Accepted Manuscript

Considerations for treatment-free remission in patients with chronic myeloid leukemia: a joint patient-physician perspective

Giuseppe Saglio, Giora Sharf, Antonio Almeida, Andrija Bogdanovic, Felice Bombaci, Jelena Čugurović, Nigel Deekes, Valentín Garcia-Gutiérrez, Jan de Jong, Šarūnas Narbutas, Peter Westerweel, Daniela Zackova

PII: S2152-2650(18)30385-9

DOI: 10.1016/j.clml.2018.04.005

Reference: CLML 1098

To appear in: *Clinical Lymphoma, Myeloma and Leukemia*

Received Date: 18 April 2018

Accepted Date: 19 April 2018

Please cite this article as: Saglio G, Sharf G, Almeida A, Bogdanovic A, Bombaci F, Čugurović J, Deekes N, Garcia-Gutiérrez V, de Jong J, Narbutas Š, Westerweel P, Zackova D, Considerations for treatment-free remission in patients with chronic myeloid leukemia: a joint patient-physician perspective, *Clinical Lymphoma, Myeloma and Leukemia* (2018), doi: 10.1016/j.clml.2018.04.005.

Title: Considerations for treatment-free remission in patients with chronic myeloid leukemia: a joint patient-physician perspective.

Names of authors: Giuseppe Saglio,[1] Giora Sharf,[2] Antonio Almeida,[3] Andrija Bogdanovic,[4] Felice Bombaci,[5] Jelena Čugurović,[6] Nigel Deekes,[7] Valentín Garcia-Gutiérrez,[8] Jan de Jong,[9] Šarūnas Narbutas,[10] Peter Westerweel,[11] and Daniela Zackova[12]

Authors' affiliations:
[1]Department of Clinical & Biological Sciences, University of Turin, Turin, Italy;
[2]CML Advocates Network, Netanya, Israel;
[3]Hospital da Luz, Lisbon, Portugal;
[4]Clinical Centre of Serbia, University of Belgrade, School of Medicine, Belgrade, Serbia;
[5]Gruppo AIL Pazienti Leucemia Mieloide Cronica, Rome, Italy;
[6]CML Association of Serbia, Belgrade, Serbia;
[7]CML UK, Birmingham, UK;
[8]Hospital Universitario Ramón y Cajal, Ramón y Cajal Health Research Institute, Madrid, Spain;
[9]Hematon Foundation, Utrecht, The Netherlands;
[10]POLA, Lithuanian Cancer Patient Coalition, Kaunas, Lithuania;
[11]Albert Schweitzer Hospital, Dordrecht, The Netherlands;
[12]Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Brno, Czech Republic

Running head: Joint patient-physician perspectives on TFR in CML

Contact information for correspondence: Giuseppe Saglio gsaglio@unito.it

Word count:
Abstract: 198 words
Main text: 2,256 words

Acknowledgements
The authors would like to thank Cello Health iScience for editorial assistance.

Abstract: Treatment-free remission after discontinuation of tyrosine kinase inhibitor therapy is now an emerging treatment goal in patients with chronic myeloid leukemia, who have achieved a deep and stable response to treatment. While guidance are now available, considering patients' questions on this progressive concept have yet to be addressed. The overall aim of this European Steering Group is a patient-centered approach that educates patients on their treatment options, including treatment-free remission, facilitates better patient-physician relationships, and meets patients' emotional and psychological needs. This article outlines five key topic areas on discontinuing tyrosine kinase therapy and the implications of treatment-free remission for patient-physician consideration: what treatment-free remission is and when it is appropriate; which patients may and may not be eligible for treatment-free remission; what patient considerations for discontinuing therapy are, such as tyrosine kinase withdrawal syndrome, potential psychological implications, molecular recurrence and re-treatment. This Steering Group advocates that patients with chronic myeloid leukemia should have access to high quality, frequent molecular monitoring and be managed in a specialist centre with appropriate medical and psychological support. As patient concerns on attempting treatment-free remission become forefront in patient-physician discussions, a greater number of eligible patients may be willing to discontinue therapy.

Main text

Introduction: The introduction of tyrosine kinase inhibitors (TKIs) has considerably improved outcomes for patients with chronic myeloid leukemia (CML), with survival rates now almost equal to that of the healthy, general population. While incidence of this rare disease remains at about 1 case per 100 000 population,[1] improved survival has resulted in increased prevalence, and 400 000 patients with CML are expected in Europe by 2050.[2] With better survival and increasing prevalence of CML comes a different set of challenges for patients and physicians, including the side effects of continuous treatment on a patient's health, well-being and quality of life (QoL), and the increasing healthcare burden and costs associated with managing a lifelong disease.[2]

The concept of discontinuing TKI therapy in certain patients, an approach first put forward in 2006,[3] has the potential to reduce side effects associated with lifelong TKI therapy, and be a cost-effective measure for healthcare providers.[2] While discontinuation of TKI therapy is still largely conducted in controlled clinical trials, and standard protocols for TKI discontinuation in clinical practice are yet to be developed, there are guidelines and recommendations available for eligible patients considering TKI withdrawal and attempting treatment-free

remission (TFR).[2,4-7] This guidance considers both patient selection criteria, and the eligibility of centres to adequately follow up patients with standardized and timely molecular monitoring of *BCR-ABL1* transcripts.[4,6,8]

Treatment-free remission after discontinuation of TKI therapy is now an emerging treatment goal in patients who have a deep and stable response to treatment. For the purposes of this paper, TFR can be described as a state in which a patient with CML who has discontinued TKI therapy remains in major molecular response (MMR, also known as MR3.0, or a level of 0.1% on the international scale), thereby remaining free of TKI therapy. While recent 2017 guidelines on patient eligibility for discontinuing TKIs and attempting TFR are now available from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO),[4,8] with the European Leukemia Net (ELN) guidelines due to be published in early 2018,[6] publications considering patients' concerns and questions on this progressive concept have yet to be addressed.

With the patients' perspective in mind, a European Steering Group of six healthcare professionals (specialist hematologists) and six experienced CML patient advocates (some with a personal experience of TFR), convened in July 2017 in Vienna to discuss key areas and patient concerns relating to discontinuing TKI therapy in patients with CML. The overall aim of this Steering Group, founded in July 2016 from members of the CML Advocates Network (an international network connecting 116 patient organisations from 86 countries that advocate the sharing of best practice in CML), is for a patient-centred approach that addresses the unmet needs of patients with CML. The group's main objectives include: educating patients on their treatment options, including with respect to TFR, facilitating better patient-physician relationships using patient-empowerment as a means to improve CML care, and meeting patient needs (including emotional and psychological needs) within the CML community.

This article outlines five key topic areas/questions about discontinuing TKI therapy and the implications of TFR for patient-physician consideration (Table 1). In view of recent guidelines, this collective narrative also provides timely discussion points from an experienced Steering Group of specialist hematologists and CML patient advocates, offering a unique, joint patient-physician perspective that compliments current guidance and literature. For accessibility of information in this article, a glossary of terms is provided (Table 2).

What is treatment-free remission and when is it appropriate?

Treatment-free remission is achieved when a patient who has discontinued TKI therapy maintains MMR and does not need to restart therapy. Steering Group members agreed that, in general, patients in the chronic phase of CML with a stable, prolonged, and deep molecular response (DMR) for at least 2 years may be ready to discontinue TKI therapy and attempt TFR.

For patients in controlled clinical trials, the achievement of DMR can be defined as *BCR–ABL1* transcripts present at ≤0.01%, i.e. an MR4.0-, MR4.5-, MR5.0-log reduction from standardized baseline (MR4.0 or deeper).[8] In the largest TFR trial to date (EURO-SKI), achievement of MR4.0 was sufficient for TFR eligibility in many patients.[9] However, eligibility for the recent ENEST freedom study was based on the more stringent criteria of MR4.5 (*BCR–ABL1* transcript levels ≤0.0032%).[5]

Analysis of EURO-SKI data suggests that responses deeper than MR4 have no advantage in terms of long-term TFR,[9] but this finding has yet to be confirmed by ongoing trials, such as the ENESTPath trial (clinical trials identifier: NCT01743989).

Currently, the ESMO and NCCN guidelines recommend attempting TFR outside clinical trials, as long as proper, high-quality, well-regulated, and certified monitoring is ensured.[4,8]

The 2017 ESMO guidelines recommend that before discontinuing therapy, patients need to have achieved MR4.5, and a stability of DMR (at least MR4.0) for at least 2 years, after ≥5 years of TKI therapy.[8]

The NCCN guidelines state that TFR can be attempted in carefully selected patients who have achieved and maintained a DMR (≥MR4.0) for ≥2 years.[4]

Following the achievement of a stable DMR, TFR should be seen by the CML community as an option in CML treatment; it should not be thought of as a cure for CML, because molecular recurrence, both early and occasionally late, does occur in some patients.

Which patients may be eligible to attempt treatment-free remission?

Members of the Steering Group agreed that the following factors should be taken into account when a patient is considering a TFR attempt. Patients were in the chronic phase of CML at diagnosis, not have experienced resistance to any TKI therapy at any time, and to have been in DMR for at least 2 years. Patients also need to be well-informed about TFR, and well-motivated to discontinue treatment, but not feel under pressure to stop therapy.[4,7] Patients should also fully understand that molecular recurrence is not a 'failure', and that

treatment will be restarted. Molecular monitoring test results should also be available within 2–4 weeks.[4,7]

A longer duration of TKI therapy before attempting TFR is associated with a higher chance of sustaining a MMR.[9-11] Overall, for first-line TKIs, 31% of patients are eligible for TFR at 6 years.[12]

Which patients may not be eligible to attempt treatment-free remission?

For patients who have achieved MMR/MR3.0, but have not reached a DMR, and are therefore not eligible to attempt TFR, the Steering Group acknowledged that these patients should be reassured by their physicians that they have still reached a treatment goal/safe haven, and can continue on TKI treatment and have a similar life expectancy to the general population. If these patients continue to adhere to treatment they can remain on the same therapy and wait to reach a deeper molecular response, at which time, once sustained, TFR may be an option. If a patient wants to stop treatment and has a specific desire or need to change therapy, the physician should discuss with the patient the possibility of switching to a second-generation TKI that may enable a deeper molecular response to be achieved. At this time patients should be advised about the side effect profiles of TKI treatments.

The recommendations provided by the Steering Group are supported by the literature. Patients who have achieved a MMR/MR3.0 are at minimal risk of disease progression and have a similar life expectancy to the general population as long as they continue to adhere to their TKI therapy.[13,14] Patients who have not achieved a MR3.0 on their current therapy can be switched to a different TKI if necessary, which may increase their chances of attaining a DMR. Patients are more likely to achieve both a DMR on second-generation TKIs, and achieve this faster than on first-generation TKIs; adherence to therapy is a critical factor in achieving DMR.[8]

Patient considerations for discontinuing TKI therapy

The Steering Group recommends that physicians discuss the following points with patients thinking about discontinuing TKI therapy. Before discontinuing TKI therapy, the importance and frequency of follow-up visits should be emphasized and, therefore, the commitment from patients to attend clinics more frequently. Treatment-free remission does not mean a cure, and molecular recurrence may occur at any time, requiring TKI treatment to be restarted. Even if TFR is achieved, physicians should remind patients that they still need to attend routine clinic visits and undergo regular, lifelong monitoring.

TKI withdrawal syndrome

The Steering Group insists that physicians discuss TKI withdrawal syndrome with patients thinking about discontinuing TKI therapy, and how this can be managed. On withdrawal of TKI treatment, some patients may experience musculosketal pain; generally, this can be managed with over-the-counter pain medications. As well as ongoing disease surveillance, clinical monitoring enables the identification of long-term toxicity of previous TKI therapy, or even of its discontinuation; withdrawal symptoms should be monitored and treated.

Study data have suggested that up to 30% of patients who stop TKI therapy experience withdrawal syndrome, usually in the form of musculoskeletal pain.[15-17] While TKI withdrawal syndrome can last months, it can often be managed with non-prescription drugs such as paracetamol or non-steroidal anti-inflammatories (NSAIDs), and, in more severe cases, corticosteroids.[16,17] TKI withdrawal syndrome does not appear to be dependent on the particular TKI the patient was taking before stopping therapy,[17] and occurrence of the TKI withdrawal syndrome has been associated with a higher chance of achieving successful TFR.[10]

Psychological implications of discontinuing TKI therapy and attempting treatment-free remission

While current guidelines do not address psychological issues related to discontinuing TKI therapy and attempting TFR, Steering Group members advocate that screening for potential psychological issues associated with TFR should form part of routine monitoring for patients, as professional psychological help may be necessary in certain patients. Physicians should also be aware that patients may experience anxiety as a result of fluctuating BCR-ABL1 blood levels during TFR.

It is well-recognized that psychological and emotional factors, as well as clinical variables, play a vital part in a patient's decision to discontinue TKI therapy, and these factors need to be considered when discussing TFR with patients.[18] The main reasons for patients wanting to discontinue TKIs are to reduce potential side effects of a long-term TKI therapy, decrease medication costs, and ease the inconvenience of taking daily medication.[19,20] The main anxiety that patients experience around stopping TKI therapy is a fear of disease recurrence or progression,[18,19] but, to date, this has not been documented.[2,7]

A recent Italian observational study found that about 82% of patients would be willing to stop TKI therapy if their disease was likely to remain stable, and there was a high probability of response to TKI therapy if treatment needed to be restarted. Patients were also more likely

to attempt TFR if their risk of recurrence was less than 30%.[18] It is worth noting that not all patients who are eligible for TFR are willing to discontinue treatment. In a recent survey, 49% of Italian patients with CML (total n=1133) and 34% of US patients with CML (total n=84) would not discontinue treatment due to concerns over disease recurrence.[19,20] While patients and their physicians should discuss all concerns, including psychological and emotional concerns, of attempting TFR, it is recognized that, currently, these do not form part of a routine clinic visit.[20]

Molecular recurrence and retreatment

The Steering Group highlighted that patients should be prepared for drug-free periods which may last from only few months to many years, and recommended that physicians advise patients about the possibility of re-initiation of therapy due to molecular recurrence.

Data have shown that not all patients eligible for TFR can sustain a response once TKI therapy is discontinued: 40–60% of eligible patients have sustained TFR over 1–2 years.[4,5,7,10,11,21] Most molecular recurrences occur within the first 6 months of stopping TKI therapy,[11] and the confirmed loss of MR3.0 should be seen as a trigger for restarting therapy.[22] Late molecular recurrences do occur, so patient adherence to monitoring during TFR is vital to detect recurrence, and ensure protection from disease progression.[8,11] Factors that are potentially predictive of molecular recurrence are prior TKI treatment duration and prior duration of DMR.[2] Studies have shown that resuming TKI therapy immediately after loss of MMR results in regaining MMR in almost all patients. There is no risk, to date, of developing resistance to TKIs,[5,10,11,21] and attempting a second TKI discontinuation following molecular recurrence is possible, once a prolonged DMR has once more been achieved. There is some data to show that this may be effective in approximately 30% of cases after an adequate duration of the re-achieved DMR. The speed of molecular recurrence after the first attempt at TFR is the only factor associated with a poorer outcome on the second attempt.[23]

Conclusions

This Steering Group considers the patient's perspective, a potentially overlooked area of CML management.[2] This innovative approach, facilitating collaboration between specialist hematologists and CML patient advocates, highlights practical considerations for eligible patients attempting TFR, and advocates that patients with CML should have access to high quality, frequent molecular monitoring and be managed in a specialist centre with appropriate medical and psychological support. Despite the current uncertainties regarding which patients are the best candidates to attempt TFR, and what factors predict loss of

MMR/MR3.0 after discontinuing TKI therapy, treatment interruption is a safe option, providing there is adequate high quality and timely monitoring, and prompt reintroduction of TKI therapy once MMR/MR3.0 is lost. Worldwide, over 2,000 patients with CML have attempted TFR, and no instances of disease progression have been reported. It is possible that as attempting TFR becomes a standard part of CML care, and patients' concerns are forefront to patient-physician discussions, a greater number of eligible patients may be willing to discontinue TKI therapy and attempt treatment-free remission.

Table 1. Summary of Steering Group discussion recommendations for physicians and their patients with CML considering discontinuation of tyrosine kinase inhibitor (TKI) therapy and attempting treatment-free remission (TFR)

	Summary of Steering Group recommendations for patient-physician discussion
Treatment goals in CML	The initial treatment goal is rapid reduction of tumour burden/number of leukemic cells, with best OS in the long-term, as well as for patients to achieve the same QoL as before their CML diagnosis
What is TFR and when is it appropriate?	TFR is achieved when a patient who has discontinued TKI therapy maintains MMR and does not need to restart therapy. In general, patients in the chronic phase of CML with a stable, prolonged and DMR for at least 2 years may be ready to discontinue TKI therapy and attempt TFR
Which patients may be eligible to attempt TFR?	The following factors should be considered before attempting TFR: • Patients were in the chronic phase of CML at diagnosis, not have experienced resistance to any TKI therapy at any time, and to have been in DMR for at least 2 years • Patients need to be well-informed about TFR, well-motivated to discontinue treatment, but not under pressure to stop therapy[4,7] • Patients should fully understand that molecular recurrence is not a 'failure', and that treatment will be restarted • Molecular monitoring test results should be available within 2–4 weeks[4,7]
Which patients may not be eligible to attempt TFR?	Patients who have achieved MMR/MR3.0, but have not reached a DMR, and are therefore not eligible to attempt TFR, should be reassured by their physicians that they have still reached a treatment goal/safe haven and can continue on TKI treatment and have a similar life expectancy to the general population: • If these patients continue to adhere to treatment they can remain on the same therapy and wait to reach a deeper molecular response, at which time, once sustained, TFR may be an option • If a patient wants to stop treatment and has a specific desire or need to change therapy, the physician should discuss with the patient the possibility of switching to a second-generation TKI that may enable a deeper molecular response to be achieved. At this time, patients should be advised about the different side effect profiles of TKI treatments
Patient considerations for discontinuing TKI therapy	The following factors should be considered before a patient discontinues TKI therapy: • Physicians should emphasize the importance and frequency of follow-up visits, and therefore the commitment from patients to attend clinics more frequently • TFR does not mean a cure, and molecular recurrence may occur at any time, requiring TKI treatment to be restarted • Even if TFR is achieved, physicians should remind patients that they still need to attend routine clinic visits and undergo regular, lifelong monitoring
TKI withdrawal syndrome	Physicians should discuss TKI withdrawal syndrome with patients thinking about discontinuing TKI therapy, and how this can be managed. On withdrawal of TKI treatment, some patients may experience musculoskeletal pain; generally this can be managed with over-the-counter pain medications. As well as ongoing disease surveillance, regular clinical monitoring enables the identification of long-term toxicity of previous TKI therapy, or even of its discontinuation; withdrawal symptoms should be monitored and treated
Psychological implications of discontinuing TKI therapy and attempting TFR	While current guidelines do not address psychological issues related to discontinuing TKI therapy and attempting TFR, Steering Group members advocate that screening for potential psychological issues associated with TFR should form part of routine monitoring for patients, as professional psychological help may be necessary in certain patients. Physicians should also be aware that patients may experience anxiety as a result of fluctuating blood levels of *BCR-ABL1* during TRF monitoring
Molecular recurrence and retreatment	Patients should be prepared for drug-free periods which may last from only a few months to many years, and physicians need to explain and advise patients about the possibility of re-initiation of therapy due to molecular recurrence

CML, chronic myeloid leukemia; DMR, deep molecular response; MMR, major molecular response; OS, overall survival; QoL, quality of life; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor

Table 2. Glossary of terms

Glossary of terms	
BCR-ABL1	Fusion gene responsible for chronic myeloid leukemia (CML)
Deep molecular response (DMR)	*BCR-ABL1* transcripts present at ≤0.01% (MR4.0, MR4.5, MR5.0) according to the International Scale
International Scale (IS)	Standardization of the level of *BCR-ABL1* transcripts in patients with CML to allow common evaluation of treatment response
Major molecular response (MMR/MR3.0)	*BCR-ABL1* transcripts at 0.1% or less on the International Scale
Molecular monitoring	Analysis of percentage of *BCR-ABL1* transcript in peripheral blood to determine response to TKI therapy
Molecular recurrence	The loss of major molecular response (MMR/MR3.0) and the trigger for restarting TKI therapy
Transcript	RNA molecule derived from the transcription of a specific gene
Treatment-free remission (TFR)	A state in which a patient with chronic CML who has discontinued TKI therapy maintains major molecular response and does not need to restart therapy
Tyrosine kinase	An enzyme that is able to phosphorylate proteins and is produced by cells to control and regulate growth and differentiation processes
Tyrosine kinase inhibitor (TKI)	Targeted drugs that are able to inhibit the tyrosine kinase activity of BCR-ABL proteins, and used to treat patients with CML

References

1. Hoffman V, Baccarani M, J Hasford, et al. The EUTOS population-based registry: Incidence and clinical characteristics of 2904 CML patients in 20 European countries. Leukaemia. 2015;29:1136-1143.
2. Saußele S, Richter J, Hochhaus A, Mahon F-X. The concept of treatment-free remission in chronic myeloid leukemia. Leukaemia. 2016;30:1638-1647.
3. Goldman J & Gordon M. Why do chronic myelogenous leukemia stem cells survive allogeneic stem cell transplantation or imatinib: does it really matter? Leukemia & Lymphoma. 2006;47(1):1-7.
4. Radich, J. P. NCCN Clinical Practice Guidelines in Oncology: Chronic myeloid leukemia. *Hematol. Oncol. Clin. North Am.* **17,** 1159–1173 (2017).
5. Hochhaus A, Masszi T, Giles FJ, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. Leukemia. 2017;31:1525-1531.
6. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884.
7. Hughes TP & Ross DM. Moving treatment-free remission into mainstream clinical practice in CML. Blood. 2016;128(1):17-23.
8. Hochhaus A, Saußele S, Rosti G, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017;28(supplement 4):iv41-iv51.
9. Mahon F-X, Richter J, Guilhot J, et al. Cessation of Tyrosine Kinase Inhibitors Treatment in Chronic Myeloid Leukemia Patients with Deep Molecular Response: Results of the Euro-Ski Trial. Blood. 2016;128(22):787.
10. Lee S-E, Choi SY, Song H-Y, et al. Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: The KID study. Haematologica. 2016;101(6):717-723.
11. Mahon F-X, Réa D, Guilhot J, 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;11:1029-1035.
12. Geelen I, Thielen N, Janssen J, et al. Treatment outcome in a population-based 'real-world' cohort of chronic myeloid leukemia patients. Haematologica. 2017;102(11):1842-1849.
13. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow up of patients receiving imatinib for chronic myeloid leukemia. New England Journal of Medicine. 2006;355(23):2408-2417.
14. Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM-L. Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. J Clin Oncol. 2016;34(24):2851-2857.
15. Richter J, Soderlund S, Lubking A. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? J Clin Oncol. 2014;32(25): 2821-2823.
16. Park JS, Lee S-E, Jeong SH, et al. Change of health-related profiles after imatinib cessation in chronic phase chronic myeloid leukemia patients. 2015;57(2):341-347.
17. Berger MG, Pereira B, Oris C, et al. Osteoarticular pain after discontinuation of tyrosine kinase inhibitors (TKI): A French cohort. Blood. 2015;126(23):137.
18. Riva S, Cortelezzi A, Cutica I, et al. The role of psychological variables for tyrosine kinase inhibitors (TKI) discontinuation in chronic myeloid leukemia (CML) patients:

implication for medical decision making practice. Poster presented at: 22nd Congress of the European Hematology Association; 2017 Jun 22-25; Madrid, Spain.

19. Goldberg S & Hamarman S. Patients with chronic myelogenous leukaemia may not want to discontinue tyrosine kinase inhibitor therapy. Blood. 2015;126(23):1584.
20. Breccia M, Efficace, F, Sica S, et al. Adherence and future discontinuation of tyrosine kinase inhibitors in chronic phase chronic myeloid leukemia. A patient-based survey on 1133 patients. Leukemia Research. 2015;39:1055-1059.
21. Ross DM, Branford S, Seymour JF, 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):515-522.
22. Rousselot P, Charbonnier A, Cony-Makhoul P, 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):424-430.
23. Legros L, Nicolini FE, Etienne G, et al. Second tyrosine kinase inhibitor discontinuation attempt in patients with chronic myeloid leukemia. Cancer. 2017;123(22):4403-4410.