Treatment free remission in patients with chronic myeloid leukemia: recommendations of LALNET expert panel

Tracking no: ADV-2020-003235R1

Carolina Pavlovsky (FUNDALEU, Argentina) Virginia Abello Polo (Hospital de San José, Colombia) Katia Pagnano (Hematology and Hemotherapy Center-University of Campinas, Brazil) Ana Varela (Hospital J.M. Ramos Mejia, Argentina) Claudia Aguadelo Lopez (Clinica Colsanitas, Colombia) Michele Bianchini (CIO-FUCA, Instituto A. Fleming, Argentina) Carla Boquimpani (Hemorio, Institute of Hematology, Brazil) Renato Centrone (Institute Hemedem, Brazil) Monika Conchon (Hospital Santa Marcelina, Brazil) Nancy Delgado (Instituto Mexicano del Seguro Social, Mexico) Vaneuza Funke (Federal University of Paraná, Brazil) Isabel Giere (FUNDALEU, Argentina) Ingrid Pinto (National Cancer Institute of Brazil, Brazil) Luis Meillon-Garcia (Centro Médico ABC, Mexico) Beatriz Moiraghi (Hospital J.M. Ramos Mejia, Argentina) Juan Navarro (Hospital Rebagliati, Peru) Lilian Pilleux (Hospital de Valdivia, Chile) Ana Prado (Hospital Maciel, Uruguay) Maria Soledad Undurraga (Hospital del Salvador, Chile) Jorge Cortes (Georgia Cancer Center, United States)

Abstract:
Tyrosine kinase inhibitors (TKI) have dramatically changed the survival of chronic myeloid leukemia (CML) patients and treatment-free remission (TFR) has recently emerged as a new goal of CML treatment. The aim of this work was to develop recommendations for TKI discontinuation in Latin America (LA), outside clinical trials. A working group of CML experts from LA discussed 22 questions regarding TFR and reached a consensus for TFR recommendations in the region. TFR is indicated in patients in first CP, with typical BCR-ABL transcripts, under TKI treatment for a minimum of 5 years, in sustained deep molecular response (DMR: MR4.5) for 2 years. Sustained DMR must be demonstrated on at least 4 IS qPCR tests, separated by at least 3 months, in the immediate prior 2 years. After 2nd line therapy, TFR is indicated in previously intolerant patients, not resistant. Molecular monitoring is recommended monthly the first 6 months, every 2-3 months from months 7 to 12, and every 3 months during the second year, indefinitely. Treatment should be reintroduced if loss of major molecular response. Monitoring of withdrawal syndrome, glucose levels, and lipid profile are recommended after discontinuation. After TKI reintroduction, molecular monitoring is indicated every 2-3 months until MR4.0 achievement, later every 3-6 months. For TFR attempt, is mandatory to have standardized, and reliable BCR-ABL PCR tests. These recommendations will be useful for safe discontinuation in the daily practice and will benefit patients who wish to stop treatment in emergent regions, in particular, with TKI related chronic adverse events.

Conflict of interest: COI declared - see note

COI notes: CAROLINA PAVLOVSKY: Research Support (to the Institution): Pint Pharma Speaker Honoraria: Novartis, Pfizer, BMS. Janssen, Pint Pharma/Takeda Advisory Board: Novartis, Pfizer. VIRGINIA ABELLO POLO: Research funding: Takeda, Dr Reddy's, Novartis, Amgen, Abbvie Speaker Honoraria: Novartis, Janssen, Amgen, Astra, Abbvie. KATIA PAGNANO Advisory Board: Astellas, Novartis Speaker Honoraria: Pintpharma, ESM, Astellas ANA INES VARELA Speaker Honoraria: Novartis CLAUDIA AGUDELLO Advisory Board: Novo Nordisk, Amgen, Takeda, Legrand. Speaker Honoraria: Novo Nordisk, Janssen, Novartis, Abbvie. MICHELE BIANCHINI No Conflict of interests CARLA BOQUIMPA advisory Board: Novartis Speaker Honoraria: Novartis, Janssen, Abbvie MONICA CONCHON No Conflict of interests NANCY DELGADO No Conflict of interests VANUEZA FUNKE No Conflict of interests ISABEL GIERE No Conflict of interests INGRID LUISE No Conflict of interests LIS MEILTON Advisory Board: AstraZeneca, Novartis. Speaker Honoraria: Novartis, Amgen, Sandzo, Roche, BMS, AstraZeneca, Pint-pharma, Janssen. BEATRIZ MOIRAGHI Speaker Honoraria : Novartis Pfizer, Pint Farma/Takeda, BMS, Varifarma, BMS, JUAN RAMON NAVARRO Research: Apellis, Pfizer Speaker Honoraria: Abbvie, Novartis Advisory Board: Tecnofarma, Novartis, Abbvie LILIAN PILLEUX Advisory Board: Novartis ANA INES PRADO NO Conflict of interests SOLEDAD UNDURRAGA Advisory Board: Novartis, Pfizer, Janssen, Roche, Abbvie, Pint Pharma, TecnoFarma. JORGE CORTES Research support (to the institution): BMS, Novartis, Pfizer, Sun Pharma, Takeda Consultant: Novartis, Pfizer, Takeda

Author contributions and disclosures: CP, AIV and JC: Designed the project, formulated the questions to LALNET members, ordered the answers, filled in the questionnaire, participated personally in every meeting, wrote and revised the manuscript, approved the final version of the manuscript. VA, KP and IC: Ordered the answers to the questions; participated personally in every meetings, wrote and revised the
manuscript, and approved the final version of the manuscript. CA, CB, RC, ND, VF, IL, LM, BM, JRN, LP, AIP, SU: Filled in the questionnaire, wrote and revised the manuscript, approved the final version of the manuscript. MB and MC: Filled in the questionnaire, revised the manuscript, approved the final version of the manuscript.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: emails for corresponding author

Clinical trial registration information (if any):
Treatment free remission in patients with chronic myeloid leukemia: recommendations of LALNET expert panel

Running Head: CML treatment discontinuation recommendations.

Carolina Pavlovsky¹, Virginia Abello Polo², Katia Pagnano³, Ana Ines Varela⁴, Claudia Agudelo⁵, Michele Bianchini⁶, Carla Boquimpani⁷, Renato Centrone⁸, Monica Conchon⁹, Nancy Delgado¹⁰, Vaneuza Funke¹¹, Isabel Giere¹, Ingrid Luise¹², Luis Meillon¹³, Beatriz Moiraghi⁴, Juan Ramon Navarro¹⁴, Lilian Pilleux¹⁵, Ana Ines Prado¹⁶, Soledad Undurraga¹⁷, Jorge Cortes¹⁸.

1. FUNDALEU, Buenos Aires, Argentina
2. Fundación Universitaria de Ciencias de la Salud, Hospital de San José, Bogotá, Colombia.
3. Centro de Hematologia e Hemoterapia, University of Campinas, Campinas, SP, Brazil.
4. Hospital J.M.Ramos Mejia, Buenos Aires, Argentina.
5. Clínica Colsanitas, Bogotá, Colombia.
6. CIÓ-FUCA, Instituto A. Fleming, Buenos Aires, Argentina.
7. HEMORIO and Oncoclinica, Rio de Janeiro, Brasil.
8. Instituto Hemomed, São Paulo, Brasil.
9. Hospital Santa Marcelina, São Paulo, Brasil.
10. Instituto Mexicano del Seguro Social, Instituto Politécnico Nacional Instituto, Ciudad de Mexico, Mexico.
11. Universidade Federal do Parana, Curitiva, Brasil.
12. National Cancer Institute of Brazil, Rio de Janeiro, Brazil.
13. Instituto Mexicano del Seguro Social, Instituto Politécnico Nacional, Ciudad de Mexico, Mexico.
14. Hospital Rebagliati, Lima, Perú.
15. Hospital de Valdivia, Los Ríos, Chile.
16. Hospital Maciel, Montevideo, Uruguay.
17. Hospital del Salvador, Santiago, Chile.
18. Georgia Cancer Center, Augusta, GA, USA.

Corresponding author:
Carolina Pavlovsky
J.E.Uriburu 1520, PC 1024, Buenos Aires, Argentina.
+54 11 48771075
cpavlovsky@fundaleu.org.ar
Abstract
Tyrosine kinase inhibitors (TKI) have dramatically changed the survival of chronic myeloid leukemia (CML) patients and treatment-free remission (TFR) has recently merged as a new goal of CML treatment. The aim of this work was to develop recommendations for TKI discontinuation in Latin America (LA), outside clinical trials. A working group of CML experts from LA discussed 22 questions regarding TFR and reached a consensus for TFR recommendations in the region. TFR is indicated in patients in first CP, with typical BCR-ABL transcripts, under TKI treatment for a minimum of 5 years, in sustained deep molecular response (DMR: MR4.5) for 2 years. Sustained DMR must be demonstrated on at least 4 IS qPCR tests, separated by at least 3 months, in the immediate prior 2 years. After 2nd line therapy, TFR is indicated in previously intolerant patients, not resistant. Molecular monitoring is recommended monthly the first 6 months, every 2-3 months from months 7 to 12, and every 3 months during the second year, indefinitely. Treatment should be reintroduced if loss of major molecular response. Monitoring of withdrawal syndrome, glucose levels, and lipid profile are recommended after discontinuation. After TKI reintroduction, molecular monitoring is indicated every 2-3 months until MR4.0 achievement, later every 3-6 months. For TFR attempt, is mandatory to have standardized, and reliable BCR-ABL PCR tests. These recommendations will be useful for safe discontinuation in the daily practice and will benefit patients who wish to stop treatment in emergent regions, in particular, with TKI related chronic adverse events.

KEY POINTS
• LALNET TFR Recommendations in CML patients are an unmet need as to be able to carry out this new goal in Latin America.
• TFR Recommendations adapted to Latin American needs will make discontinuation feasible and safe in real-life in the region.
Introduction
The recognition of the BCR-ABL oncprotein as the constitutively active tyrosine kinase responsible for the development of chronic myeloid leukemia (CML) prompted the development of tyrosine kinase inhibitors (TKIs). These molecules have radically changed the clinical course of CML for most patients, turning it from a fatal leukemia to a chronic disorder. Nowadays, individuals with an optimal response may have a life expectancy close to that of the general population (1-3). Despite the favorable outcome with current therapies, TKIs do not eradicate the CML stem cells. Because of this, the treatment recommendations, until recently, were to continue therapy indefinitely for all patients. The prolonged use of TKIs is associated with clinically relevant adverse events (AEs), such as cardiovascular events, pleural effusions, fatigue, muscular pain and the possible increase in the incidence of second cancers (4-7). When present, these AEs jeopardize quality of life. High cost of indefinite TKI treatment has become a burden to the health care system and patients all over the world. That is especially relevant in low-middle income countries in Latin America (LA).
Recent studies have shown that TKI treatment can be safely discontinued in a selected group of chronic phase (CP) CML patients that achieve deep molecular response (DMR), making treatment-free remission (TFR) a new goal of therapy (8-13). TFR was first investigated in TWISTER (13) and STIM1 trials (8). The latter, showed that 41% who had achieved sustained complete molecular response (CMR) on quantitative polymerase chain reaction (qPCR), after long-term treatment with imatinib, continued in CMR after 1 year of TKI discontinuation (8). Several other studies have confirmed the results with imatinib and provided similar data after discontinuation of nilotinib or dasatinib (14). EURO-SKI, the largest discontinuation trial, demonstrated that approximately 50% of patients can persist without molecular relapse at 2 years (15). Discontinuation trials are ongoing in Latin America, and have shown feasibility and similar outcomes in preliminary reports (16, 17).
The recent ELN recommendations 2020 version (18) as well as the NCCN Guidelines (19) consider TKI discontinuation feasible in selected patients.
ESMO Guidelines also include recommendations for TFR, especially focusing on the institutional and patients’ requirements for a safe TFR (20). Latin America is a vast and heterogenous region where the application of some advances in hematology practice is challenging. Public health policies are different among the various countries, but they all share many of the same limitations for care, usually related to healthcare access barriers and limited resources. During the last decade, cooperative efforts in LA have successfully organized a harmonization platform for BCR-ABL1 measurement (www.ph.is.com) with the participation of 30 LA labs from 10 different LATAM countries. To have an immediate clinical benefit on molecular response monitoring for patients in low-resource regions, this platform identified existing flaws in BCR-ABL quantification and brought up several technical recommendations to improve comparability between laboratories (21).

The strict and more frequent monitoring, as recommended to make TFR feasible, has not yet been recognized by all government health authorities and insurance companies in LA countries. Various LA countries have local cooperative working groups with special interest in CML management but no regional collaborative approach in TFR local recommendations have been developed until now. As there are still many unanswered questions concerning TFR, the need for local TFR management guidelines in LA to conduct this strategy outside clinical trials, was identified as a priority to discuss in recent Latin America Leukemia Net (LALNET) meetings. Careful patient selection and optimal monitoring must be assured in order to consider TFR a safe decision for LA CML population. It is the hope of all participants, that this collective effort might help better educate patients and physicians in the region about this approach and create awareness in healthcare authorities and third party payers about the potential benefits that TFR carries, but also the risks if not properly implemented by all those with shared responsibilities in the process.

**Methods**

A working meeting was held on March 29, 2019 in FUNDALEU, Buenos Aires, Argentina to discuss TFR and its reality and impact in our region with CML experts and representatives from Argentina, Brazil, Chile, Colombia, Mexico,
Peru and Uruguay. A questionnaire addressing the various aspects of TFR was sent to all participants before the meeting. Responses were reviewed and discussed. Each CML expert answered 22 questions related to optimal criteria for TKI discontinuation, molecular monitoring and other clinical aspects. During the event, opinions were harmonized and a consensus was reached in the majority of the questions. This manuscript reflects the consensus for TFR recommendations for LA that resulted from that meeting and multiple later reviews with the whole panel.

Results
Recommendations

1. **Patient selection**
   Taking into account that TFR has become a new goal for selected CML patients, information about it should be shared as early as possible after the diagnosis. An extensive discussion, considering PROS and CONS of TFR must be had again with the patient and family members, once the criteria to discontinue treatment have been met. Informed consent is recommended to ensure proper understanding including information on monitoring plan, withdrawal syndrome (20), risk of recurrence and late relapse (22) that make lifelong monitoring necessary.

1.1. **TKI treatment duration**
   Treatment duration required to consider a patient eligible for TFR has varied in different trials; a minimum of 2 years was required in most published studies. The analysis of TKI treatment duration to predict the possibilities to maintain TFR after imatinib discontinuation in STIM study showed that patients with ≥50 months of treatment experienced significantly fewer molecular relapses than those who received imatinib for less than 50 months (53% vs 83%) (8, 23). In EuroSKI, a prognostic analysis of 405 patients who received imatinib first-line treatment, revealed that 5.8 years or more of treatment before discontinuation resulted in 63% molecular relapse free-survival at 6 months in comparison to 41% for patients who were treated for less than 5.8 years (15). While some trials have showed a trend for better chances of maintaining TFR with longer TKI treatment, none of them has demonstrated to be statistically significant (11,
In the LALNET recommendations survey, the question regarding minimal time on treatment with TKI to consider discontinuation was answered as follows: 2 years (8%), 3 years, (34%), 4 years (25%), and 5 years (33%). When the question was asked referring only to imatinib, the minimal time on treatment before discontinuation, responses varied: 3 years (17%), 4 years (25%), and 5 years (58%). After discussing the evidence, the consensus was to recommend a minimum of 5 years of treatment before the discontinuation for all TKIs.

**LA recommendation:** A minimum of 5 years of TKI treatment is recommended before considering TFR.

### 1.2. Deep molecular response (DMR) duration and qPCR assay considerations

Duration of DMR may be more important than duration of therapy. Most of recent recommendations consider MR 4.5 sustained for ≥2 years. Several discontinuation trials established sustained MR4.0 for at least 2 years as the criteria for considering treatment discontinuation, although this specific eligibility criteria varies across TFR trials. The EURO-SKI trial found that duration of DMR (defined as MR4 or a 4-log reduction in BCR-ABL1 transcripts) before discontinuation is the most relevant factor predicting molecular relapse-free survival at 6 months. The best cut-off for DMR duration was 3.1 years, with a probability of molecular relapse-free survival of 61% for those with more than 3.1 years compared to 44% for those with a shorter DMR duration. Additionally, there is a linear increase in the probability of TFR maintenance per additional year in deep molecular response in patients treated with imatinib (15). There was a consensus in the LA survey members that a minimum of 2 years of DMR duration is required to attempt discontinuation keeping in mind that more evidence is being generated and more time (3 years or more) may improve outcomes. In search of the best possible outcome the panel defined MR 4.5 IS as DMR to attempt TFR. PCR tests should be performed in standardized laboratories according to the ELN recommendations for BCR-ABL quantification (6). Results should be available within 2 to 3 weeks to minimize delays in resumption of therapy when needed. For centers without access to a reliable
qPCR 4.5 test that do not have the possibility to send samples to a reference center, the panel strongly suggested not attempting TFR outside a clinical trial since an unreliable qPCR result could jeopardize patient safety.

**LA recommendation:**
- A minimum of 2 years of sustained DMR duration (DMR, defined as MR 4.5 (BCR-ABL1 IS \(\leq 0.0032\%\)), is required to consider discontinuation. Sustained DMR must be demonstrated on at least 4 IS qPCR tests, separated by at least 3 months, in the immediate prior 2 years.
- It is recommended to confirm the DMR with a reliable qPCR (MR 4.5 IS), no more than 30 days before treatment discontinuation.
- If adequate IS qPCR is not available, the group strongly recommends not to attempt TFR.

### 1.3. Status of the disease at diagnosis
All studies on TFR have excluded patients with prior history of accelerated phase or blast crisis. There was a consensus in the group to recommend that only patients in first chronic phase should be considered for TFR.

**LA recommendation:** Only patients in first chronic phase CML should be considered for TFR.

### 1.4. Type of BCR/ABL transcript
Atypical BCR-ABL transcripts have been described in a minority of patients with CML at diagnosis. These patients cannot be monitored with qPCR IS and thus determining MMR or MR4.5 is not feasible (25).

There was a consensus of the panel to recommend that all patients must have a typical quantifiable transcript at diagnosis that can be measured in IS.

**LA recommendation:** All patients considered for TFR must have a transcript at diagnosis (\(b3a2 b3a2 [e14a2]\) and/or \(b2a2 [e13a2]\), typic isoform of p210)
1.5. Sokal score

In the STIM trial Sokal score was significantly associated with the probability of molecular relapse after treatment discontinuation (80% at 72 months for high-risk Sokal vs 50% for low/intermediate-risk) (23). This has not been confirmed in subsequent trials with imatinib (15) or with second generation TKI discontinuation (14, 24, 26). NCCN 2019 and LeukemiaNet 2020 guidelines, do not take into account Sokal score to consider discontinuation (18, 19) but ESMO 2017 includes not having a high-risk Sokal score at diagnosis as one of the optimal criteria to support TFR attempt (20).

The LA panel considered that if treatment discontinuation is contemplated for a patient with high-risk Sokal score, special attention must be taken to explain to the patient that there might be a higher risk of losing MMR, especially after frontline imatinib. In the LA recommendation survey, 69% of participants considered that Sokal score at diagnosis should not be considered to select patients for TFR.

**LA recommendation:** Sokal risk at diagnosis should not be used as a criterion to define TFR candidates, but patients with high-risk Sokal score should be informed of the possibility of a higher risk of molecular relapse.

1.6. Failure to first line TKI

Several studies have shown that TFR after second line TKI is possible, but to date, TFR studies have not uniformly clarified the impact of a patient’s history of resistance in the probability of TFR (10, 14, 15, 24). The dasatinib discontinuation (DADI) study reported a significantly higher rate of molecular relapse in patients attempting TFR if they had a history of prior failure to first line treatment: at 36 months TFR rate of 7.7% compared to 54% in patients without prior imatinib resistance (p= 0.015) (14). The STOP-2G-TKI study showed that the strongest adverse baseline prognostic factor for relapse was suboptimal or resistance to TKI (29.8% with previous history vs. 63.6% with no previous history of resistance) (27). In contrast, the ENEStop trial analyzed TFR rates according to reason for switch in TFR patients after second-line nilotinib and did not find a similar association. Evaluable patients who had
switched to nilotinib due to intolerance, resistance, or physician preference, showed similar TFR rates at 48 weeks (58.8%, 53.3%, and 61.4%, respectively) (28).

The LA group considered that most of the evidence suggests that patients with previous failure to TKI are at higher risk of relapse when attempting TFR. The panel recommended considering the ELN definitions when considering whether a patient has experienced failure.

**LA recommendation:** TFR should only be considered in CP CML patients under treatment with 2nd line TKI therapy when the indication for change was due to intolerance and not for resistance.

A conversation about TFR must be planned and initiated early, ideally at diagnosis (29). During the TFR process, some patients may experience anxiety when faced with minor fluctuations of PCR values (30, 31). If anxiety occurs after discontinuation, the patient should be properly informed, with additional interventions if necessary (e.g., psychological support) (31). Patients must be able to openly express their feelings and problems to their physicians, in a claimed and non-rushed environment, participating actively in their follow-up, to guarantee a successful TFR (32).

**LA recommendation:**
- The psychosocial situation of each patient should be analyzed when TFR is being considered.
- Risk of molecular relapse should be clearly discussed with the patient before attempting TFR.
- During the initial information session, enough emphasis should be made on the importance of close follow-up and the need for lifelong monitoring since TFR does not mean a cure.
- During monitoring physicians should be alert for any signs of anxiety and seek professional psychological help if needed.
3. **Clinical and Molecular Monitoring during TFR**

3.1. **Optimal frequency of monitoring after treatment discontinuation**

International published studies showed different monitoring strategies during the TFR period. In the STIM trial, patients were monitored monthly during the 1st year with qPCR at a very high sensitivity. Between months 12 and 24, monitoring was done every 2 months and after the third year every 3 months (8). In the EuroSKI trial, patients were monitored with a less strict schedule: from months 1 to 6 every 4 weeks, from month 7 to 12 every 6 weeks and from the second year on, every 3 months (15). International treatment guidelines have made specific recommendations for monitoring BCR-ABL during TFR period with some variability among them. The NCCN 2019 guidelines suggest monthly monitoring for the first 12 months after TKI discontinuation, every 2 months during months 13-24, and every 3 months thereafter (19). ESMO guidelines suggest monthly IS qPCR during the first 6 months, every 6 weeks from month 7 to 12 and every 12 weeks thereafter (20).

Notably, in the different studies the vast majority of cases of molecular relapses were observed within the first 6 months of TFR. In the STIM trial, 95% of molecular relapses occurred within the first 7 months of imatinib discontinuation (8). In the TWISTER trial, 68% of relapses occurred in the first 6 months (13) and in the EURO-SKI trial this was the case for 80% of the recurrences (15).

During the TFR period the patient’s adherence to the molecular monitoring visits is vital, to avoid a catastrophic situation where unnoticed relapses may occur. In the LA recommendation survey, 83% of the panel considered that BCR-ABL IS qPCR must be performed every 4 weeks during the first 6 months. Discussion on monitoring from months 6 to 12 took into account the need to make TFR an option that is safe and feasible in LATAM also optimizing health resources. Fifty percent of the panel considered monitoring every 2 months and 33% every 3 months. As the great majority of relapses occur in the 1st semester, the option to control every 2-3 months from month 7 to 12 is recommended. Seventy percent of participants agreed that monitoring every 3 months should continue indefinitely.

If after the 4-weekly monitoring phase loss of response from MR4.5 to MR4.0, is detected, it is recommended to resume the monthly monitoring testing for closer follow up until the disease regains stability. As previously mentioned, it is vital...
that the qPCR assay used to monitor patients is standardized and expressed in the International Scale.

**LA recommendation:**
- Monthly qPCR during the first 6 months after discontinuation.
- Every 2 or 3 months qPCR monitoring from months 7 to 12.
- Every 3 months qPCR from month 13, indefinitely.

### 3.2. Definition of Molecular Relapse

Molecular relapse that triggered restart of TKI therapy in the STIM trial was defined as qPCR positivity with a 5-log sensitivity, confirmed in a second analysis (8). The A-STIM trial was a multicenter observational study that first suggested that MMR can be safely used as the trigger to restart TKI therapy, since approximately 30% of patients have fluctuation on BCR-ABL transcript levels below the MMR threshold without clinical disease recurrence. Using this criterion, TFR was estimated to be 64% at 12 months (33). After that trial, most TFR studies have used MMR loss as the definition for relapse and the criterion for resuming therapy (11, 15, 24). Accordingly, NCCN, LeukemiaNET and ESMO guidelines suggest restarting treatment when MMR is lost (18-20).

In the LA recommendation survey, 100% of the panel agreed that loss of MMR (MMR: BCR-ABL >0.1%) should trigger resumption of TKI. TKI resumption is recommended as soon as possible, within 4 weeks from the loss of MMR.

**LA recommendation:** Lost of MMR defined as BCR-ABL IS >0.1% is considered molecular relapse and should trigger TKI reintroduction.

### 3.3. Monitoring after TKI re-initiation

In the EURO-SKI trial, in case of molecular relapse, TKI treatment was restarted and patients were followed every 3 months until MR4.0 was achieved again, and 6 months further. After restarting treatment, in a median follow-up time of 11 months, 321 (86%) of 373 patients achieved MMR, and 302 (81%) a deep molecular response. The median time to achieve MMR after resuming
therapy was 2.8 months (95% CI 2.7–2.9) and to reach deep molecular response 3.7 months (15). In the observational study of CML Italian patients who discontinued TKI in clinical practice, 39% patients resumed treatment. The frequency of monitoring after TKI re-start was not reported, but 94% of the patients who were retreated regained at least MMR and 82% of them achieved DMR (34). In a Brazilian discontinuation trial (EDI-PIO), after TKI re-start, patients were monitored monthly until achieving MR4.0, then every 3 months. The median time to achieve MMR after imatinib resumption was 2.7 months (16). In the STOP 2G-TKI trial, MMR was achieved by all patients after a median time of 2 months after dasatinib or nilotinib re-start (24). The NCCN guidelines for CML, recommends TKI resumption within 4 weeks from loss of MMR, and molecular monitoring every 4 weeks until MMR is regained, then every 3 months for patients who reach MMR. Patients who fail to respond after 3 months of TKI resumption, should have BCR-ABL mutation screening and monthly follow-up (19). The French guidelines recommend, after TKI resumption, monitoring BCR-ABL transcripts every 3 months until an MMR and a DMR are regained and then every 3 to 6 months. If MMR is not achieved again within 6 months, they recommend to screen for BCR-ABL mutations and to switch therapy according to the mutation (22). Mutations in this setting are rare, but there is a report of a patient from ENESTfreedom trial who relapsed after treatment discontinuation and had a detectable F359V BCR-ABL1 kinase domain mutation. This patient achieved MMR after nilotinib recommencement but lost the response and had to be removed from the trial for lack of efficacy (11). Only one patient from the A-STIM trial has progressed to a sudden blast crisis after imatinib resumption, after achieving MMR (35).

In the LA recommendation survey, part of the panel considered that qPCR must be performed every 4 weeks until MMR is regained, while others considered it should be performed every 3 months.

**LA recommendation:** Patients should be monitored every 2-3 months after TKI reintroduction, until achieving MR4.0. Then, every 3-6 months. If the patient does not regain MMR in 3-6 months, mutation screening is recommended.
4. **Monitoring and management of withdrawal syndrome**

TKI withdrawal syndrome (WS) is a well described event that has been reported in different TFR clinical trials occurring in approximately 30% of patients (36-39). It consists in musculoskeletal pain mainly upper body joints, shoulders or hips. It may resemble rheumatic polymyalgia and requires multiple symptomatic treatments in 30% of patients, including NSAIDs, corticosteroids, physical therapy, or, occasionally, resumption of TKI to treat the symptoms associated with WS (39). Although 80% of events are considered mild, and usually resolve after a median of 7 months (3-30 months), 5% of patients can present with a more severe form.

Univariate and multivariate analyses identified two risk factors: duration of TKI treatment (risk ratio (RR) = 1.68 (1.02–2.74)) with a 93-month cut-off time, and history of prior osteoarticular symptoms (RR = 1.84 (1.04–3.28)). WS seems to be a TKI class effect and its pathophysiology remains unclear (33, 40).

Patients and physicians should be aware of the possibility of TKI WS before discontinuation as this can be a quality of life-affecting event. Although symptoms also rapidly resolved in patients who restarted TKI, this approach is not routinely recommended since in the vast majority of patient’s symptoms resolve eventually and can be controlled with appropriate treatment (15, 41). Monitoring patients to identify symptoms suggestive of WS is necessary, especially those who have received TKI for more than 93 months or who report a history of previous osteoarticular pain (10).

**LA recommendation:**

- Adequate information about withdrawal syndrome should be provided to patients when considering TFR. Patients should be actively monitored for osteoarticular symptoms.

5. **Important considerations for TFR in LA: Pharmaco-economics**

The long-term treatment of CML has a huge financial impact, for patients and for the public health systems. TKI discontinuation have been associated with substantial cost savings in CML treatment. In the EURO-SKI trial, there were estimated savings of €22 million (15). A recent Brazilian pharmaco-economic study estimated the saving costs of USD $1,540,340.00 over 29 years, based
on successful discontinuation of TKI in 19 patients (42). For this reason, pharmaco-economic analysis of CML treatment may have an important impact for Latin America. TFR in South America is also impaired by the lack of standardized laboratories and reimbursement for qPCR tests. Combined policies, designed by expert physicians, members of health care organizations and pharmaceutical industry, and public health systems could bring universal solutions and provide a protocol based on evidence that is equally efficient and sustainable.

**LA recommendation:**
- Each country should have epidemiological data about incidence, prevalence and cost-efficiency during CML treatment.
- Pharmaco-economic studies should be conducted as these will demonstrate the positive financial impact of TFR. This in turn will contribute to the approval of PCR testing during treatment and for TFR monitoring, making TFR feasible and safe.

and lipid profile after TKI discontinuation. Patients with CML with type 2 diabetes mellitus have reduction in fasting plasma glucose and glycosylated hemoglobin at 1 and 6 months while using imatinib (43). In the Brazilian discontinuation trials, polycythemia, hyperglycemia and hypertriglyceridemia were observed after stopping imatinib (44). The French guidelines recommends monitoring of fasting glucose and glycosylated hemoglobin in diabetic patients 3 to 6 months after the discontinuation of nilotinib, because of the effect of this drug in the glucose metabolism (45). Because of the drug-drug interaction of TKIs with most statins, they also suggest monitoring cholesterol levels every 3 to 6 months after TKI discontinuation.

Thyroid dysfunction is a common adverse event with TKI therapy, in particular with 2nd generation TKI. Under treatment with imatinib, nilotinib, and dasatinib, thyroid abnormalities were detected in 25%, 55%, and 70%, respectively (46). It is recommended to check T4 and thyroid-stimulating hormone levels 6 to 12 weeks after TKI discontinuation and to adjust the dose of thyroid replacement drugs if necessary.
A more frequent monitoring of international normalized ratio values in patients taking warfarin should be done after TKI discontinuation, because imatinib, dasatinib and nilotinib usually increases oral anticoagulant levels (47).

**LA recommendation:** After TKI discontinuation, additional monitoring of glucose levels, lipid profile and other comorbidities should be done.

**Conclusion**

Multiple studies have demonstrated that TKI cessation is feasible and safe in CML patients who have achieved a durable DMR on therapy. The concept of lifelong treatment for all patients is no longer a universal need for all patients. To make TFR a safe and possible new goal of therapy in Latin America, the focus of these recommendations takes into account peculiarities of CML management in the region that justify differences with previously published recommendations (Table 1).

However, we recognize that some questions remain unanswered, some points may be debatable, and revisions to the recommendations may be needed in the future as new knowledge emerges.

There is a need for local real-world evidence in this topic but while such data is being generated, agreement was reached on the importance and need to continue working cooperatively with colleagues and Health Care providers. We need to continue communicating the importance of adequate CML treatment in order to achieve each specific milestone to allow that at least some patients with CML only have to take the costly TKI treatment for a limited period of time and eventually attempt TFR. Clinical trials are still needed to solve pending issues such as biological investigations aimed at developing approaches that may expand the access to TKI discontinuation to more patients and better controlling LSCs to decrease the risk of relapse and eventually with the idea of curing the disease in all patients.

In conclusion, the present recommendations contribute to reassure the feasibility and safety of TKI treatment discontinuation in real-life clinical practice in LA, under close molecular monitoring. Resolution of TKI-related toxicity might translate into a potential health improvement for the patients, and shortening the
time on therapy for at least some patients will represent significant cost savings for health systems throughout the region.

Authorship

Contributions
CP, AIV and JC: Designed the project, formulated the questions to LALNET members, ordered the answers, filled in the questionnaire, participated personally in every meeting, wrote and revised the manuscript, approved the final version of the manuscript.
VA, KP and IG: Ordered the answers to the questions; participated personally in every meetings, wrote and revised the manuscript, and approved the final version of the manuscript.
CA, CB, RC, ND, VF, IL, LM, BM, JRN, LP, AIP, SU: Filled in the questionnaire, wrote and revised the manuscript, approved the final version of the manuscript.
MB and MC: Filled in the questionnaire, revised the manuscript, approved the final version of the manuscript.

Disclosure of Conflicts of Interest
CP: Research Funding (to the Institution): Pint Pharma. Speaker Honoraria: Novartis, Pfizer, BMS. Janssen, Pint Pharma/Takeda. Advisory Board: Novartis, Pfizer.
VAP: Research funding: Takeda, Dr Reddy’s, Amgen, Abbvie. Speaker Honoraria: Novartis, Janssen, Amgen, Aztra, Abbvie.
KP: Advisory Board: Astellas, Novartis. Speaker Honoraria: Pintpharma, EMS, Astellas
AIV: Speaker Honoraria: Novartis
CA: Advisory Board: Novo Nordisk, Amgen, Takeda, Legrand. Speaker Honoraria: Novo Nordisk, Janssen, Novartis, AbbVie.
CB: Advisory Board: Novartis. Speaker Honoraria: Novartis, EMS and Pint Pharma.
RC: Speaker Honoraria: Novartis, Janssen, Abbvie
LM: Advisory Board: AstraZeneca, Novartis. Speaker Honoraria: Novartis, Amgen, Sandoz, Roche, BMS, AstraZeneca, Pint-Pharma, Janssen.
BM: Speaker Honoraria: Novartis Pfizer, Pint Pharma/Takeda, BMS, Varifarma, BMS.
JRN: Research: Apellis, Pfizer, Speaker Honoraria: Abbvie, Novartis. Advisory Board: Tecnofarma, Novartis, Abbvie.
LP: Advisory Board: Novartis
SU: Advisory Board: Novartis, Pfizer, Janssen, Roche, Abbvie, Pint Pharma, TecnoFarma.
JC: Research support (to the institution): BMS, Novartis, Pfizer, Sun Pharma, Takeda
Consultant: Novartis, Pfizer, Takeda
MB, MC, ND, VF, IG, IL, AIP: No Conflict of interests
References

1. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348(11):994-1004.

2. Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017;376(10):917-27.

3. Bower H, Bjorkholm M, Dickman PW, Hoglund M, Lambert PC, Andersson TM. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. J Clin Oncol. 2016;34(24):2851-7.

4. Assunção PM, Lana TP, Delamain MT, Duarte GO, Zulli R, Lorand-Metze I, et al. Cardiovascular Risk and Cardiovascular Events in Patients With Chronic Myeloid Leukemia Treated With Tyrosine Kinase Inhibitors. Clin Lymphoma Myeloma Leuk. 2019;19(3):162-6.

5. Cortes J, Mauro M, Steegmann JL, Saglio G, Malhotra R, Ukopec JA, et al. Cardiovascular and pulmonary adverse events in patients treated with BCR-ABL inhibitors: Data from the FDA Adverse Event Reporting System. Am J Hematol. 2015;90(4):E66-72.

6. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-84.

7. Sasaki K, Kantarjian HM, O'Brien S, Ravandi F, Konopleva M, Borthakur G, et al. Incidence of second malignancies in patients with chronic myeloid leukemia in the era of tyrosine kinase inhibitors. Int J Hematol. 2019;109(5):545-52.

8. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicoli n F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010;11(11):1029-35.

9. Mahon FX. Discontinuation of tyrosine kinase therapy in CML. Ann Hematol. 2015;94 Suppl 2:S187-93.

10. Mahon FX, Boquimpani C, Kim DW, Benyamin i N, Clementino NCD, Shuvaev V, et al. Treatment-Free Remission After Second-Line Nilotinib Treatment in Patients With Chronic Myeloid Leukemia in Chronic Phase: Results From a Single-Group, Phase 2, Open-Label Study. Ann Intern Med. 2018;168(7):461-70.

11. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gome z Casares MT, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. Leukemia. 2017;31(7):1525-31.

12. Takahashi N, Tauchi T, Kitamura K, Miyamura K, Saburi Y, Hatta Y, et al. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. Int J Hematol. 2018;107(2):185-93.

13. Ross DM, Branford S, Seymour JF, Schwarzer AP, Arthur C, Yeung DT, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. Blood. 2013;122(4):515-22.

14. Okada M, Imagawa J, Tanaka H, Nakamae H, Hino M, Murai K, et al. Final 3-year Results of the Dasatinib Discontinuation Trial in Patients With Chronic Myeloid Leukemia Who Received Dasatinib as a Second-line Treatment. Clin Lymphoma Myeloma Leuk. 2018;18(5):353-60.e1.
15. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol. 2018;19(6):747-57.
16. Pagnano K, Miranda E, Torresian M, Oliveria G, Virgilio B, Vianna J, et al. Pilot Study of Imatinib Discontinuation in Patients with Chronic Myeloid Leukemia with Deep Molecular Response (EDI-PIO) — Evaluation of Pioglitazone in Treatment-Free Remission. Blood. 2017;130.
17. Pagnano K. Study of Imatinib Discontinuation in Chronic Myeloid Leukemia With Deep Molecular Response (EDI-PIO). ClinicalTrialsgov Identifier: NCT028524862016.
18. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-84.
19. Deninger M, Shah N, Altman J. NCCN Guidelines: Chronic Myeloid Leukemia. National Comprehensive Cancer Network (NCCN) Guidelines [Internet]. 2019.
20. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JWM, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv41-iv51.
21. Ruiz MS, Sánchez MB, Vera Contreras YM, Agrielo E, Alonso M, Altuna ME, et al. Programme for Harmonization to the International Scale in Latin America for BCR-ABL1 quantification in CML patients: findings and recommendations. Clin Chem Lab Med. 2020;58(12):2025-35.
22. Rea D, Mahon FX. How I manage relapse of chronic myeloid leukaemia after stopping tyrosine kinase inhibitor therapy. Br J Haematol. 2018;180(1):24-32.
23. Etienne G, Guilhot J, Rea D, Rigal-Huguet F, Nicolini F, Charbonnier A, 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):298-305.
24. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-Bresler A, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. Blood. 2017;129(7):846-54.
25. Dao K-H, Tyner J. What’s different about atypical CML and chronic neutrophilic leukemia? Hematology Am Soc Hematol Educ Program. : Am Soc Hematol; 2015. p. 264-71.
26. Ross DM, Masszi T, Gomez Casares MT, Hellmann A, Stentoft J, Conneally E, et al. Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENESTfreedom study. J Cancer Res Clin Oncol. 2018;144(5):945-54.
27. Rea D, Nicolini, E F, Tulliez, Michel, Rousselot, et al. Prognostication of Molecular Relapses after Dasatinib or Nilotinib Discontinuation in Chronic Myeloid Leukemia (CML): A FI-LMC STOP 2G-TKI Study Update. Blood. 2019;134:30.
28. Hughes T, Boquimpani C, Takahashi N, Benyamini N, Clementino N, Shuvaev V. ENEStop 192-week results: Treatment-free remission (TFR) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after stopping second-line (2L) nilotinib (NIL). Journal of Clinical Oncology. 2019;37:7005.
29. Zorrilla Ayllon I. El paciente con cáncer: estrategias terapéuticas Impacto emocional y Social del Cáncer. In: Paradigma G, editor. Impacto Emocional y Social del Cáncer2007. p. 63-91.
30. Boquimpani C, Szczudlo T, Mendelson E, Benjamin K, Masszi T. Attitudes and Perceptions of Patients (pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Toward Treatment-Free Remission (TFR). Blood. 2014;124(21):4547-454.

31. Saglio G, Sharf G, Almeida A, Bogdanovic A, Bombaci F, Ćugurović J, et al. Considerations for Treatment-free Remission in Patients With Chronic Myeloid Leukemia: A Joint Patient-Physician Perspective. Clin Lymphoma Myeloma Leuk. 2018;18(6):375-9.

32. Tralongo P, Ferraù F, Borsellino N, Verderame F, Caruso M, Giuffrida D, et al. Cancer patient-centered home care: a new model for health care in oncology. Ther Clin Risk Manag. 2011;7:387-92.

33. Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. J Clin Oncol. 2014;32(5):424-30.

34. Fava C, Rege-Cambrin G, Dogliotti I, Cerrano M, Berchialla P, Dragani M, et al. Observational study of chronic myeloid leukemia Italian patients who discontinued tyrosine kinase inhibitors in clinical practice. Haematologica. 2019;104(8):1589-96.

35. Papalexandri A, Saloum R, Anagnostopoulos A. Blast Crisis of CML After TKI Discontinuation in a Patient With Previous Stable Deep Molecular Response: Is It Safe to Stop? HemaSphere. 2018;2(6):e157.

36. Richter J, Söderlund S, Lübking A, Dreimane A, Lotfi K, Markevärn B. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? Journ Clin Oncol. 2014;32(25):2821-3.

37. Katagiri S, Tauchi T, Saito Y, Suguro T, Asano M, Yoshizawa S, et al. Musculoskeletal pain after stopping tyrosine kinase inhibitor in patients with chronic myeloid leukemia: a questionnaire survey. Rinsho Ketsueki. 2016;57(7):873-6.

38. Berger M, Pereira B, Oris C, Saugues S. Osteoarticular Pain after Discontinuation of Tyrosine Kinase Inhibitors (TKI): A French Cohort Blood. 2015;126(23).

39. Mahon FX. Treatment-free remission in CML: who, how, and why? Hematology Am Soc Hematol Educ Program. 2017;2017(1):102-9.

40. Berger MG, Pereira B, Rousselot P, Cony-Makhoul P, Gardembas M, Legros L, et al. Longer treatment duration and history of osteoarticular symptoms predispose to tyrosine kinase inhibitor withdrawal syndrome. Br J Haematol. 2019;187(3):337-46.

41. Narra R, Flynn K, Atallan E. Chronic Myeloid Leukemia- The Promise of Tyrosine Kinase Inhibitor Discontinuation. Curr Hematol Malig Rep. 2017;12(5):415-23.

42. Centrone R. Impacto financeiro da descontinuação de imatinibe – um estudo farmacoeconômico. Hematology, transfusion and cell therapy. Hematology, Transfusion and Cell Therapy. 2019;41(Abstract 442):S168.

43. Gómez-Sámano M, Baquerizo-Burgos JE, Coronel MFC, Wong-Campoverde BD, Villanueva-Martinez F, Molina-Botello D, et al. Effect of imatinib on plasma glucose concentration in subjects with chronic myeloid leukemia and gastrointestinal stromal tumor. BMC Endocr Disord. 2018;18(1):77.

44. Pagnano K, FernandaMiranda, ElianaBendit, Isabel. Duration of Major Molecular Response and Discontinuation in Deep Molecular Response (MR4.5) Were Associated with Longer Treatment-Free Survival after Imatinib Discontinuation - Results from Two Prospective Brazilian Trials. Blood. 2019;134:1655.
45. Rea D, Ame S, Berger M, Cayuela JM, Charbonnier A, Coiteux V, et al. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia: Recommendations for clinical practice from the French Chronic Myeloid Leukemia Study Group. Cancer. 2018;124(14):2956-63.

46. Kim TD, Schwarz M, Nogai H, Grille P, Westermann J, Plockinger U, et al. Thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Philadelphia chromosome-positive chronic myeloid leukemia. Thyroid. 2010;20(11):1209-14.

47. Asnani AM, Anastasia Mansour, Moussa Ruskin, Jeremy Hochberg, Ephrain Ptaszek, Leon. Management of atrial fibrillation in patients taking targeted cancer therapies. Cardio-Oncology. 2017;3.

| Table 1 |
|----------------------------------|
| **Patient selection** |
| **TKI treatment duration** | A minimum of 5 years of TKI treatment is recommended before considering TFR |
| **Deep molecular response (DMR) duration and qPCR assay considerations** | - A minimum of 2 years of sustained DMR duration (DMR, defined as MR 4.5 (BCR-ABL1 IS ≤ 0.0032%), is required to consider discontinuation. Sustained DMR must be demonstrated on at least 4 IS qPCR tests, separated by at least 3 months, in the immediate prior 2 years. |
| | - It is recommended to confirm the DMR with a reliable qPCR (MR 4.5 IS), no more than 30 days before treatment discontinuation. |
| | - If adequate IS qPCR is not available, the group strongly recommends not to attempt TFR. |
| **Status of the disease at diagnosis** | - Only patients in first chronic phase CML should be considered for TFR. |
| **Type of BCR/ABL transcript** | - All patients considered for TFR must have a transcript at diagnosis (b3a2 b3a2 [e14a2] y / o b2a2 [e13a2], typic isoform of p210) |
| **Sokal score** | - Sokal risk at diagnosis should not be used as a criterion to define TFR candidates, but patients with high-risk Sokal score should be informed of the possibility of a higher risk of molecular relapse |
| **Failure to first line TKI** | - TFR should only be considered in CP CML patients under treatment with 2nd line TKI therapy when the indication for change was due to intolerance and not for resistance. |
| **Psychosocial considerations and communication before and during TFR** |
| | - The psychosocial situation of each patient should be analyzed when TFR is being considered. |
| | - Risk of molecular relapse should be clearly discussed with the patient before attempting TFR. |
| | - During the initial information session, enough emphasis should be made on the importance of close follow-up and the need for lifelong monitoring since TFR does not mean a cure. |
| | - During monitoring physicians should be alert for any signs of anxiety and seek professional psychological help if needed. |
| **Clinical and Molecular Monitoring during TFR** |
| **Optimal frequency of monitoring after treatment discontinuation** | - Monthly qPCR during the first 6 months after discontinuation. |
| | - Every 2 or 3 months qPCR monitoring from months 7 to 12. |
| | - Every 3 months qPCR from month 13, indefinitely. |
| **Definition of Molecular Relapse** | - Lost of MMR defined as BCR-ABL IS >0.1% is considered molecular relapse and should trigger TKI reintroduction. |
| **Monitoring after TKI re-initiation** | - Patients should be monitored every 2-3 months after TKI reintroduction, until achieving MR4.0. Then, every 3-6 months. If the patient does not regain MMR in 3-6 months, mutation screening is recommended. |
| **Withdrawal syndrome Monitoring and management of withdrawal syndrome** | - Adequate information about withdrawal syndrome should be provided to patients when considering TFR. Patients should be actively monitored for osteoarticular symptoms. |
| **Important considerations for TFR in LA: Pharmaco-economics** |
| **Considerations** | - Each country should have epidemiological data about incidence, prevalence and cost-
efficiency during CML treatment. Pharmaco-economic studies should be conducted as these will demonstrate the positive financial impact of TFR. This in turn will contribute to the approval of PCR testing during treatment and for TFR monitoring, making TFR feasible and safe.

| Additional laboratory follow up after discontinuation |
|-------------------------------------------------------|
| **Recommended labs**                                  |
| - After TKI discontinuation, additional monitoring of glucose levels, lipid profile and other comorbidities should be done. |