# Treatment Recommendations for People Living with CML

## Foreword by CML Workgroup

Chronic myeloid leukaemia (CML) is a disease of the blood and bone marrow that results when there is a cancerous transformation of a stem cell. Stem cells are like seeds in the bone marrow that mature into any of the three major blood cells: white blood cells (WBCs), red blood cells (RBCs) or platelets.

CML stem cells are abnormal and result mainly in the overproduction of WBCs that enter the bloodstream and circulate throughout the body. Usually, the spleen enlarges. Eventually the CML cells replace the normal cells in the bone marrow and prevent production of normal blood cells. As the disease progresses, the number of healthy, normal WBCs will decline, and, in addition, there may be an overproduction of leukaemia cells known as blasts.

Most CML cells have a reciprocal translocation (i.e., a part of one chromosome is exchanged with a part of another chromosome) leading to the formation of the so-called Philadelphia chromosome. A reciprocal translocation is also called a chromosomal rearrangement. When present, a gene called ABL that normally is found on chromosome 9 moves to the gene called BCR that is normally found on chromosome 22. The fusion of the BCR and ABL genes produces an abnormal protein with increased tyrosine-kinase activity that is thought to be the cause of CML. Treatment targeted against tyrosine-kinase activity of BCR-ABL encoded proteins has revolutionized the treatment of CML in the past 10 years. In 2009, the European LeukemiaNet (ELN) published CML management recommendations in the Journal of Clinical Oncology (JCO). These recommendations have since been recognised as the standard of care by CML treating physicians.

However, the recommendations can be complex and difficult to understand. For this reason, we have developed this document to provide CML patients with a summary of the information contained in the ELN recommendations. We want you to have the information you need to better understand CML management and better communicate with your doctors regarding treatment choices.

This tool includes some complicated language and information. Definitions are included, where possible. You should consider taking this document with you to your doctor's office to discuss any questions that you have, or to better understand your doctor's recommendations.

Of note, there have been some advances in treatment since the publication of the ELN CML management recommendations in 2009; however, the summary included here focuses only on the 2009 publication content.

The information included in this document is valid until the ELN provides a new and/or updated version of the CML Treatment Recommendations.
This document was produced by a workgroup of patient-advocates and CML experts that received support through in-kind resources from Bristol-Myers Squibb.

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## Treatment recommendations for people living with CML

Chronic myeloid leukaemia (CML) has evolved from a life-threatening disease to a well manageable disease in general and, if well treated, for most patients it is no longer the threat it once was. In recent years, people with CML have benefited from better treatments, including:

- **Imatinib** (Glivec®) was approved by the European Medicines Agency (EMA) in 2001.
- **Dasatinib** (Sprycel®) was approved by the EMA in 2006.
- **Nilotinib** (Tasigna®) was approved by the EMA in 2007.

Since imatinib was approved, doctors have learned more about how best to use these drugs to treat patients. Today, the goal of treatment is for CML patients to survive—and enjoy a good quality of life.

For these reasons, the European LeukemiaNet (ELN) chose to issue updated treatment recommendations in 2009. These recommendations were developed for doctors to help CML patients like you get the best standard of care. Below is a summary based on the best available scientific data at the time of publication.

It is important to remember that individual patients may find that their own therapy might differ from the recommendations below based on their personal disease experience. You can use this summary as a starting point for talking with your doctor. And you can always ask for an explanation if your doctor does not follow these recommendations.

## Standard CML treatments*

Treatments are prescribed in a certain order. These are known as first-line, second-line and third-line treatments. A patient will probably take a BCR-ABL inhibitor. These work by lowering the activity of BCR-ABL, the gene that causes the leukaemia. These drugs can stall the progress of the disease and restore health, but will probably not cure the leukaemia.

### 1 Imatinib

Imatinib is a BCR-ABL inhibitor that usually produces good responses in most CML patients. However, some patients might not respond at all or might not respond well enough to the treatment, and some patients might not tolerate the drug, or might develop resistance to the treatment.

### 2 Dasatinib or nilotinib

Your doctor could prescribe another BCR-ABL inhibitor—either dasatinib or nilotinib, often referred to as second generation tyrosine kinase inhibitor. The reason for this could be your current medical history or your leukaemia cells have changed in certain ways for example, by gaining or exhibiting new biological changes (e.g. mutations) leading leukaemia cells to resist to the current treatment. Some resistant cells will not respond well to dasatinib. Others will not respond well to nilotinib. Still others will not respond well to either drug. The choice might be guided by the presence of certain mutations or the side effect profile of the drug, or other drugs you are taking in parallel, in the context of your medical condition.

### 3 Stem cell transplant

If none of these drugs are working well, or if you are in the accelerated phase (AP) or blast phase (BP) of your disease, your doctor may talk to you about getting healthy stem cells from a donor. This is called an allogeneic stem cell transplant.

The new stem cells can help your body make enough healthy red blood cells, white blood cells, and platelets. If it succeeds, the transplant can cure you of your disease. But transplants also carry a strong risk of health problems and even death. That's why in most cases, transplant is not the first option.

### 4 Interferon-Alpha

Before imatinib was introduced, Interferon-Alpha was the medical treatment of choice if stem cell transplant was not available. Interferon-Alpha causes cell death in CML cells. Administered as single therapy in high doses, good responses can be achieved not to the extent seen with BCR-ABL inhibitors. In addition, side effects are common with the high doses required for single therapy. Today, it is sometimes used in low doses in combination with BCRABL inhibitors to induce an additional immune effect against CML.

**Of note, there have been some advances in treatment since the publication of the ELN CML management recommendations in 2009. This document focuses only on the 2009 publication content. Your doctor can provide you with an update e.g. on changes in first line treatments of CML.*

## Updated treatment recommendations

The charts below show the latest treatment recommendations from the ELN. Under these recommendations:

- A treatment has failed if your blood counts have not returned to the normal range after 3 months. Having a normal blood count means you have the same number of red blood cells, white blood cells, and platelets as the healthy population.
- A response to a treatment is suboptimal if more than 65 percent of cells in your bone marrow carry the Philadelphia (Ph) chromosome after 6 months.
- A treatment has failed if more than 95 percent of cells in your bone marrow carry the Ph chromosome after 6 months. For these reasons, you should get tested for the Ph chromosome frequently. And you should find out your blood counts as often as your doctor suggests.

## Goals of CML treatment

People living with CML respond differently to treatment, but there are general goals that can show you and your doctor if your treatment is working. These may include:

- Getting rid of CML symptoms
- Returning blood counts to normal
- Getting rid of or reducing the number of leukaemia cells, as determined by Ph chromosome (cytogenetic response) or the BCR-ABL fusion (molecular response)
- Reducing the number of BCR-ABL protein to undetectable levels

These goals are general recommendations. Your actual treatment goals may change over time based on the state of your CML at diagnosis, your age, the side effects you experience, your response to treatment, and your overall health.

Throughout your treatment, your doctor will track your CML with blood and bone marrow tests. These tests will help your doctor assess if your treatment goals are being met. The charts below will help you make sense of your test results.

## Glossary

The following charts contain many medical terms and acronyms. You may want to take these charts and glossary with you to your next appointment to discuss with your doctor. It might help to bring a family member or friend with you to take notes. In these charts, the following definitions might be helpful:

**Response Definitions:**

- **Optimal response** means that there is no indication that a change in treatment is required.
- **Suboptimal response** means that taking a certain treatment could work well in the long term, but the chance of an optimal outcome is lower. So you may benefit from a change in treatment.
- **Failure** means that a certain treatment is not likely to work in the long run. So you and your doctor should discuss the option of using a different treatment if possible.
- **Warnings** are signs that the traits of your disease may lower your response to a certain treatment. So your doctor may need to keep a closer eye on your treatment. Your doctor will use these warning signs to decide if your response to a certain treatment is optimal, suboptimal, or failure.

**Response Abbreviations:**

- **CHR** stands for **complete haematologic response.**
- **CCgR or CCyR** stands for **complete cytogenetic response.**
- **MCgR or MCyR** stands for **major cytogenetic response.**
- **PCgR** stands for **partial cytogenetic response.**
- **CgR or CyR** stands for **minor cytogenetic response.**
- **MMR** stands for **major molecular response.**
- **CMR** stands for **complete molecular response.**

**Genetic and Chromosomal Definitions:**

- **Ph** stands for Philadelphia Chromosome, which is the exchange of parts of Chromosome 22 and Chromosome 9 which causes formation of a new gene: BCR-ABL gene.
- **BCR-ABL** is the genetic change resulting in a protein responsible for CML.
- **RT-qPCR** stands for quantitative real time polymerase chain reaction, a method for quantification of BCR-ABL.
- **Mutations** means that changes have taken place in the BCR-ABL gene making them less sensitive to BCR-ABL inhibitors.
- **CCA** stands for **clonal chromosome abnormalities.** These are additional chromosomal abnormalities.
- **CCA/Ph+** means that there are additional chromosomal changes in bone marrow cells that also carry the Philadelphia Chromosome.
- **CCA/Ph-** means that there are additional chromosomal changes in bone marrow cells that do not carry the Philadelphia Chromosome.

## Remission and testing in patients with CML

The goal of CML treatment is to achieve disease remission. For CML, remission is defined by:

- **Complete haematologic response (CHR)**—The blood cell count has returned to normal, and tests don't show any immature white blood cells. Also, the spleen has returned to a normal size if it was enlarged.
- **Complete cytogenetic response (CCgR or CCyR)**—No cells with the Ph chromosome can be found in the blood or bone marrow.
- **Complete molecular response (CMR)**—The PCR test can't detect BCR-ABL in the blood. Most people with CML don't have a complete molecular response. Even if they do, they might still have a tiny amount of the BCR-ABL gene in their blood.
- **Major molecular response (MMR)**—The PCR can still detect BCR-ABL, but at a very low level. Doctors still consider this to be an excellent response.

Unlike other cancer patients, CML patients who are in remission are not cured and current knowledge cannot recommend stopping treatment. Even if tests can't find any trace of CML in your cells, the disease can still reappear and result in a relapse.

Your doctor will want you to have tests done at various times so that he or she can monitor your body's response to the disease and treatment. This chart outlines what your lab numbers will look like if you are in remission and how often you should be tested.

**Table 1.**

| | Remission | Testing |
|---|---|---|
| **Haematologic**<br>Complete (CHR) | Platelet count < 450 x $10^9$/L<br>White blood count (WBC) count < 10 x $10^9$/L<br>Differential: no immature granulocytes<br>Basophils < 5%<br>Non palpable spleen | Test at diagnosis. Then every 15 days until CHR has been achieved and confirmed.<br>Test at least every 3 months or as required. |
| **Cytogenetic**<br>Complete (CCyR)[4]<br>Partial (PCgR)<br>Minor<br>Minimal<br>None | No Ph+ metaphases<br>1-35% Ph+ metaphases<br>36-65% Ph+ metaphases<br>66-95% Ph+ metaphases<br>95% Ph+ metaphases | Test at diagnosis, at 3 months, and at 6 months.<br>Test every 6 months until a CCyR has been achieved and confirmed.<br>Test every 12 months if regular molecular testing cannot be assured.<br>Check always for cases of treatment failure, resistance, and for cases of unexplained anaemia, leukopenia, or thrombocytopenia. |
| **Molecular**<br>Complete (CMR)<br><br>Major (MMR) | The PCR test can't detect any of the BCR-ABL gene in the blood<br><br>≤ 0.1% BCR-ABL on the international scale | **RT-qPCR:** (quantitative real time polymerase chain reaction): Every 3 months, until MMR has been achieved and confirmed. Then at least every 6 months.<br>**Mutational analysis:**<br>In cases of suboptimal response or failure, always required before changing to other treatments. |

[4]If marrow cell metaphases cannot be obtained or assessed by chromosome banding analysis (a way of identifying chromosomal aberrations), the definition of CCgR (or CCyR) may be based on interphase fluorescence in situ hybridization (FISH), another method to detect the Philadelphia chromosome of blood cells.

• In many studies, PCgR and CCyR are counted together and reported as major CgR.

## Response and warnings in patients taking imatinib

Are you in the early phase of CML and taking 400 mg of imatinib daily for the first time? Read this chart. See the definitions for response and monitoring in the Glossary.

**Table 2.**

| Time | Optimal response | Suboptimal response | Failure | Warnings |
|---|---|---|---|---|
| **At diagnosis** | N/A (does not apply at this stage | N/A (does not apply at this stage | N/A (does not apply at this stage | High risk[0]<br>CCA/Ph+[3] |
| **3 months** | CHR and Ph+ <66% | Ph+ >95% | Less than CHR | N/A (does not apply at this stage |
| **6 months** | Ph+ <36% | Ph+ >35% | Ph+>95% | N/A (does not apply at this stage |
| **12 months** | CCyR | Ph+ between 1 and 35% | Ph+>35% | Less than MMR |
| **18 months** | MMR | Less than MMR | Less than CCyR | N/A (does not apply at this stage |
| **Any time during treatment** | Stable or improving MMR | Loss of MMR<br>Mutations[1] | Loss of CHR<br>Loss of CCyR<br>Mutations[2]<br>CCA/Ph+[3] | Increase in transcript levels<br>CCA/Ph- |

[0]As defined by Sokal or Hasford scores
[1]BCR-ABL1 kinase domain mutations still respond to imatinib.
[2]BCR-ABL1 kinase domain mutations respond poorly to imatinib and other TKIs.
[3]CCA/Ph+ (clonal chromosome abnormalities in Ph-positive cells) is a "warning" sign at diagnosis.

- If it shows up during treatment, it's a sign that treatment has failed.
- In order to qualify as a warning sign, you must get two positive test results for Ph+ cells in a row. And the tests must show the same CCA in at least two Ph+ cells.

## Treatment recommendations for patients with Chronic Phase (CP) CML

Are you in the chronic phase of your disease? Read this chart to learn options for the first, second, and third line of treatment. Of note, there have been some advances in treatment since the publication of the ELN CML management recommendations in 2009; this chart focuses only on the 2009 publication content.

**Table 3.**

| Chronic Phase (CP) | Which patients? | Which treatment? |
|---|---|---|
| **1st line** | All patients | Imatinib 400 mg daily, and in some countries nilotinib or dasatinib |
| **2nd line (after imatinib)** | Patients experiencing toxicity and intolerance | Dasatinib or nilotinib |
| | Patients with treatment suboptimal response | Continue imatinib same dose, or test high dose imatinib, dasatinib, or nilotinib. |
| | Patients with treatment failure | Dasatinib or nilotinib<br>Stem cell transplant in patients in Accelerated or Blastic Phase and in patients who carry the T315I mutation |
| **3rd line** | Patients with treatment suboptimal response to dasatinib or nilotinib | Continue dasatinib or nilotinib<br>Consider stem cell transplant in patients with warning signs (such as mutations and blood counts that don't respond well to imatinib), and a low transplant risk score |


*Baccarani, M et al: Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet, Vol. 27 (no. 35), Dec. 10, 2009: 6041-6051.*

## Treatment recommendations for patients with Accelerated Phase (AP) and Blastic Phase (BP) CML

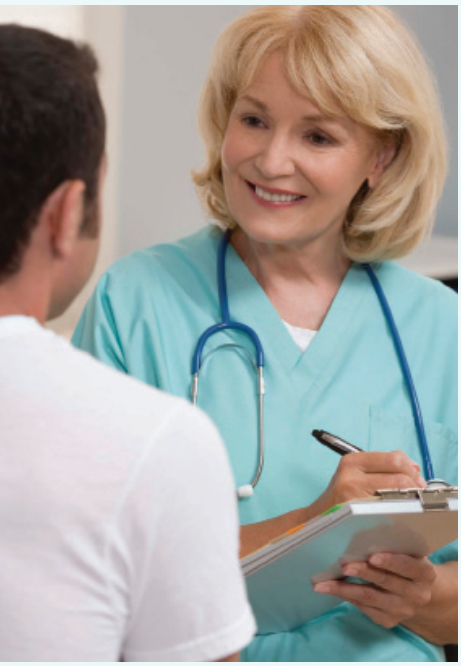
Are you in either the accelerated or blastic phase of your disease? Read this chart.

Of note, there have been some advances in treatment since the publication of the ELN CML management recommendations in 2009; this chart focuses only on the 2009 publication content.

**Table 4.**

| Accelerated Phase (AP) and Blastic Phase (BP) | Which patients? | Which treatment? |
|---|---|---|
| **1st line** | Patients who have never used a BCR-ABL inhibitor | Imatinib 600 or 800 mg daily<br>Dasatinib or nilotinib in case of mutations that don't respond well to imatinib<br>If drugs fail, stem cell transplant |
| **2nd line** | Patients who have used imatinib before | Dasatinib or nilotinib<br>If drugs fail, stem cell transplant, whenever possible |


*Baccarani, M et al: Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet, Vol. 27 (no. 35), Dec. 10, 2009: 6041-6051.*



## Be an active patient

These recommendations are not meant to replace medical advice, but are meant to provide you with a clearer understanding of CML treatment, tests, and results. In order to achieve the best results, you may want to be an active patient. Consider these tips:

1. Find a doctor who knows a lot about your disease and has treated many CML patients before. This is especially true if your disease is advanced, if your test results are not clear, or if you have had severe or unusual side effects from treatment.
2. Be sure to talk with your doctor at any stage of your disease, especially before stopping or changing your treatment.
3. Only drugs that are taken can actually work. Make sure you take your treatment as prescribed. There is evidence that not following CML treatment as prescribed can threaten success of your CML treatment. Address your concerns to your doctor before you consider stopping or skipping your treatment.
4. Make sure your doctor keeps an eye on how well your treatment is working. Don't miss your regular check-ups as CML is a life-threatening disease if not under control.
5. Ask your doctor whether clinical trials are an option for you. In certain cases these might not only be of potential benefit to you, but also to future CML patients.
6. Give your treatment time to work. The choice to switch to a new treatment should be based on good data. If your test results are not clear, it may be wise to get tested again.
7. Having side effects? Talk to your doctor about them. He or she may be able to help you manage them.
8. Get support. Talk with your doctor about ways to cope with CML. Connect with other people who are living with the disease, and with support groups for CML patients—there are groups in almost every country. You can visit the CML Advocates Network for a list of worldwide CML support groups here: **www.cmladvocates.net**

Tell your family and friends how they can help. Remember—you don't have to go through this alone.

## To learn more

This summary is based on the article *Chronic Myeloid Leukemia: An Update of Concepts and Management Recommendations of European LeukemiaNet*. It appeared in the *Journal of Clinical Oncology* in 2009. Your doctor, university library or patient group may be able to get you a copy.

## Questions and considerations as you manage your CML

**1. Do you know what phase of CML you are currently in?**

❍ Yes ❍ No

**2. Have you and your doctor defined your personal treatment goals?**

❍ Yes ❍ No

**3. Do you know and record your medication treatment history?**

❍ Yes ❍ No

**4. Do you know your most recent test results?**

| | | |
|---|---|---|
| Your blood counts? | ❍ Yes | ❍ No |
| Cytogenetic test results? | ❍ Yes | ❍ No |
| Molecular test results? | ❍ Yes | ❍ No |

**5. If your treatment does not work as expected, have you discussed an updated treatment plan with your doctor?**

❍ Yes ❍ No

**6. Do you record all of your CML or medication side effects?**

❍ Yes ❍ No

**7. Do you talk to your doctor about your CML or medication side effects?**

❍ Yes ❍ No

If you have answered "no" to any of the questions above, you may want to talk to your doctor about how you can be more involved in your CML treatment.

Learn all you can about your disease and treatment options. This brochure is a good starting point. Ask your doctor any questions you have, and keep asking until you get answers you understand. And if you need help understanding, bring a family member or friend to the appointment who can help you listen and take notes.

## Trying to find a CML support group?

Patient advocacy groups can help you get in touch with other patients who have CML, learn more about your disease, identify helpful information, or find an experienced doctor for a second opinion.

To find a group in your country, visit the CML Advocates Network group list here:

**www.cmladvocates.net/members**