the TD cohort. One event of progression was registered 55 months after the end of TD, when the patient was contributing to the reference cohort. The TAR of progression was 0.019/100 person-years (95% CI [0.003–0.138]) in the overall group; 0.0 (95% CI [0–0.163]) in the discontinuation cohort; and 0.030 (95% CI [0.004–0.215]) in the reference cohort. These differences are not statistically significant. Molecular relapses occurred in 172/505 (34.1%) patients after TD, and in 64/365 (17.5%) patients in the reference cohort, $p < .0001$. Similar rates were observed in TD patients in first, second or third line of treatment. CML progression in patients eligible for TD is rare and not related to TD. Fears about the risk of disease progression among patients attempting TD should be dissipated.

1 | INTRODUCTION

Chronic myeloid leukemia (CML) patients in chronic phase (CP) now enjoy a normal life expectancy thanks to the routine use of tyrosine kinase inhibitors (TKIs).^{1,2} These drugs are able to induce not only a complete cytogenetic response (CCyR) in over 80% of subjects,³ but also a deep molecular response (DMR or MR4), defined as *BCR::ABL1* transcript levels $\leq 0.01\%$ according to the International Scale (IS), in more than 50% of patients.^{4,5}

The possibility of treatment discontinuation (TD) was pioneered by the French CML group⁶ and subsequently confirmed by several studies,^{7–15} which consistently indicate that approximately one half of patients who try TD can achieve a treatment-free remission (TFR) at 3 years (48%–61% in several studies),¹⁶ defined as the maintenance of at least a major molecular response (MMR or MR3).¹⁰ Adequate disease control off therapy affords several benefits for patients, such as a lower occurrence of drug-related AEs and a feeling of cure. A minimum of 5 years of TKI therapy and a stable MR4 for at least 2 years before attempting TD are recommended by the European Society for Medical Oncology (ESMO)¹⁷ and European LeukemiaNet (ELN),¹⁸ while even less stringent criteria are proposed by the US National Comprehensive Cancer Network (NCCN).¹⁹

Under the recommended conditions and with optimal molecular monitoring, TD is generally considered safe. In fact, about 95% of patients who experience molecular recurrence regain their initial molecular level after restarting TKI therapy.¹⁸ In addition, the

occurrence of disease progression (i.e., the transformation of CP-CML to the advanced state of accelerated phase [AP] or blast phase [BP]) was considered virtually impossible for a long time.¹¹

However, at least six cases of CML progression during or after TD have been reported, some of which were fatal.^{10,20–23} In all cases, the transformation to AP/BP dramatically changed the prognosis of the disease.

These are case reports from which a precise assessment of the denominator, that is, the number of patients at risk, and the time of observation, is missing. A large-scale, precise quantification of the risk of CML progression after TD in the setting of TFR has not been performed. Sudden blastic transformation has also been reported as a rare event in patients in optimal molecular response who did not discontinue therapy,^{24,25} suggesting that transformation may occur independently of TD.²⁶

The main goal of the Treatment-Free Remission—PROgression (TFR-PRO) study is to obtain a precise assessment of the risk of disease progression in a cohort of CP-CML patients eligible for TD, regardless of whether they underwent a TD.

2 | METHODS**2.1 | Study design and participants**

TFR-PRO is a multicenter, international, retro-prospective, observational study.

Eligible patients were aged 18 years or older and had a diagnosis of *BCR::ABL1*-positive CP-CML. The target population included all CML patients eligible for TD regardless of whether they had discontinued. To be considered eligible for TD, patients needed at least 4 years of TKI treatment (regardless of the number of TKIs used) and at least 18 months of DMR, determined through at least three consecutive molecular analyses by RT-qPCR performed at their own centers. DMR was defined as MR4 (either detectable disease with *BCR::ABL1* ratio $\leq 0.01\%$ on the IS or undetectable disease in cDNA with at least 10 000 *ABL1* copies). The date of the first DMR and the dates and level of molecular response by RT-qPCR during the 18 months of stable DMR were registered. Patients with previous allogeneic hematopoietic stem-cell transplantation (HSCT) and with a diagnosis of CML in advanced phase (AP or BP) were excluded.

Two cohorts were considered: patients that met the eligibility criteria started contributing to the non-discontinuation (reference) cohort; when patients started TD, they were moved to the discontinuation cohort. TD was terminated when the patients lost MR3 and resumed treatment. Events developing in patients after the end of TD were considered associated to discontinuation if they developed within 36 months from the end of discontinuation. Thereafter, they were no longer considered to be associated to discontinuation and the patient returned to the reference cohort for the remaining time. This rule applied also to subsequent TD attempts.

Collection of data was both retrospective and prospective. Patients registered before the opening of this study (July 24, 2020) contributed to the retrospective cohort and, after the opening of the study they also contributed to the prospective cohort. Those who were registered after the opening of the study contributed only to the prospective cohort. Monitoring of disease status was performed to assess the maintenance of the molecular remission during the study period, according to the policies of each center. Data from patients belonging to the retrospective cohort were collected starting from 2011. The cut-off date for this analysis was January 1, 2023.

A flexible statistical approach allowed attributing patients to the two groups in different periods according to their condition concerning TD (yes or no).

The ethics committee at each center approved the protocol in accordance with local rules and regulations. The informed consent for the prospective cohort had to be signed and dated before starting the collection of data.

2.2 | Outcomes

The primary endpoint of TFR-PRO was the time-adjusted rate (TAR) of progression to AP or BP. Definitions of AP and BP were made according the 2006 ELN criteria.²⁷ Secondary endpoints included: progression-free survival (PFS), defined as time from eligibility to progression to AP or BP; the rate of molecular relapse, defined as the loss of MMR after TD (in the discontinuation cohort) or after eligibility (in the reference cohort); the percentage of patients with molecular relapse who achieved a new MMR after losing it.

2.3 | Statistical analysis

Time to molecular relapse was measured from the date on which the patient satisfied the eligibility criteria to the date of the RT-qPCR assessment which defined molecular relapse. Time to disease progression was measured from the date the patient satisfied the eligibility criteria to the minimum between the date of AP or BP diagnosis and the end of the follow-up. Study group classification in the analysis of time to molecular relapse was defined as a binary, non-reversible, time-varying factor, where eligible patients were divided into two groups at the beginning of the follow-up depending on the presence or absence of TD, and in the latter case could start discontinuation during the follow-up and thus dynamically changed study group classification. Study group classification in the analysis of time to progression was defined as in the case of the analysis of time to molecular relapse, but it was a reversible binary variable where patients who developed molecular relapse under discontinuation and restarted treatment were kept under discontinuation for a further time lag of 36 months and then reclassified dynamically as absence of TD.

Descriptive statistics on the main endpoints were obtained by the “Simon-Makuch” version of the Kaplan–Meier curves and log-rank test and time adjusted rates accounting for the time varying nature of the classification according to presence or absence of TD.²⁸

Kaplan–Meier curves and log-rank test were used to describe the cumulative incidence of achievement of novel MMR since molecular relapse in patients who did/did not have a prior discontinuation.

The follow-up length was described using the “reverse Kaplan–Meier” method. The exponential model and Clopper Pearson exact method were used for significance and 95% confidence interval calculation of rates and proportions, respectively. All the analyses and graphics were performed by using Stata software version 18.

3 | RESULTS

3.1 | Patients and follow-up

Between July 2020 and November 2022, we registered 907 patients with CP-CML from 20 centres in five countries (Italy, France, Germany, Spain, and Canada). Thirty-seven patients were excluded after screening as not eligible or without follow up information. Thus, data were available for 870 patients at the time of the analysis. A total of 505 patients (58.0%) attempted TD during the observation period (43 patients had two TD attempts) and 365 (42.0%) never attempted TD (Figure S1).

Patient demographics, clinical characteristics, and follow-up information are reported in Table 1. Median age at diagnosis was 50 years (interquartile range [IQR] 40–61) and median age at eligibility was 57 years (IQR 47–68). Sokal score was available only in 477 (54.8%) of the 870 patients; 221 (46.3%) had low, 166 (34.8%) had intermediate, and 90 (18.9%) had high Sokal score.

Median number of RT-qPCR analyses performed for monitoring of *BCR::ABL1* transcript levels was three per year (IQR 2–4) during the

TABLE 1 Patients' characteristics and follow-up information.

	Overall cohort	Reference cohort	Discontinuation cohort	p-value (between reference and discontinuation cohort)
N	870 (100%)	365 (42%)	505 (58%)	-
Sex				.6
Female	393 (45.2%)	169 (46.3%)	224 (44.4%)	-
Male	477 (54.8%)	196 (53.7%)	281 (55.6%)	-
Age at diagnosis (years)	50 (40–61)	50 (40–61)	50 (40–61)	-
Sokal score ^a				.5
Low	221/477 (46.3%)	35/173 (20.2%)	55/304 (18.1%)	-
Intermediate	166/477 (34.8%)	54/173 (31.2%)	112/304 (36.8%)	-
High	90/477 (18.9%)	84/173 (48.6%)	137/304 (45.1%)	-
Unknown Sokal score	393/870 (45.2%)	192/365 (52.6%)	201/505 (39.8%)	-
Time from TKI start to CCyR (years)	0.6 (0.3–1.1)	0.5 (0.3–1.1)	0.6 (0.3–0.1)	-
Time from TKI start to MMR (years)	1 (0.6–2.0)	1 (0.5–2.1)	1.0 (0.6–2.0)	-
Time from TKI start to DMR (years)	2.9 (1.5–5.4)	2.9 (1.4–5.1)	2.9 (1.5–5.6)	-
Time from TKI start to eligibility (years)	5.2 (4.0–8.2)	4.9 (4.0–7.6)	5.6 (4.0–8.5)	-
Age at eligibility (years)	57 (47–68)	56 (46–67)	57 (47–68)	-
TKI at eligibility				<.001
Imatinib	496 (57.0%)	187 (51.2%)	309 (61.2%)	-
Nilotinib	182 (20.9%)	58 (15.9%)	124 (24.5%)	-
Dasatinib	140 (16.1%)	85 (23.3%)	55 (10.9)	-
Bosutinib	39 (4.5%)	23 (6.3%)	16 (3.2%)	-
Ponatinib	6 (0.7%)	5 (1.4%)	1 (0.2%)	-
Unknown	7 (0.8%)	7 (1.9%)	0 (0%)	-
Line of TKI at eligibility/TD ^b				.002
First	625 (71.8%)	242 (66.3%)	383 (75.8%)	-
Second	204 (23.5%)	101 (27.7%)	103 (20.4%)	-
Third or subsequent	41 (4.7%)	22 (6.0%)	19 (3.8%)	-
Time from eligibility to TD (years)	-	-	1.1 (0.0–3.4)	-
Duration of TKI therapy before TD (years)	-	-	8.2 (6.0–11.5)	-
Duration of DMR before TD (years)	-	-	4.5 (3.1–6.2)	-
Follow-up time since eligibility (years)	5.5 (2.6–8.6)	4.2 (1.8–7.8)	6.1 (3.2–9.0)	-
Follow-up time since TD (years)	-	-	3.6 (1.8–6.1)	-
N of person-years of follow-up	5188.2	3330.8	1857.4	
Median N of RT-qPCR per year since registration	3 (2–4)	3 (2–4)	3 (2–4)	

Note: For continuous variables, median values and interquartile ranges are reported.

Abbreviations: CCyR, complete cytogenetic response; DMR, deep molecular response; EP, endpoint; MMR, major molecular response; N, number; RT-qPCR, real-time, quantitative polymerase chain reaction; TD, treatment discontinuation; TKI, tyrosine kinase inhibitor.

^aData were missing for 393 patients.

^bThe line of TKI is reported referring to the date of eligibility for the reference cohort and the date of TD for the discontinuation cohort.

entire study. However during the period of TKI discontinuation (that is from discontinuation onwards for patients who never developed molecular relapse, or from discontinuation to the date of molecular relapse for patients who developed it), almost all patients had 3 RT-qPCR assessment per year (median 3, IQR 3–3).

At eligibility, 496 patients (57.0%) were on treatment with imatinib, 182 (20.9%) with nilotinib, 140 (16.1%) with dasatinib, 39 (4.5%)

with bosutinib, and six (0.7%) with ponatinib. A total of 245 patients (28.2%) were receiving their TKI as a second or subsequent line of therapy. The two cohorts were homogeneous for the main demographic and clinical characteristics, except for the type of TKI at eligibility. Compared with the reference cohort, in the discontinuation cohort significant differences existed regarding the TKI being used: there was a tendency towards higher percentages of patients in the

TD cohort to receive imatinib (61.2% vs. 51.2%) and nilotinib (24.5% vs. 15.9%), while lower percentages were on dasatinib (10.9% vs. 23.3%), bosutinib (3.2% vs. 6.3%), and ponatinib (0.2% vs. 1.4%). Furthermore, patients who were on treatment with a TKI as a second or subsequent line of therapy at the time of eligibility (for the reference cohort) or at the time of TD (for the discontinuation cohort) were less represented in the discontinuation cohort (24.2%) than in the reference cohort (33.7%) (Table 1).

Median duration of follow-up since eligibility was 5.5 years (IQR 2.6–8.6) in the overall cohort, with 5188.2 person-years available for the analysis of the primary endpoint, of which approximately 75% were collected retrospectively and 25% prospectively.

3.2 | Survival

A total of 24 deaths were reported, for a TAR of 0.5/100 person-years (95% confidence interval [CI] [0.3–0.7]). Of these, 12 occurred in the reference cohort, for a TAR of 0.4/100 person-years (95% CI [0.2–0.7]), and 12 in the discontinuation cohort, for a TAR of 0.6/100 person-years (95% CI [0.3–1.0]) ($p = .378$). The results of the Kaplan–Meier estimates for overall survival among patients of the whole cohort are represented in Figure 1. The estimated 10-year overall survival probability was 94.8% (95% CI [91.7–96.7]). All deaths were unrelated to CML.

3.3 | Molecular relapse

Overall, 236 events of molecular relapses occurred, 172 in the discontinuation cohort and 64 in the reference cohort. The corresponding TARs of molecular relapse were 5.6/100 person-years

(95% CI [5.0–6.4]) in the overall cohort, 11.8/100 person-years (95% CI [10.1–13.7]) in the discontinuation cohort, and 2.3/100 person-years (95% CI [1.8–3.0]) in the reference cohort ($p < .0001$). A graphical representation of the estimated proportion of RFS probability is provided in Figure 2A. In the discontinuation cohort the 6, 12, 24-month and 10-year estimates of RFS probability were 76.5% (95% CI [72.5–80.0]), 70.9% (95% CI [66.6–74.7]), 68.2% (95% CI [63.8–72.2]), and 59.9% (95% CI [54.2–65.1]), respectively; in the reference cohort they were 99.4% (95% CI [98.4–99.8]), 99.1% (95% CI [97.9–99.6]), 94.1% (95% CI [91.8–95.9]), and 82.4% (95% CI [76.7–86.8]), respectively.

In the discontinuation cohort the RFS values did not change between patients who were in first line treatment and those in second or subsequent lines of TKI therapy (Figure 3A): RFS probabilities at 5 years were 61.3% (95% CI [55.4–66.7]), 61.9% (95% CI [51.3–70.9]), and 77.8% (95% CI [51.1–91.0]), respectively, with no statistically significant difference. Thus, although patients in subsequent lines of therapy were underrepresented in the discontinuation cohort, if they decided to interrupt treatment, their chances of maintaining TFR were similar to patients in first line treatment.

Among patients who discontinued being in second or subsequent line, having a previous history of TKI resistance carried a higher risk of relapse compared with those without a previous TKI resistance (Figure 3B): RFS probabilities at 5 years were 51.2% (95% CI [34.6–65.6]) and 71.5% (95% CI [59.6–80.5]), respectively (p -value = .04).

3.4 | Achievement of MMR after molecular relapse

Among 172 patients who experienced molecular relapse after TD, 170 (98.8%) resumed TKI treatment after a median time of 0.7 months after molecular relapse (IQR 0.3–1.4). The remaining two

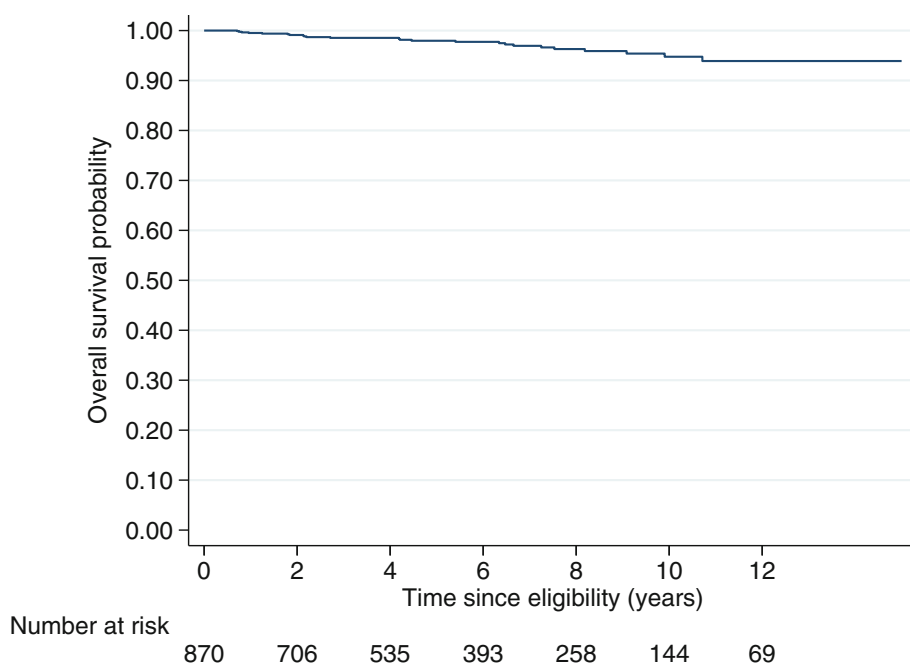
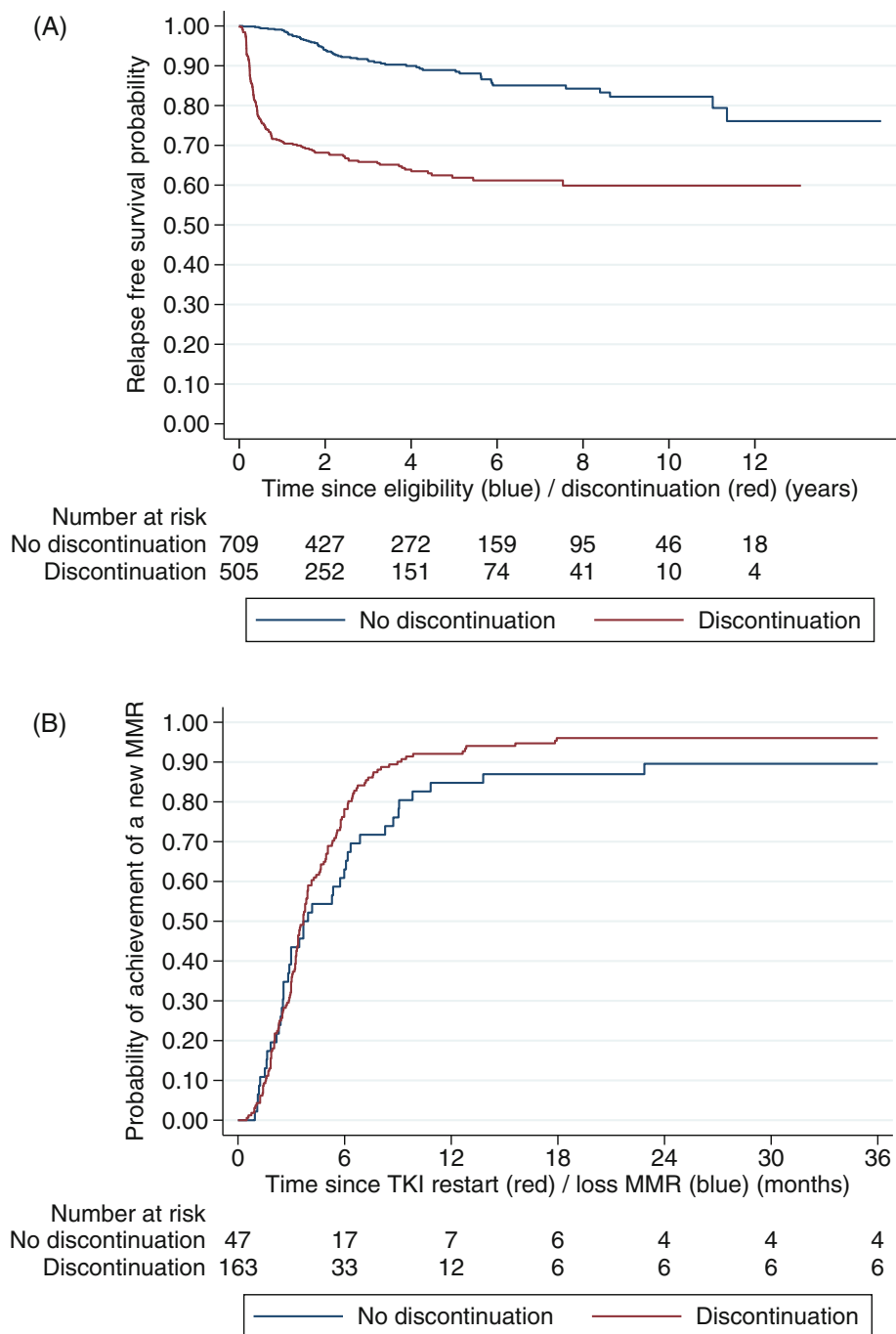


FIGURE 1 Overall survival in the total cohort. The results of the Kaplan–Meier estimates for overall survival among patients of the whole cohort. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Relapse-free survival and achievement of a new MMR in the reference cohort and discontinuation cohort. (A) Results of the Kaplan–Meier estimates for relapse-free survival among patients in the reference cohort and in the discontinuation cohort. Patients contributing to the reference cohort were all patients who never attempted TD, patients who attempted TD at a certain time of their history but only for the time they did not discontinue (i.e., for the time between eligibility and TD) and patients who experienced a molecular relapse after TD and after 36 months since treatment resumption, assuming a new TD did not occur; patients who discontinued were censored from this calculation at the date of discontinuation. (B) Cumulative incidence of achievement of a new MMR after molecular relapse following TD (discontinuation cohort) or after loss of MMR (reference cohort). MMR, major molecular response; TKI, tyrosine kinase inhibitor. [Color figure can be viewed at wileyonlinelibrary.com]



patients had fluctuating RT-qPCR values around the MMR threshold, they never confirmed MMR loss on two consecutive assessments and were still in MMR at the last follow up. Therefore, they never resumed treatment.

The proportions of patients in the discontinuation cohort who achieved MMR once again after molecular relapse were 78.2% (95% CI [71.3–84.4]) at 6 months, 92.1% (95% CI [87.1–95.7]) at 12 months, and 96.0% (95% CI [92.1–98.4]) at 24 months. In comparison, the proportions of patients in the reference cohort who achieved a new MMR after MMR loss were 63% (95% CI [49.4–76.7]) at 6 months, 84.8% (95% CI [73.0–93.3]) at 12 months, and 89.6% (95% CI [78.6–96.4]) at 24 months. Figure 2B presents the

Kaplan–Meier survival curves relative to the proportion of patients who achieved a new MMR after MMR loss in the two cohorts.

3.5 | Progression

One patient progressed to lymphoid BP 55 months after the end of TFR. Because this event developed more than 36 months after the end of TFR, as per study protocol, the patient was contributing to the reference cohort at the time of progression. Therefore, the risk of progression was 1/870 or 0.1% (95% CI [0.0–0.6]) in the overall cohort. This value ranges from 0/505 or 0%, (95% CI [0.0–0.6]) for

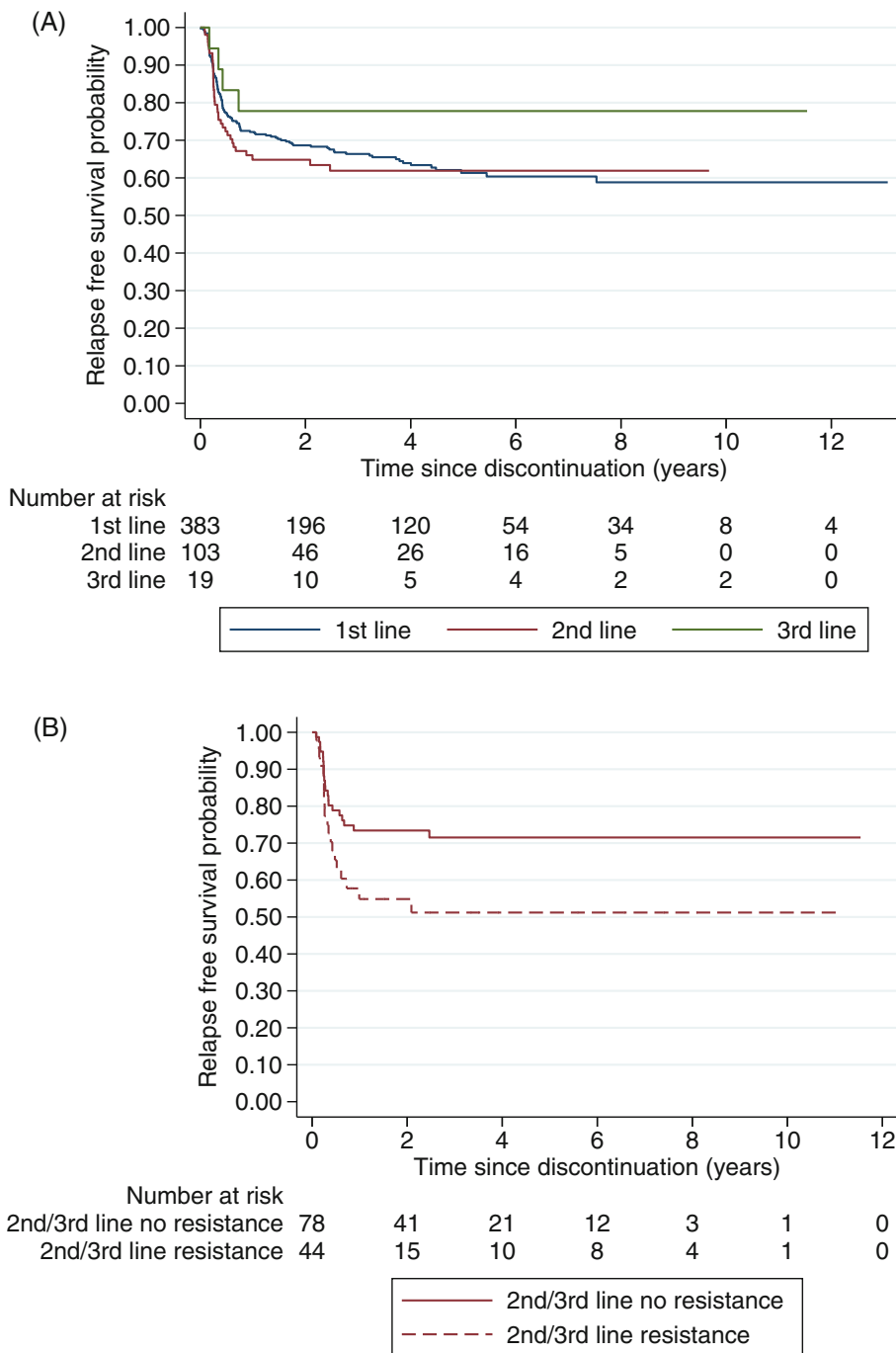


FIGURE 3 Relapse-free survival in the discontinuation cohort according to the line of TKI therapy at discontinuation (A) and according to the presence or absence of a previous TKI resistance (B). [Color figure can be viewed at wileyonlinelibrary.com]

the discontinuation cohort, to 1/365 or 0.3% (95% CI [0.0–1.5]) for the reference cohort. The TAR of progression was 0.019/100 person-years (95% CI [0.003–0.138]) for the overall cohort, ranging from 0.0 (95% CI [0–0.163]) for the discontinuation cohort to 0.030 (95% CI [0.004–0.215]) for the reference cohort. No statistically significant differences exist between the two cohorts.

The subject who developed disease progression was a male patient, diagnosed with CP-CML in January 2009, when he was 45 years old. He had started TKI therapy with imatinib, achieving an MMR 3 months later. In February 2013 TD was initiated. After 20 months, in October 2014, he experienced a molecular relapse. The

patient was recommended to resume imatinib but he demonstrated a very poor compliance to retreatment, which was reflected by the subsequent RT-qPCR assessments, revealing fluctuating *BCR::ABL1* transcript levels, ranging from MR1 to MR4 (Figure S2 in the Supplementary Appendix). In March 2019 he lost MMR for the fifth time and in May (55 months after the first molecular relapse), he developed an abrupt lymphoid BP. He received chemotherapy combined with ponatinib and in October 2019 he underwent allogeneic HSCT. At the last follow-up in September 2022, the patient was alive in good general condition, with a complete hematological response, undetectable levels of *BCR::ABL1* by RT-qPCR and no signs of GVHD.

4 | DISCUSSION

The current management of CML includes the possible discontinuation of TKI treatment in a sizeable proportion of patients. This practice carries clear advantages, including sparing the patient potential long-term adverse events and significantly reducing the cost of treatment.

About half of patients attempting TD, regardless of the TKI being used, must resume therapy due to loss of MMR,¹⁶ but most achieve a new MMR once back on treatment.¹⁸

However, anecdotal reports of CML patients experiencing a transformation to acute leukemia during or shortly after TD were alarming because they suggested the possibility of a progression of CML from a safe condition such as DMR to acute leukemia, which dramatically worsens patient prognosis and quality of life. At the time of presenting these results, described cases of progressions grew to 12.^{10,20–23,29–32} The TFR-PRO results presented here indicate that there is no cause for alarm. TFR-PRO represents the first study in which consecutive patients eligible for TD were enrolled and followed. More than 5000 patient-years were available for analysis.

In this study we report that disease progression among patients in TD or among patients eligible for TD represents an exceedingly rare event, but a possible one. The TAR data suggest, for example, that in a center managing 100 patients eligible for TD, at most one event of progression could happen once every 8 years.

In the TFR-PRO cohort, the relationship between TD and progression is doubtful. The only patient who experienced progression attempted TD but his progression occurred almost 5 years after MMR was lost, therefore outside of the 36-month limit the protocol set for considering an event linked to TD. The analysis of this patient's clinical course clearly points to the lack of compliance to treatment after the end of TD as the main cause for the subsequent progression.

This emphasizes a key point regarding selecting patients for TD. While multiple variables have been included in guidelines for TD,^{18,19} the willingness of the patient to resume treatment in the case of TD failure must also be evaluated. It is assumed that patients who achieve a DMR are more likely to be compliant but, as shown from the case presented, patient compliance can change over time. The population studied within TFR-PRO showed an excellent health status, with a 95% survival rate at 10 years and no CML-related death.

TFR-PRO followed patients treated as per standard of care for their CML, in whom monitoring does not always match recommended guidelines, as previously reported.^{18,19} For instance, almost 50% of patients did not have a Sokal score evaluated at diagnosis to assess risk of treatment failure. In addition, 25% of patients in the TFR-PRO study had less than two RT-qPCR tests per year in the whole study period, although during the discontinuation period this number raised to three. Although these numbers are lower than what recommended in many TFR guidelines,^{18,19} it is noteworthy that the prognosis for patients remained very good even in this out-of-trial cohort and that no progression linked to TD was observed.

The loss of MMR was clearly associated with TD. However, loss of MMR was also observed among patients who did not try TD. The

reasons for this are heterogeneous and may range from a lack of compliance with treatment, to the need to interrupt treatment because of comorbidities or surgical procedures, or to the possible induction of increased metabolism of TKI over time.

Imatinib represented the most common TKI used by patients eligible for TFR-PRO, in whom it was given as a first line therapy, as expected. It is interesting to note that patients in second or subsequent lines of therapy had similar RFS values than patients in first line treatment once they decided to start TD. This result indicates that once patients became eligible for TD the line of treatment had a limited impact on outcome, although most patients enrolled in the TFR-PRO study were on first line treatment.

Within this group, the RFS probability resulted significantly lower in patients with a previous history of TKI resistance, compared to those without such a history. This could reflect a possible higher biologic instability of the leukemic stem cells in the first group of patients, which could require a closer monitoring during TD.

Imatinib and nilotinib tended to be overrepresented in patients who attempted TD compared to patients who did not.

The TFR-PRO study represents the only study which enrolled consecutive CML patients eligible for TD independently of their decision to stop therapy; the results emanating from it will therefore contribute to our knowledge and will help physicians treating CML patients.

The low likelihood of disease progression and the lack of an evident relationship between disease progression and TD represent useful and encouraging information that should allay fears about a disease progression among patients who attempt TD.

AUTHOR CONTRIBUTIONS

Carlo Gambacorti-Passerini, Elisabetta Abruzzese, Alberto Alvarez-Larran, Sarit Assouline, Brian J. Druker, Philipp le Coutre, Susanne Saussele and Giovanni Paolo Maria Zambrotta made substantial contributions to the study conception and design. Giovanni Paolo Maria Zambrotta, Franck E. Nicolini, Sarit Assouline, Lambert Busque, Ester Pungolino, Elisabetta Abruzzese, Maria Cristina Miggianno, Chiara Elena, Alberto Alvarez-Larran, Ana Triguero, Alessandra Iurlo, Cristina Bucelli, Marco Cerrano, Isabella Capodanno, Francesca Lunghi, Philipp le Coutre, Sara Galimberti, Giovanni Caocci, Margherita Maffioli, Fabio Stagno, Susanne Saussele, Rocco Piazza, Carmen Fava, Veronica Guglielmana, Federica Colombo and Carlo Gambacorti-Passerini enrolled patients, collected and analyzed data. Carlo Gambacorti-Passerini and Giovanni Caocci made substantial contributions to analysis and data interpretation. Laura Antolini performed statistical analysis. Giovanni Paolo Maria Zambrotta and Carlo Gambacorti-Passerini wrote the paper. Sarit Assouline and Franck E. Nicolini critically reviewed the drafts. All authors approved the final version and agreed to submit the paper for publication.

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University of Milano-Bicocca (Monza, Italy) was the formal sponsor of the study. Canadian data were derived from the Registre de la LMC du GQR LMC-NMP.

FUNDING INFORMATION

University of Milano-Bicocca (Monza, Italy) allowed the performance of the study.

CONFLICT OF INTEREST STATEMENT

Franck E. Nicolini reports institutional grants from Incyte Biosciences and Novartis, consultant fees from Novartis, Sun Pharma Ltd, Kartos, and honoraria bureau from Incyte Biosciences, Novartis, and Pfizer; Franck E. Nicolini also reports participation on a Board for Incyte Biosciences and Novartis, outside the submitted work. Sarit Assouline reports grants from Abbvie Canada, Novartis Canada Ltd and consulting fees from Abbvie, Beigene, Genentech/Roche, Astrazeneca, Bristol Myers Squibb, Palladin, Janssen, Novartis; Sarit Assouline also reports honoraria from Jenssen, Astrazeneca, Abbvie, Novartis, outside the submitted work. Lambert Busque reports honoraria from Novartis, BMS, Pfizer, Taiho. EA reports honoraria from BMS, Incyte, Novartis, and Pfizer, outside the submitted work. CE reports personal fees for participation on a Board for Blueprint, Gilead, Cogent, outside the submitted work. AI reports honoraria from BMS, Incyte, Novartis, AOP, GSK, and Pfizer, outside the submitted work, and participation on a Board for BMS, Incyte, Novartis, AOP, outside the submitted work. MC reports participation on an Advisory Board for Novartis and Incyte, outside the submitted work. FS participates on a Board for Novartis, outside the submitted work. SS reports grants, consulting fees and honoraria from Novartis and Incyte, grants and honoraria from BMS, honoraria from Pfizer and Roche, outside the submitted work. BJD reports the following potential competing interests. SAB: Adela Bio, Aileron Therapeutics (inactive), Therapy Architects/ALLCRON (inactive), Cepheid, DNA SEQ, Nemucore Medical Innovations, Novartis, RUNX1 Research Program; SAB & Stock: Aptose Biosciences, Blueprint Medicines, Enliven Therapeutics, Iterion Therapeutics, GRAIL, Recludix Pharma; Board of Directors & Stock: Amgen, Vincerx Pharma; Board of Directors: Burroughs Wellcome Fund, CureOne; Joint Steering Committee: Beat AML LLS; Advisory Committee: Multicancer Early Detection Consortium; Founder: VB Therapeutics; Sponsored Research Agreement: Enliven Therapeutics, Recludix Pharma; Clinical Trial Funding: Novartis, Astra-Zeneca; Royalties from Patent 6 958 335 (Novartis exclusive license) and OHSU and Dana-Farber Cancer Institute (one Merck exclusive license, one Cytolmagine, Inc. exclusive license, and one Sun Pharma Advanced Research Company non-exclusive license); US Patents 4 326 534, 6 958 335, 7 416 873, 7 592 142, 10 473 667, 10 664 967, 11 049 247. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Data available in article supplementary material

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SUPPORTING INFORMATION

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

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