

No. 34 in a series providing the latest information for patients, caregivers and healthcare professionals

## Highlights

- Treatment of chronic myeloid leukemia (CML) has changed dramatically in the last two decades with the discovery of the *BCR-ABL1* fusion gene and the development of tyrosine kinase inhibitor (TKI) therapy.
- Treatment-free remission (TFR) is achieved when a patient who has discontinued TKI therapy maintains a deep molecular response (DMR) and does not need to restart treatment.
- Patients in the chronic phase of CML who have maintained a stable and deep molecular response (DMR) for at least two years are considered good candidates for TKI therapy discontinuation.
- Patient motivators to attempt TFR include convenience, economic savings and quality-of-life factors. CML patients may be reluctant to try this approach due to fear of relapse or disease progression.
- Patients should be advised that TFR periods may last from a few months to many years. The majority of patients who need to restart therapy are able to obtain and maintain a major molecular response again.
- The FDA expanded the approval of the drug **nilotinib (Tasigna®)** to include the safe discontinuation of this medication for a select group of patients who meet specific criteria.

## Introduction

The treatment of chronic myeloid leukemia (CML) has changed dramatically in the last two decades because of advances in the understanding of the disease as well as the very successful treatment of patients with CML by using tyrosine kinase inhibitor (TKI) therapy. Treatment-free remission (TFR) is now an emerging treatment goal for many patients with CML who have achieved a deep and stable response to treatment. Treatment-free remission is achieved when a patient who has discontinued TKI therapy maintains a deep molecular response (DMR) and does not need to restart treatment. This fact sheet offers information on treatment-free remission and includes patient eligibility, considerations for TKI discontinuation, and the potential psychosocial implications of this approach.

## About Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a type of blood cancer that accounts for 14 percent of estimated new cases of leukemia in 2018. The median age at diagnosis is 65 years; however, CML can occur in people of any age. In 2018, an estimated 8,430 people will be diagnosed with this disease in the United States. CML is distinguished from other cancers by the presence of the Philadelphia chromosome (Ph), abbreviated as Ph+ CML. The Philadelphia chromosome is the result of a reciprocal translocation between chromosomes 9 and 22 [t(9;22)]. The translocation gives rise to the fusion gene *BCR-ABL1*, a gene that is not found in normal blood cells. This gene directs the production of a protein called a tyrosine kinase, which causes too many white blood cells called granulocytes and/or too many platelets to be made.

CML occurs in three different phases (chronic, accelerated and blast phase) and is generally diagnosed in the chronic phase. If left untreated, chronic-phase CML will eventually progress to advanced-phase disease in about 3 to 5 years.

Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) for more information about chronic myeloid leukemia.

## Treatment-Free Remission for Chronic Myeloid Leukemia Patients

**The Evolution of CML Treatment.** Between the years 1970 and 2000, most patients with CML were treated with a drug called interferon, but eventually they needed a bone marrow transplant to have any realistic hope of long-term survival. Transplant was restricted to a small number of patients because of its high risk and toxicity. The discovery of the Philadelphia chromosome (Ph+) and the BCR-ABL1 tyrosine kinase revolutionized treatment. It allowed for the first targeted therapy for CML, **imatinib (Gleevec®)**, to be tested in the late 1990s.

Imatinib, a selective inhibitor of the ABL kinase, effectively blocked the proliferation (spread) of CML cells in the laboratory. This led to a clinical trial of patients with CML who had unfavorable responses to interferon, the preferred treatment at the time. Not only did imatinib result in better responses than interferon-based treatment but it was also much better tolerated by patients. In 2001, imatinib was the first TKI approved by the U.S. Food and Drug Administration to treat CML. Thus, it is called a “first-generation” TKI. Imatinib became the standard of care for CML, and hematopoietic transplantation was reserved for cases of TKI failure.

About ten years later, newer “second generation” TKIs further changed the outlook for CML patients. These newer drugs were able to induce faster and deeper responses and also offered an alternative treatment to the minority of patients who did not respond or could not tolerate imatinib therapy. The second-generation drugs **dasatinib (Sprycel®)**, **nilotinib (Tasigna®)** and **bosutinib (Bosulif®)** were added to the list of therapeutic options. Subsequently, the third-generation TKI **ponatinib (Iclusig®)** was also approved to treat CML patients. TKI therapy has proved so effective that recent studies have shown life expectancy for CML patients who respond well to TKI treatment is now approaching that of the general population. The goals of CML therapy have completely changed in the last two decades and are now focused on the achievement of faster and more durable molecular responses, which correlate with better outcomes for patients.

**TKI Therapy.** Each TKI works in a slightly different way. A patient may start with one drug and later try a different one if the first treatment choice does not work or stops working over time.

- **Imatinib (Gleevec®)** – Attaches to the kinase domain of BCR-ABL1 in its inactive form to stop growth signals. It also blocks other kinases, including PDGFR and KIT. It is indicated for newly diagnosed adults and children with Ph+ chronic phase CML; and for patients with Ph+ CML in chronic, accelerated or blast phase after failure of interferon therapy.
- **Dasatinib (Sprycel®)** – More potent than imatinib. Attaches to active and inactive forms of the BCR-ABL1 kinase to block growth signals. It also blocks SRC, PDGFR, and KIT kinases. Approved for newly diagnosed adults in Ph+ chronic phase CML. Also approved for adults resistant to or intolerant of prior therapy in chronic, accelerated or blast phase CML; and for pediatric patients with Ph+ chronic phase CML.
- **Nilotinib (Tasigna®)** – Works in almost the same way as imatinib but is more potent. It also blocks PDGFR and KIT kinases. Indicated for newly diagnosed adults and children age 1 year and older in chronic phase Ph+ CML; for adults resistant to or intolerant of prior therapy in chronic or accelerated phase CML; and for pediatric patients aged 1 year and older who were resistant to or intolerant of prior TKI therapy.
- **Bosutinib (Bosulif®)** – Attaches to active and inactive sites on the BCR-ABL1 protein and blocks growth signals. It also works against SRC kinases. Approved for newly diagnosed adults with chronic phase Ph+ CML and for adults with chronic, accelerated or blast phase CML with resistance to or intolerance of prior therapy.
- **Ponatinib (Iclusig®)** – Blocks many tyrosine kinases including BCR-ABL1. It works against all BCL-ABL1 mutations including T315I. Indicated for adults with chronic, accelerated or blast phase CML; and for adults with chronic, accelerated, or blast phase T315I-positive CML. Not recommended for newly diagnosed chronic phase CML.

Common side effects of TKIs include low blood counts, nausea, diarrhea, vomiting and rash. Patients may also feel tired and get headaches and fevers. TKIs may cause severe side effects such as kidney failure and heart and liver problems. It is important to communicate all side effects to members of your treatment team.

**How Treatment Response Is Assessed.** Monitoring treatment response is an essential strategy in managing CML. **Quantitative polymerase chain reaction (qPCR)** is an extremely sensitive test that detects and measures

## Treatment-Free Remission for Chronic Myeloid Leukemia Patients

the quantity of the *BCR-ABL1* gene in a patient's blood or bone marrow sample. It can detect very small amounts of the gene to a level of one CML cell among 100,000 to 1,000,000 normal cells.

**The International Scale (IS).** Across labs, different scales are used to measure and report qPCR test results, making results difficult to compare. The International Scale (IS) was created as a standardization tool for quantifying and interpreting molecular responses, allowing for comparisons of results from different testing sites. The IS defines the standard baseline as "*BCR-ABL1* 100 %." A "log reduction" is a mathematical term used to show the relative number of cells, germs, microbes, etc. reduced in or on something. When it is used in CML, it refers to the reduction of one's CML, or specifically *BCR-ABL1*.

- **1-log reduction** indicates that the *BCR-ABL1* levels have decreased to 10 times below the standardized baseline. This means that approximately 10 percent of cells (10 out of every 100 cells) have the *BCR-ABL1* gene. This is also written as "*BCR-ABL1* 10%."
- **2-log reduction** means that *BCR-ABL1* levels have decreased to 100 times below the standardized baseline. This means that approximately 1 percent of cells (1 out of every 100 cells) have the *BCR-ABL1* gene. This is also written as "*BCR-ABL1* 1 %."
- **3-log reduction** indicates that the *BCR-ABL1* levels have decreased to approximately 1,000 times below the standardized baseline. This means that 0.1 percent of cells (1 out of every 1,000 cells) have the *BCR-ABL1* gene. This is written as "*BCR-ABL1* 0.1 %."
- **4.5-log reduction** is referred to as a "complete molecular response" (CMR) or a "deep molecular response" (DMR). Doctors may refer to this as "MR4.5." A 4.5-log reduction indicates that approximately 0.0032% of cells (1 out of every 32,000 cells) have the *BCR-ABL1* gene.

For CML, treatment results are discussed in terms of achievable milestones. These milestones are:

- **EMR (early molecular response)** – defined as *BCR-ABL1* <10% (1-log reduction) at 3 months and 6 months after the start of treatment. It can predict the likelihood that a patient will respond to treatment in the long term.
- **CCyR (complete cytogenetic response)** – defined as the absence of the Ph chromosome in the bone marrow, as measured by cytogenetic testing. A CCyR

is equal to *BCR-ABL1* 0.1% to *BCR-ABL1* 1%. It is ideally achieved within 12-18 months of starting treatment.

- **MMR (major molecular response)** – defined as *BCR-ABL1* <0.1%. This means that 1 out of every 1,000 cells has the *BCR-ABL1* gene. This is also referred to as a "3-log reduction."
- **CMR (complete molecular response)**, also referred to as a **DMR (deep molecular response)** – indicates that approximately 0.0032% of cells (1 out of every 32,000 cells) have the *BCR-ABL1* gene. For this type of response, a lab that can detect at least a 4.5-log reduction is needed. Patients who achieve and then sustain a deep molecular response for at least two years may be considered candidates for discontinuing drug therapy. See *What Is Treatment-Free Remission*, below.

For more information about CML treatment and treatment response, please see the free LLS publication *Chronic Myeloid Leukemia*.

### What Is Treatment-Free Remission?

Treatment-free remission (TFR) is achieved when a patient who has discontinued TKI therapy maintains a major molecular response (MMR) and does not need to restart therapy. Patients in the chronic phase of CML who have been taking a TKI for at least three years and who have a stable, prolonged and deep molecular response (DMR) for at least two years, are considered good candidates to discontinue TKI therapy and attempt treatment-free remission (TFR).

Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend that eligible patients try TFR as long as proper, high-quality, well-regulated and certified monitoring can be ensured.

**TKI Discontinuation Clinical Studies.** The feasibility and safety of discontinuing TKI therapy, along with close monitoring of carefully selected patients who have achieved and maintained deep molecular response (DMR) for at least two years, has been evaluated in several studies.

The possibility of TFR after discontinuing imatinib was first evaluated in the STIM1 study in 100 patients with a deep molecular response (DMR) for at least 2 years. This study had a follow-up of 77 months after discontinuation of therapy and the molecular relapse-free survival rate was 43 percent at 6 months and 38 percent at 60 months.

# Treatment-Free Remission for Chronic Myeloid Leukemia Patients

More recent studies have also confirmed the feasibility of TFR after discontinuing dasatinib or nilotinib in patients with chronic-phase CML who have achieved and maintained a DMR for 12 months after two years or more of TKI therapy, used as either first-line or second-line treatment.

As of December 2017, the FDA expanded the nilotinib product label to include treatment discontinuation indications for both:

- Adult patients with newly diagnosed CML in chronic phase who were treated with nilotinib for three or more years and who have achieved DMR for at least one year
- Adult chronic-phase CML patients who received frontline treatment with imatinib and who switched to nilotinib due to resistance to or intolerance of imatinib, and who received nilotinib for three or more years and achieved DMR for at least one year

## Patient Considerations

**Why Consider TFR?** There are many potential advantages of treatment-free remission for patients who have CML. These may include a combination of treatment, cost, and patient-related factors. Becoming treatment-free may:

- Reduce the risk of TKI side effects and future drug interactions. Although TKIs are generally well tolerated, they do produce side effects that may affect health and quality of life
- Benefit young female patients who are considering starting a family and may need treatment-free periods
- Ease the inconvenience of taking daily medication
- Eliminate patient co-pays and insurance costs for ongoing treatment, reducing expenses for both patients and the healthcare system.

**TKI Withdrawal Syndrome.** After discontinuing TKI therapy, some patients might experience musculoskeletal pain or develop a rash. Generally, the pain can be managed with over-the-counter pain medication. Although this syndrome can last for months, it can often be controlled with nonprescription drugs or non-steroidal anti-inflammatory drugs, and in more severe cases, with corticosteroids. Pain does not appear to be dependent on the particular TKI the patient was

taking before stopping therapy, but it may be less frequent in patients who discontinue dasatinib.

TKI withdrawal syndrome has been reported in about 10 to 30 percent of patients who discontinued TKI therapy. Whether the syndrome may be minimized by tapering TKI doses over several months before discontinuation is a question to be evaluated in clinical studies.

**Patient Concerns.** The main anxiety that patients experience regarding stopping TKI therapy is fear of recurrence or progression of CML. Ask questions and ask for additional information. Make sure all questions are answered before making a decision to proceed.

**Patient Eligibility.** Psychosocial and emotional factors, in combination with clinical factors, play an important role in a patient's decision to attempt TFR. **Table 1** on *this page* and **Table 2** on *page 5* list the patient clinical criteria and psychosocial prerequisites associated with TKI therapy discontinuation. Psychosocial, emotional and clinical factors are all part of a patient's decision to attempt successful treatment-free remission.

## Patient Clinical Criteria for TKI Discontinuation

Parameter	Criteria
Age	18 yrs and older
CML Phase	Chronic phase only
<i>BCR-ABL1</i> Transcripts	e13a2, e14a2, or e13a2 + e14A2
TKI Treatment Duration	At least 3 years
Molecular Response	MR4.5
DMR Duration	At least 2 years
Prior Treatment History	No progression, resistance, or suboptimal response

**Table 1.** Clinical criteria for TKI therapy discontinuation. DMR = deep molecular response; MR4 = molecular response 4; TKI = tyrosine kinase inhibitor.

## Psychosocial and Emotional Prerequisites for TKI Therapy Discontinuation

### Recommendations for the patient:

- Be well informed about TFR and well-motivated to discontinue treatment.
- Do not experience any pressure to stop TKI therapy.
- Understand that molecular recurrence is possible; this does not constitute a failure.
- Understand the need for frequent monitoring, especially during the first year.
- Have access to proper monitoring: reliable qPCR test with a sensitivity of detection of at least MR4.5 that also provides results within 2 weeks.
- Be reassured that in case of relapse, treatment can be restarted promptly and successfully.
- Understand the risk of TKI withdrawal syndrome.

**Table 2.** Psychosocial and emotional prerequisites for patients when considering discontinuation of TKI therapy.

**Monitoring During TFR.** Frequent and highly sensitive molecular testing is essential for ensuring the safety of patients attempting TFR, particularly during the first year of TKI discontinuation and during re-treatment, if needed.

The NCCN guidelines recommend monthly monitoring (by qPCR) for the first year of TFR, every 6 weeks for the second year and every 12 weeks after that. Clinical visits with the treatment team are also encouraged on a quarterly basis (4 times a year) for the first year and every 3 to 6 months thereafter.

Doctor appointments are important because they provide the opportunity for the healthcare team to address patient concerns, discuss qPCR results and adjust monitoring tests and schedules as needed.

**What Happens If Relapse Occurs?** Approximately 40 to 60 percent of patients who discontinue TKI therapy after achieving DMR do experience a recurrence within 12 months of stopping treatment, in some cases as early as one month into discontinuing TKI therapy. Restarting therapy immediately after recurrence results

in the achievement of undetectable disease in almost all patients. Late molecular responses do occur; thus, it is important that patients adhere to monitoring during TFR in order for the doctor to detect a relapse and ensure protection from disease progression.

Several factors may help predict the risk of relapse after TKI therapy discontinuation. These include:

- Higher Sokal risk score (see *page 6*)
- Female gender
- Lower natural killer cell counts (NK cells are white blood cells)
- Suboptimal response or resistance to imatinib
- Shorter duration of TKI therapy
- Shorter duration of deep molecular response prior to stopping treatment

Patients who are interested in stopping their treatment should talk to their hematologist-oncologist to discuss the benefits and risks.

**Feedback.** To give suggestions about this booklet, visit [www.LLS.org/PublicationFeedback](http://www.LLS.org/PublicationFeedback).

## Glossary

The following terms can help you understand some of the information found in this publication.

**ABL1 gene.** A gene from chromosome 9 that breaks off and migrates to chromosome 22. The *ABL1* gene joins the *BCR* gene on chromosome 22 to form the *BCR-ABL1* fusion gene, which is found in most patients with CML. The gene symbol *ABL1* is derived from the name of scientist Herbert Abelson, who discovered the gene.

**Chromosomes.** Threadlike structures within cells that carry genes in a linear order. Genes give the instructions that tell each cell what to do. Human cells have 46 chromosomes.

**Gene.** A gene is a segment of DNA. Most genes contain the information needed to make proteins. A gene mutation can lead to the production of a protein that works incorrectly or that does not work at all.

**International Scale (IS).** A standardized scale for measuring and reporting results of a very sensitive test that measures the number of cells that have the *BCR-ABL1* gene.

**Philadelphia Chromosome (Ph Chromosome).**

An abnormality of chromosome 22 found in the bone marrow and blood cells of most patients with CML. It is formed when parts of both chromosomes 9 and 22 break off and trade places. The result is a chromosome 22 that is shorter than normal. The exchange of DNA between chromosomes 9 and 22 results in the creation of a gene called *BCR-ABL1* on chromosome 22. CML with Philadelphia chromosome is abbreviated Ph+ CML.

**Quantitative Polymerase Chain Reaction**

**(qPCR).** A technique to expand trace amounts of DNA so the specific type of the DNA can be studied. This technique has become useful in detecting a very low concentration of residual blood cancer cells, too few to be seen using a microscope.

**Relapse.** A return of the disease after a period of improvement.

**Sokal Scoring System.** A scoring system used for patients with chronic myeloid leukemia that estimates their survival. Patients are designated “low-risk,” “intermediate-risk” or “high-risk” based on their spleen size, platelet count, age and the percentage of blast cells in their peripheral blood.

**Transcript.** RNA molecule derived from transcription of a specific gene. During transcription, a strand of messenger RNA (mRNA) is made that is complementary to a strand of DNA.

**Translocation.** A genetic abnormality in which a piece of one chromosome breaks off and attaches to another chromosome. Sometimes genetic material is exchanged between two different chromosomes. When a translocation takes place, the gene at which the break occurs is altered. See also Philadelphia chromosome.

**Tyrosine Kinase.** A type of enzyme that plays a key role in cell function including cell growth and division. It is normally present in cells, and the *ABL1* gene on chromosome 9 directs its production.

**Tyrosine Kinase Inhibitor (TKI).** A type of drug that blocks the action of enzymes called “tyrosine kinases” that are made by the *BCR-ABL1* gene, so the enzymes cannot signal the leukemia cells to grow.

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## Other Resources

**The National CML Society**

[www.nationalcmlsociety.org](http://www.nationalcmlsociety.org)  
(877) 431-2573

Created by and for patients and their families in order to provide a centralized source of information about CML and its treatment and support for CML patients.

## We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our Web site at [www.LLS.org/chapterfind](http://www.LLS.org/chapterfind) or contact:

The Leukemia & Lymphoma Society  
3 International Drive, Suite 200  
Rye Brook, NY 10573  
Contact an Information Specialist at (800) 955-4572  
Email: [infocenter@LLS.org](mailto:infocenter@LLS.org)

## Treatment-Free Remission for Chronic Myeloid Leukemia Patients

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

**Consult with an Information Specialist.** Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, from 9 am to 9 pm EST)
- Email: [infocenter@LLS.org](mailto:infocenter@LLS.org)
- Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)
- Visit: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)

**Clinical Trials (Research Studies).** New treatments for patients are ongoing. Patients can learn about clinical-trials and how to access them. For more information, please call (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical-trial searches. When appropriate, personalized clinical-trial navigation by trained nurses is also available. Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information.

**Free Information Booklets.** LLS offers free education and support booklets that can either be read online or ordered. Please visit [www.LLS.org/booklets](http://www.LLS.org/booklets) for more information.

**Co-Pay Assistance Program.** LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: [www.LLS.org/copay](http://www.LLS.org/copay)

**Financial Assistance.** LLS offers financial assistance to individuals with blood cancer. Visit [www.LLS.org/finances](http://www.LLS.org/finances) for more information.

**Información en Español (LLS information in Spanish).** Please visit [www.LLS.org/espanol](http://www.LLS.org/espanol) for more information.

**Telephone/Web Education Programs.** LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit [www.LLS.org/programs](http://www.LLS.org/programs) for more information.

**LLS Community.** The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit [www.LLS.org/community](http://www.LLS.org/community) to join.

**One-on-One Nutrition Consultations.** Access free one-on-one nutrition consultations by a registered dietitian with experience in oncology nutrition. Dietitians assist callers about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit [www.LLS.org/nutrition](http://www.LLS.org/nutrition) for more information.

**Weekly Online Chats.** Moderated online chats can provide support and help cancer patients to reach out and share information. Please visit [www.LLS.org/chat](http://www.LLS.org/chat) for more information.

**Podcast.** Listen in as experts and patients guide listeners in understanding diagnosis and treatment, and suggest resources available to blood cancer patients. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Visit [www.LLS.org/TheBloodline](http://www.LLS.org/TheBloodline) for more information and to subscribe.

**LLS Chapters.** LLS offers support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: [www.LLS.org/ChapterFind](http://www.LLS.org/ChapterFind)

**Other Helpful Organizations.** LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. Please visit [www.LLS.org/ResourceDirectory](http://www.LLS.org/ResourceDirectory) for more information.

**Advocacy.** The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: [www.LLS.org/advocacy](http://www.LLS.org/advocacy)

**Information for Veterans.** Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information please

- Call: the VA (800) 749-8387
- Visit: [www.publichealth.va.gov/exposures/agentorange](http://www.publichealth.va.gov/exposures/agentorange).

**World Trade Center (WTC) Survivors.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: [www.cdc.gov/wtc/faq.html](http://www.cdc.gov/wtc/faq.html)

**People Suffering from Depression.** Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a 2-week period. For more information, please

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at [www.nimh.nih.gov](http://www.nimh.nih.gov) and enter “depression” in the search box

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## Treatment-Free Remission for Chronic Myeloid Leukemia Patients

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