Understanding Treatment-Free Remission and How It Impacts You

Frequently Asked Questions for Patients and Advocates

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1 What is treatment-free remission (TFR)?

TFR is a deliberate, carefully monitored cessation of therapy embarked upon by patients after discussion and agreement with their doctors. When it works, the outcome has been described as a "functional cure"—cure meaning the patient has completed treatment and is in remission; functional because many patients may still have evidence of chronic myeloid leukemia (CML) by a polymerase chain reaction (PCR) test but remain stable and safe off treatment.

CML Chronic Myeloid Leukemia is a cancer of the white blood cells. Ph+ CML is caused by the protein encoded by the abnormal fusion gene, BCR-ABL

PCR Polymerase Chain Reaction is a lab technique used to make many copies of a DNA segment, such as the BCR-ABL gene, enabling its detection even in very low amounts. In CML, PCR is used to measure levels of BCR-ABL for monitoring response to treatment

Is it different from a drug holiday?

Although patients in TFR do stop taking their CML medication, it is much more than a "drug holiday." The goal is to achieve continued deep remission without treatment. There are specific requirements to try TFR, the main one being a stable deep molecular response over time. Strict monitoring and prompt action (such as retreatment) in case of relapse are necessary to make it a safe and reasonable pursuit.

2 What are the disease monitoring requirements to try TFR?

What test is required?

The blood test used to monitor levels of *BCR-ABL* in patients attempting TFR is a quantitative PCR. Test results should be reported on the International Scale (IS) to allow alignment of results between laboratories. PCR can reliably detect deep responses to treatment, down to 0.01% of the *BCR-ABL* levels found in untreated CML per the IS (known as MR4) or even 0.0032% (known as MR4.5).

How often is testing done?

According to available guidelines, testing needs to be done monthly for the first 6 months of TFR, then every 6 weeks for the next 6 to 18 months. After 2 years, monitoring can continue every 3 months.

Recommended PCR Testing During TFR

Will I need testing for the rest of my life?

It is recommended that patients with successful TFR continue to be monitored indefinitely.

Can I be monitored through standard blood tests?

Standard blood tests are not a good way to monitor TFR because they cannot detect very low BCR-ABL levels. PCR testing, on the other hand, can detect very low BCR-ABL levels such as those in patients with major molecular response (MMR) or deeper molecular responses. When a patient is in TFR, their BCR-ABL levels need to be monitored closely to make sure they do not lose MMR. If they do, they must restart treatment promptly.

MMR Major Molecular Response means that the amount of BCR-ABL has been reduced to 0.1% of what it would be if untreated. Achieving MMR can reduce the risk of CML

3 What if I want to try TFR, but my local laboratory doesn't have adequate testing methods?

To be monitored correctly for a safe TFR attempt, patients need PCR testing. For PCR testing to be considered adequate, it must be readily available and sensitive enough to detect low level changes; a quick turnaround is also necessary. If your local laboratory does not have these testing options available, PCR kits can be reliably sent to a reference laboratory. If you are interested in this option, you should discuss it with your doctor. Keep in mind that this option can present challenges at different steps, such

as having blood drawn into the prepared kits, shipping and handling of the sample, and having results reported, so it is best to try it before stopping medication to ensure that it works smoothly. TFR may be possible even under seemingly challenging circumstances if we plan carefully.

Laboratory Requirements for Safe Monitoring of TFR:

Performs high-quality, accurate, sensitive, International Scale real-time quantitative PCR

+

Can provide PCR test results within 4 weeks

+

Can perform PCR test every 4 to 6 weeks, as needed

+

Regular follow-up for prompt intervention in case of relapse

Do I need to be tested at the same lab every time?

It is recommended to have your PCR test at the same laboratory every time if possible because it decreases variability. Even within the same laboratory, tests can have some variation, so adding laboratory-to-laboratory variability can make it harder to interpret any change in your test results. If you cannot use the same laboratory every time, working with a laboratory that uses the International Scale is a critical factor for consistency in your PCR test results. The IS should minimize variability; therefore, using multiple laboratories that report on the IS is reasonable.

4 How long does the process of attempting TFR usually last?

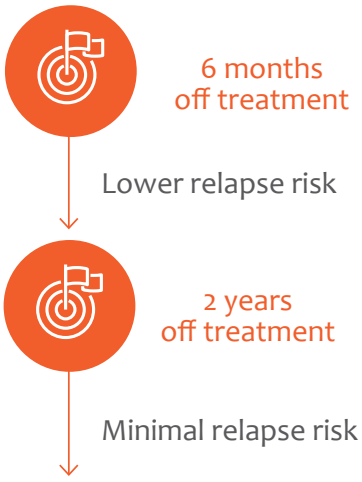
TFR can be broken down into phases or periods of time:

- Before someone can stop their CML medication (TKI), there is generally a required period of time on medication and a minimum period of time in stable and deep molecular remission, meaning either MR4 or MR4.5. This can be called the "monitoring phase"
- During the first 6 months of attempting TFR, patients are monitored monthly. This is the most crucial period because relapse (an increase in BCR-ABL level that results in loss of MMR) is most likely to happen during this time
- If someone has passed the 6-month mark and remains in relatively stable deep molecular response, their chance of relapse decreases dramatically but not entirely. The next 18 months are a period of continued monitoring (every 6 weeks), where "late relapse" is possible, but occurs in a smaller fraction of patients
- The risk of relapse after 2 years in TFR is even smaller but not zero; therefore, monitoring is done every 3 months

How is TFR success measured?

TFR success is measured by a patient feeling well off treatment and reaching key time milestones with a deep molecular response:

Key TFR Milestones

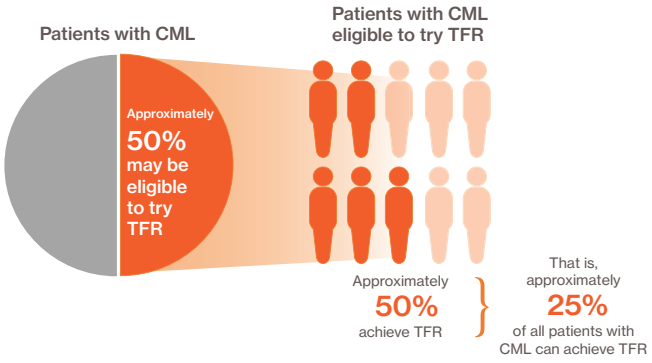


In clinical trials studying TFR, some patients have been off treatment for more than 10 years. However, currently, most patients in TFR have a shorter duration of TFR.

5 How common is TFR among the CML popuation?

What are the chances of success with TFR?

After 5 years of treatment with a tyrosine kinase inhibitor (TKI) medication, approximately 30% to 60% of patients with CML (depending on which TKI they receive) achieve the deep molecular responses required to try TFR. This means that not everyone will be able to consider TFR, at least at this time. However, with access to second-generation TKIs (nilotinib, dasatinib, and bosutinib) as first-line treatment and/or maximal use of imatinib, roughly half of CML patients could eventually be eligible for TFR. The success rate of TFR is approximately 50%, so an estimated 20% to 25% of patients with CML can achieve TFR.



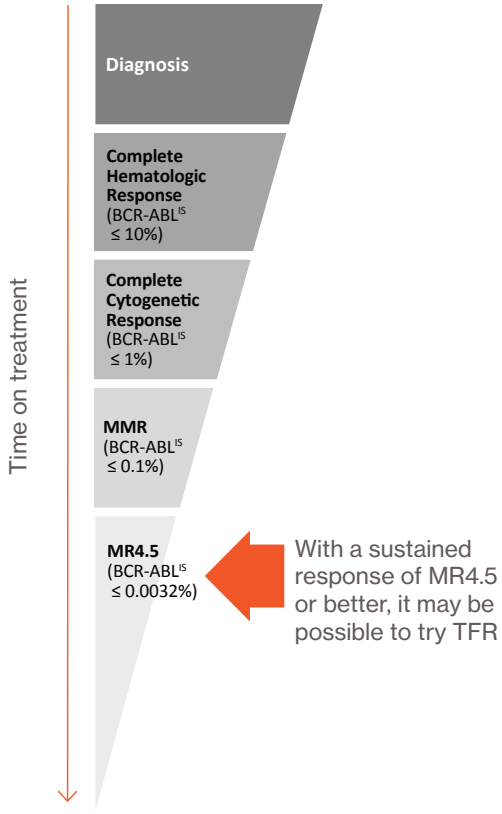
The chance of successful TFR is roughly 50%; this has been consistent across clinical trials for more than a decade even though the requirements to try TFR have evolved over the last few years. What is also consistent is that, in most cases, relapse (loss of MMR—which is grounds to restart treatment) occurs within 6 months of stopping treatment. The number of people who lose MMR between 6 and 18 months is much lower.

6 Does TFR mean that CML can be completely cured?

The term that is used for successful TFR in CML is "functional cure." In most cancer treatments, a cure is defined as the absence of any signs of the disease and being off treatment for enough time that relapse is unlikely to happen. A "functional cure" means not having "active" disease and not needing treatment for the cancer, even if there is some sign of the cancer. This is the case with CML; many patients in successful TFR still show a sign of the disease (trace amounts of *BCR-ABL*) with standard PCR testing.

How long does it take to achieve a "functional cure"?

In CML, a "functional cure" means that a person has been off treatment without loss of MMR for more than 6 months, when it is more likely they will have a successful TFR. Based on our experience so far, a "functional cure" is more firmly established if the patient has been off treatment for 2 years or more without loss of MMR. Monitoring would still be needed in every case to track ongoing success.



7 What are the risks associated with TFR?

Can I develop TKI resistance?

Resistance has generally not been observed in the setting of TFR. After TFR failure and retreatment, there have been extremely rare cases of CML progression, with the odds appearing to be less than 1 in 1000. Retreatment with the same TKI that was stopped is highly effective, with rapid recovery of MMR, MR4, or MR4.5 in nearly all cases. Longer follow-up of patients for whom TFR was not successful in clinical trials will help confirm that there is no TKI resistance or incomplete recovery of deep remission, but the experience to date is very reassuring.

In case of relapse, would I restart the same medicine or try a new one?

Retreatment with the same TKI that was stopped has been highly effective in clinical studies. Some people may switch to a different TKI if they experienced some intolerance (troubling side effects) with the medicine they stopped. In the future, there will likely be better strategies for determining the best option for retreatment (for example, a different TKI or combinations of medicines) to make a second TFR attempt possible and more successful, but this needs to be studied further.

Should I expect the same symptoms after restarting treatment?

It is reasonable to expect that similar side effects from TKI treatment will return with retreatment. Although many people worry about side effects becoming worse, this is unlikely. In fact, given the fact that people—or their systems—may have grown accustomed to TKI side effects, sometimes side effects do not return as strongly as before.

What are the chances of regaining MMR?

Retreatment has been shown to be highly successful after an unsuccessful TFR attempt, based on studies in which patients had ongoing strict monitoring and retreatment occurred quickly after loss of MMR. Regaining MMR appears universal, and deep remission returns in nearly all patients. In time, the ongoing clinical studies will tell if there is any change in the quality of deep remission after retreatment. It is important not to delay retreatment, not to keep retesting to "see if it will go back down," and not to miss monitoring visits for fear of MMR loss. Information is power, and loss of MMR is powerful information that needs to be acted on to be safe.

8 How do I know if I'm a candidate to try TFR?

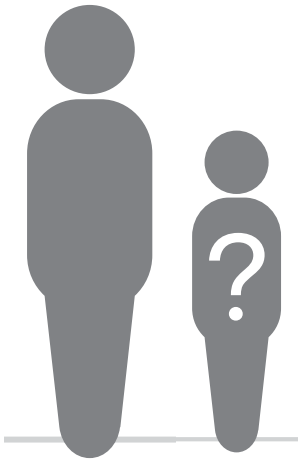
The requirements to be eligible for attempting TFR include:

- Age 18 years or older
- Chronic-phase CML without a history of accelerated- or blast-phase CML
- A non-high Sokal score at diagnosis (EU only; Sokal score is a risk assessment tool)
- TKI treatment (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least 3 years (US guidelines) or at least 5 years (EU/ESMO guidelines)
- Prior evidence of measurable *BCR-ABL*
- Stable molecular response (MR4) for 2 years, documented on at least 4 tests, performed at least 3 months apart (US guidelines); optimal response to first-line therapy, having reached MR4.5 (EU)
- Access to reliable IS PCR testing that can detect at least MR4.5 and provides results within 2 weeks (US; or 4 weeks in the EU)
- Being able to have PCR tests done every 4 to 6 weeks when required (EU); for most patients, monthly molecular monitoring for 1 year, then every 6 weeks for the second year, and every 12 weeks thereafter indefinitely for patients who remain in MMR (US)
- Promptly resuming TKI medication within 4 weeks of losing MMR, with monthly molecular monitoring until MMR is re-established; testing every 12 weeks thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after losing MMR
- Those who do not achieve MMR after 3 months of resuming TKI should be tested for *BCR-ABL* mutations and have molecular monitoring monthly for another 6 months
- Consulting with a CML Specialty Center to discuss eligibility to attempt TFR and the potential risks and benefits of stopping treatment, including TKI withdrawal syndrome (US)
- Reporting of the following to a member of the NCCN CML panel is strongly encouraged:

  1. Any significant side effect believed to be related to stopping treatment
  2. Progression to accelerated- or blast-phase CML at any time
  3. Not regaining MMR after 3 months from treatment reinitiation (US)

Can children be candidates to try TFR?

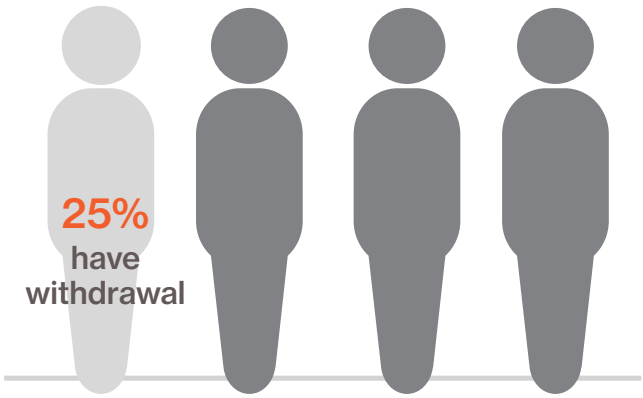
Research about TFR in children with CML is ongoing, and not as much is known about it as is known about TFR in adults. At this time, this would be considered a research question, but of course a good one to ask, and hopefully a path for children to have successful TFR will be developed. Don't hesitate to ask!



9 How do my physician and I prepare to try TFR?

Will I go through withdrawal?

Approximately 1 in 4 patients (25%) who stop a TKI will have withdrawal syndrome—physical symptoms that are caused by stopping the medication. This tends to be mild to moderate in intensity, mainly leading to muscle and joint aches and pains, and rarely skin symptoms (hives, hairfollicle rash). Stopping medication may remove effects that the TKI had on unintended targets and trigger an inflammatory response, almost like a brief allergic flare. In some cases, antihistamines may help.



Should I expect psychological/anxiety challenges?

There certainly can be many TFR-related challenges not just for the body but also for the mind. The first challenge is embracing the idea that this is a good plan—many immediately think, "Why on earth?" or "If it's not broken, don't fix it." TFR should always be viewed as an option, not a requirement or "must." It should be a decision made by the person, with the advice and guidance of their CML doctor and those who care for them (like loved ones). It needs to feel right. Studies have looked at the reasons why some choose TFR and some don't, the stress and anxiety such an endeavor brings about, and how to manage it. Communication and open dialogue are very important to help you work through the challenges; it's also important to be careful to not miss monitoring checks and understanding 'what is your PCR' is always important!

What does my physician need to know to manage my care in TFR?

CML SPECIALIST
A CML Specialist is someone who is very familiar with TFR requirements, the monitoring plan and retreatment strategy

Ideally a CML specialist—someone who is very familiar with TFR requirements, the monitoring plan, retreatment strategy, etc—should manage your care if you choose to attempt TFR. However, this may not always be possible. If the CML doctor managing the TFR has access to a CML specialist and they can work together to follow the rules carefully, this can also work well. It is a good idea to see a CML specialist at least once before making the decision to try TFR. The patient needs to be comfortable that their CML doctor can handle this important decision properly and safely. And as mentioned before, open dialogue along with easy access to the doctor's office and clinic and to the testing required needs to be worked out before attempting TFR.

Where can I find these specialists?

CML specialists are eager to help and can be found throug global organizations like The International CML Foundation (https://www.cml-foundation.org/), The Max Foundation (www.themaxfoundation.org), and the CML Advocates Network (https://www.cmladvocates.net), among others. Patients and CML doctors should be comfortable asking for help and advice on this very important topic from experts in the field at any time. People interested in TFR and CML doctors can easily find and use guidelines such as those from the National Comprehensive Cancer Network (NCCN) in the United State and the European Society for Medical Oncology (ESMO). The European LeukemiaNet (ELN) is another authority in the field, and their latest update of guidelines for CML should be available soon.

www.cml-foundation.org

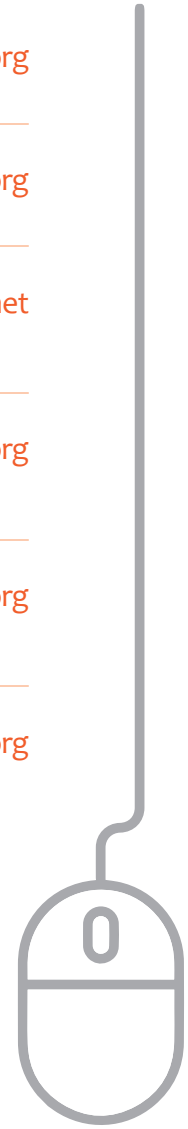
www.themaxfoundation.org

www.cmladvocates.net

www.nccn.org

www.esmo.org

www.leukemia-net.org



10 Can I take other medications while in TFR?

When someone is in TFR, medications and treatments for other health issues are reasonable. While off TKI therapy and in TFR, a "new normal" can be reached with little or no remaining concerns related to CML or its treatment. Of course, there were TKI side effects, stopping treatment may reduce the need for medication (although some TKI withdrawal symptoms may need treatment). TFR may offer an opportunity to see if medications needed during TKI therapy for side effects may no longer be necessary.

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