

# Recommendations for Managing People Living with CML

A patient-friendly summary of the 2025 European LeukemiaNet recommendations for the management of chronic myeloid leukemia

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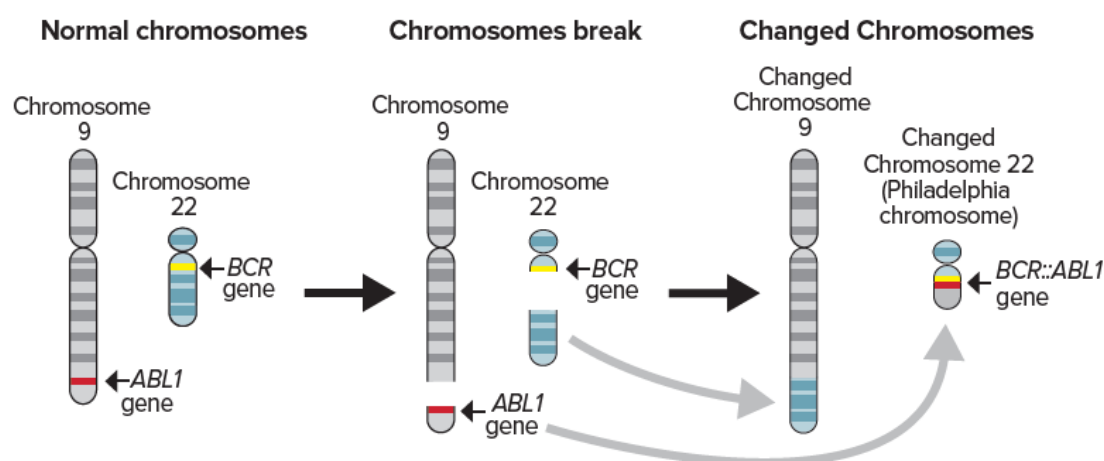
## **List of abbreviations**

<b>ACA</b>	additional chromosome abnormalities
<b>allo-SCT</b>	allogeneic stem cell transplantation
<b>AP</b>	accelerated phase
<b><i>ABL1</i></b>	<i>gene</i>
<b><i>BCR::ABL1</i></b>	<i>gene</i>
<b><i>BCR</i></b>	<i>gene</i>
<b>BP</b>	blast phase
<b>CBA</b>	chromosome banding analysis
<b>CCyR</b>	complete cytogenetic response or complete cytogenetic remission
<b>CHR</b>	complete hematologic response or complete hematologic remission
<b>CML</b>	chronic myeloid leukemia
<b>CP</b>	chronic phase
<b>DMR</b>	deep molecular response or deep molecular remission
<b>ELN</b>	European LeukemiaNet
<b>ELTS</b>	EUTOS long-time survival score
<b>FISH</b>	fluorescence in-situ hybridization
<b><i>GUSB</i></b>	<i>gene</i>
<b>IFN</b>	interferon
<b>IS</b>	International Scale
<b>mg</b>	milligram
<b>MMR</b>	major molecular response or major molecular remission
<b>MR</b>	molecular response or molecular remission
<b>MRD</b>	minimal residual disease
<b>NGS</b>	Next Generation Sequencing
<b>PCyR</b>	partial cytogenetic response or partial cytogenetic remission
<b>Ph</b>	Philadelphia chromosome
<b>PCR</b>	polymerase chain reaction
<b>SCT</b>	stem cell transplantation
<b>TFR</b>	treatment-free remission
<b>TKI</b>	tyrosine kinase inhibitor

## Foreword by the Workgroup

**Chronic Myeloid Leukemia (CML)** is a rare cancer of the blood and bone marrow. CML is a type of leukemia which begins in the stem cells of the bone marrow. Stem cells normally mature into any of the three major blood cell lines: white blood cells, red blood cells or platelets. CML starts when stem cells become abnormal and too many white blood cells are produced. As the disease progresses, CML cells replace normal cells in the bone marrow. This prevents the bone marrow from making healthy blood cells and the number of normal white blood cells decreases. However, medication available today, taken as prescribed, usually prevents CML from progressing.

In humans, each cell normally contains 22 pairs of chromosomes and two sex chromosomes (XX or XY). Each chromosome contains thousands of genes. In CML cells, a mistake occurs when a stem cell is dividing and part of chromosome 9 incorrectly joins together with part of chromosome 22. This leads to the formation of the so-called Philadelphia (Ph) chromosome in almost all people with CML. As a result, part of a gene called *ABL1* that is normally found on chromosome 9 joins to part of a gene called *BCR* located on chromosome 22. The result is an abnormal gene called *BCR::ABL1* on chromosome 22 (see Figure 1).



**Figure 1. Translocation of Chromosomes 9 and 22**

Image used with permission of Blood Cancer United, formerly The Leukemia & Lymphoma Society (*Chronic Myeloid Leukemia: In Detail*, 2025).

The *BCR::ABL1* gene controls the production of a protein which has the function of an enzyme called a tyrosine kinase. Tyrosine kinases normally help cells to divide and multiply. The abnormal gene makes an overactive tyrosine kinase and so too many white blood cells are produced.

Treatment of CML aims to reduce the abnormal tyrosine kinase activity of *BCR::ABL1* and prevent CML cells from multiplying. This can be achieved with drugs called tyrosine kinase inhibitors (TKIs). TKIs are highly effective and can reduce the disease to a minimum and so restore health.

The **European LeukemiaNet (ELN)**, an international not-for-profit research network, provided recommendations for treating CML in adult patients first in 2006. Several updates followed. In this 5<sup>th</sup> version, 38 CML experts from Europe, North America, Asia and Australia address important changes in managing CML. The changes are based on scientific data that have become available since the previous recommendations of 2020. ELN prepare these recommendations for doctors and patients to improve the understanding and management of CML. The recent updates help make care more personalized, with the goal of better outcomes and a better quality of life.

## What is new in the 2025 recommendations?

- The World Health Organization (WHO) now considers CML as having two phases instead of three.
- Former terms to describe milestones of response as 'optimal', 'warning' and 'failure' are now called 'favorable', 'warning' and 'unfavorable' to better address the risk of developing resistance to treatment.
- New TKIs are available and allow more flexibility in selecting a drug that matches an individual patient's needs.
- Lowering the dose rather than switching to another drug may be preferable to manage side effects.
- Developments in medicine have made stem cell transplants safer and possible for more patients for whom long-term disease control is not achieved through TKI therapy.
- Updated guidance is now provided for eligible patients who wish to attempt treatment discontinuation.
- Finally, more comprehensive advice has become available for women and men planning to have children.

A workgroup of patient advocates has created a **summary of the 2025 ELN recommendations for the management of chronic myeloid leukemia** for you. You can use this summary to discuss your disease and needs with your doctor and jointly make the best treatment choices.

Members of the workgroup included:

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CML Advocates Network appreciates the review of this summary by

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## Introduction

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For more than 20 years, the ELN together with other groups around the world have worked together to set standards for treating people with CML. Until now, the emphasis has been on preventing the disease from getting worse and helping people live longer. This has allowed most patients with chronic phase CML to respond well to treatment and reach their normal life expectancy. Some patients reach such a deep response that they can stop treatment and continue their lives free of medication. This is called treatment-free remission (TFR). While TFR may be a desirable goal for patients who have access to effective drugs and high-quality monitoring, most patients will still need lifelong medicine. For those patients, making sure treatment works well and supports good quality of life is just as important.

In this update, ELN share the latest findings that matter most for patient care and move toward more personalized treatment. These recommendations are for adults only and focus on new data that have become available since the last version.

## Diagnosis

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Several tests and examinations are done to confirm whether a patient has CML. These include:

- **Physical examination** – Your doctor examines you, especially for the size of your spleen and your liver. If you have CML, your spleen might be enlarged.
- **Blood tests**
  - **Complete blood count** – Blood is taken from your arm vein to assess the number and types of blood cells. In CML, the number of a certain type of white blood (myeloid) cell is increased.
  - **Biochemical blood profile** – Standard tests are carried out on a blood sample to assess the function of your organs. The results are then compared with normal values.
- **Cytogenetic testing** – A bone marrow sample (**bone marrow aspirate**) is removed from inside a bone using a hollow needle. This test allows the doctor to look for cancer cells in your bone marrow and determine the stage of your CML. A small piece of bone (**bone marrow biopsy**) may also be taken by your doctor. The presence of excessive numbers of blast cells in the bone marrow indicate that the patient might be at higher risk. Bone marrow cells are evaluated using the following cytogenetic tests:
  - **Chromosome banding analysis (CBA)** on bone marrow is recommended to detect the characteristic Philadelphia chromosome and additional chromosome abnormalities (ACA) which indicate higher risk.
  - **Fluorescence in-situ hybridization (FISH)** may be carried out (usually on blood) if *BCR::ABL1* (gene for CML) has been identified but the Philadelphia chromosome cannot be detected and/or if polymerase chain reaction (PCR) (see below) is not available.
- **Molecular testing**
  - **PCR** – This highly-sensitive test detects the presence or absence of *BCR::ABL1* in your blood or bone marrow and is recommended at the time of CML diagnosis. Thereafter, quantitative PCR test results serve as reference values and are used to assess changes in the amount of *BCR::ABL1* to monitor how you respond to treatment.

Your doctor may also ask you to undergo other diagnostic procedures. This will depend on your own patient characteristics, your medical history, the stage of your CML or the presence of other genetic changes (mutations) at diagnosis, and any other diseases that you might have.

Mutation testing for *BCR::ABL1* mutations or genetic changes that are not inherited (so-called somatic mutations) is not routinely recommended at diagnosis in chronic phase (see below). In contrast, *BCR::ABL1* mutations and genetic changes should be checked in patients presenting in or progressing to blast phase. Ideally, a test called Next Generation Sequencing (NGS) should be used.

## Disease classification

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ELN usually describes CML as a three-phase disease:

- **Chronic phase (CP)** – This is the initial stage where the body produces too many white blood cells. This phase may last months to years. If symptoms appear, they are likely to be mild and easily missed.
- **Accelerated phase (AP)** – If left untreated, the CML cells might undergo more genetic changes and the disease might progress to a more advanced stage.
- **Blast phase (BP)** – In this phase, there are 30% or more immature cancer cells called blasts in the blood or bone marrow, the disease worsens and the patient generally feels unwell.

In 2022, however, the WHO reclassified CML as having only two phases: **chronic phase** with less than 20% blasts and **blast phase** with 20% or more blasts in the blood or bone marrow. According to this classification, accelerated phase no longer exists.

The classifications by ELN and WHO exist in parallel. Both recognize that some patients may show signs of more advanced disease. They also agree that if a patient's condition changes or worsens over time, it is a sign that the disease is progressing.

## Prognosis

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The likely outcome or course of a disease for a patient is called prognosis. A prognosis is usually based on many factors which should be assessed at diagnosis before you start any drug treatment. Your age, the size of your spleen, and other measurements such as blood and blast cell counts can influence how you may respond to treatment with TKIs. These factors will be used to calculate your risk score and help choose the best treatment.

Today, the EUTOS long-time survival (ELTS) score is the preferred score to predict the risk of progression and the probability of dying from CML. The ELTS score is calculated using age, spleen size, blast percentage, and platelet count at diagnosis. The resulting risk score then indicates whether a patient has a low, intermediate or a high risk of progressing to blast phase. Most people who are newly diagnosed with CML today and who are treated with TKI have a normal life span comparable to the general population, and they do not die because of CML. People with a high risk of progression at diagnosis, however, are less likely to reach a normal life expectancy. It is important to recognize patients who may have a poorer prognosis because they might be treated differently. Older risk scoring systems than the ELTS should no longer be used.

Other prognostic factors that are present at the time of your diagnosis may also influence your outcome and should be carefully monitored. These factors include additional chromosome abnormalities (also called aberrations or ACA) in cells with the Philadelphia chromosome. Some patients may also have mutations in genes other than *BCR::ABL1*, especially in advanced phase CML. These genetic changes may be associated with disease progression and poorer treatment response, but have not been shown to influence overall survival.

## Definitions of response

The goal of TKI treatment is to achieve disease remission. In CML, doctors often use the terms “remission” and “response” to mean the same thing. Response to treatment, or remission, is evaluated by measuring the number of copies of the *BCR::ABL1* gene (also called transcripts). There are different levels of response:

- **Complete hematologic response (CHR)** — Blood cell count has returned to normal. Blood tests do not show any immature white blood cells. Also, if initially enlarged, the spleen has returned to a normal size.
- **Complete cytogenetic response (CCyR)** — Cytogenetic analysis of bone marrow cells does not show any cells carrying the Philadelphia chromosome when at least 20 cells in metaphase (metaphase is a stage during cell division) are made visible. This corresponds to a *BCR::ABL1* value of 1% or less using the quantitative PCR test.
- **Major molecular response (MMR)** — The quantitative PCR test can still detect the presence of *BCR::ABL1*, but at a lower level (below 0.1%). This is considered an excellent response. MMR is often called MR<sup>3</sup>.
- **Deep molecular response (DMR) = MR<sup>4</sup>, MR<sup>4.5</sup> or MR<sup>5</sup>** — The PCR test can still detect *BCR::ABL1*, but at a very low level (*BCR::ABL1* below 0.01% for MR<sup>4</sup> and below 0.0032% for MR<sup>4.5</sup>). Some laboratories that cannot detect *BCR::ABL1* at these low levels describe the disease as being molecularly undetectable. Testing laboratories should state the sensitivity of their PCR test. *BCR::ABL1* levels as low as  $\leq 0.001\%$  can be detected (see Table 1).

Molecular response is measured using a PCR test to determine how much *BCR::ABL1* is present in the blood. The results should be reported on the International Scale (IS) so that results from different laboratories can be compared. To determine the deep levels of response, the blood sample must be of high quality. The quality is assessed by the number of copies of the reference gene (such as *ABL1* or *GUSB*). For each level of response, a minimum number of reference gene copies is required in the sample, as shown in Table 1.

**Table 1.**

Terms and abbreviations	<i>BCR::ABL1</i> <sup>IS</sup>	Minimum number of reference gene copies in the sample
Complete cytogenetic remission (CCyR)	$\leq 1\%$	10,000 <i>ABL1</i> or 24,000 <i>GUSB</i>
Major molecular response (MMR)	$\leq 0.1\%$	10,000 <i>ABL1</i> or 24,000 <i>GUSB</i>
MR <sup>4</sup>	$\leq 0.01\%$	10,000 <i>ABL1</i> or 24,000 <i>GUSB</i>
MR <sup>4.5</sup>	$\leq 0.0032\%$	32,000 <i>ABL1</i> or 77,000 <i>GUSB</i>
MR <sup>5</sup>	$\leq 0.001\%$	100,000 <i>ABL1</i> or 240,000 <i>GUSB</i>

$\leq$  means less than or equal to

## Monitoring response to treatment

Your doctor will monitor your response to treatment with a TKI by doing the tests shown in Table 2. Some patients respond and their treatment is continued. Other patients do not respond favorably to treatment or may become resistant, meaning that they no longer respond to their TKI. They may need a dose adjustment or a TKI switch. Finally, some patients may need a treatment change because they do not tolerate their drug.

In many countries, high-quality molecular PCR testing is available. Cytogenetic testing is no longer needed to monitor response after complete cytogenetic remission and/or a PCR level <1% have been achieved. Quantitative PCR should be used whenever possible to count the amounts of *BCR::ABL1* in the blood.

**Table 2.**

<b>Blood tests</b>	Every 2 weeks until complete hematologic response is achieved. More frequent testing may be needed in certain cases. Blood tests are done during first-line treatment and after switching TKIs.
<b>Molecular testing</b>	<b>Quantitative PCR:</b> At least every 3 months even after MMR is reached and confirmed. Testing every 4 to 6 months may be sufficient if patients stay in stable MMR or deeper response levels. More frequent testing or personalized PCR tests may be needed in certain cases.
<b>Cytogenetic testing</b>	<b>Chromosome banding analysis (CBA):</b> Is recommended only <ul style="list-style-type: none"> <li>to follow up patients with rare forms of <i>BCR::ABL1</i> that cannot be measured by quantitative PCR,</li> <li>to rule out additional chromosomal abnormalities and disease progression in patients who are resistant to treatment,</li> <li>to monitor patients progressing to blast phase.</li> </ul> <b>Fluorescence in situ hybridization (FISH):</b> <ul style="list-style-type: none"> <li>May be needed in patients with rare or unusual forms of <i>BCR::ABL1</i> genes.</li> </ul>

MMR is an excellent response to treatment and can be achieved by many patients. However, being in remission is not the same as being cured. Even if tests cannot find any trace of CML in your cells, the disease is still present, but at undetectable levels, and so may increase once more. This is why on-going treatment and regular monitoring are very important.

## Milestones of response




The following monitoring milestones are used to assess whether your treatment is effective or a switch of drug may be advised to reach a deeper response:

- **Favorable response** means that your treatment leads to a reduction in the amount of *BCR::ABL1* as shown in Table 3. *BCR::ABL1* is reduced to  $\leq 0.1\%$  within the first year of treatment. The development of resistance is unlikely. Your current treatment should be continued.
- **Warnings** are signs that your disease is not responding to treatment as well as in a patient in the favorable category but good responses may still be achieved with time. The development of resistance is possible. Your doctor may check you more frequently to decide if you need to switch your TKI.
- **Unfavorable response** means that your treatment is unlikely to be effective. The development of resistance is highly likely. You and your doctor should discuss switching your TKI.

The previous terms ‘optimal’, ‘warning’ and ‘failure’ have been replaced, but the definition of the milestones remain the same.

Table 3 shows milestones of response in CML, measured by PCR tests. Milestones are the same for first-line, second-line and third-line treatment.

**Table 3.**

Time	 Favorable response (treatment switch unnecessary)	 Warning (treatment switch may become necessary)	 Unfavorable response (treatment switch preferred)
<b>At diagnosis</b>	Does not apply at this stage	High-risk additional chromosome abnormalities in cells with the Philadelphia chromosome, high risk ELTS score	Does not apply at this stage
<b>At 3 months</b>	$BCR::ABL1^{IS} \leq 10\%$	$BCR::ABL1^{IS} > 10\%$	$BCR::ABL1^{IS} > 10\%$ if confirmed within 1–3 months
<b>At 6 months</b>	$BCR::ABL1^{IS} \leq 1\%$	$BCR::ABL1^{IS} > 1-10\%$	$BCR::ABL1^{IS} > 10\%$
<b>At 12 months</b>	$BCR::ABL1^{IS} \leq 0.1\%$	$BCR::ABL1^{IS} > 0.1-1\%$	$BCR::ABL1^{IS} > 1\%$ (1–10%, see below for other considerations)
<b>At any time</b>	$BCR::ABL1^{IS} \leq 0.1\%$	$BCR::ABL1^{IS} > 0.1-1\%$ Loss of MMR ( $> 0.1\%$ )	Loss or previous response, resistant to <i>BCR::ABL1</i> mutations, high-risk additional chromosome abnormalities in cells with the Philadelphia chromosome

Previous advice to switch treatment on failure to reach these molecular milestones has been changed. The decision to switch should now be tailored to each patient depending on individual circumstances.

- A switch should not be based on a single PCR result alone. Instead, results should be considered along with previous results and individual patient factors. For example, PCR results may increase because patients miss taking their medication as prescribed.
- Some patients may be slow to respond because they are intolerant or had a dose reduction.
- Some patients with *BCR::ABL1<sup>IS</sup>* results in the ‘unfavorable’ category are older and/or have other diseases. For them, a switch to a more effective drug with more side effects may do more harm than good. A switch is preferred in patients who, regardless of age, can tolerate a more effective TKI.
- A switch in a patient with unfavorable responses should not be motivated by the wish to reach deep

molecular response (MR<sup>4</sup> or better) and attempt TFR. Patients who do not reach the milestones of favorable response in the first 12 months are less likely to achieve and maintain TFR.

Further molecular monitoring may be needed if test results are unclear, or if patients cannot take their medication as prescribed because of side effects or intolerance. Patients with an unfavorable response or warning after one or more TKIs should be screened for mutations. Poor treatment compliance may also be a reason why patients do not achieve favorable responses.

## **Current treatments for CML**

The treatment of CML is mainly based on TKIs which have changed CML from a life-threatening cancer to a manageable disease. Since the last version of these recommendations, more TKIs have become available and several others are being tested in clinical studies. The choice among the different drugs makes it possible to achieve the best treatment outcomes for patients, but more drugs to choose from can make treatment decisions difficult. In addition, not all TKIs are approved in all countries.

CML treatments are defined according to the order that they are usually prescribed: first line (given as the first treatment line after diagnosis), second line, third line and so forth.

## **First-line treatment**

Currently, six TKIs are approved for first-line treatment of CML: **imatinib (Glivec<sup>®</sup> or Gleevec<sup>®</sup>)**, **dasatinib (Sprycel<sup>®</sup>)**, **nilotinib (Tasigna<sup>®</sup>)**, and **bosutinib (Bosulif<sup>®</sup>)** in many countries, **asciminib (Scemblix<sup>®</sup>)** only in some countries, and **radotinib (Supect<sup>®</sup>)** in South Korea. Imatinib was the first TKI used to treat CML. This is why it is called a first-generation TKI. Dasatinib, nilotinib, and bosutinib are second-generation drugs and asciminib is a fourth-generation TKI. The third-generation drug, ponatinib, is not used in first line because of a higher risk of side-effects. Imatinib and the second-generation drugs are now widely available as generic drugs. Since the last CML recommendations in 2022, various clinical studies have been conducted comparing TKIs for first-line treatment and the findings are summarized below.

Second-generation TKIs provided faster responses and better protection from progression to accelerated phase or blast phase compared to imatinib. Overall survival, however, was not better than with imatinib. A study comparing nilotinib and dasatinib suggested that both TKIs are equally effective when used in first line.

Another clinical study compared asciminib to a TKI chosen by the study doctor. After 1 and 2 years of treatment, more patients treated with asciminib achieved MMR than with the chosen TKI. There were also fewer serious adverse events reported with asciminib than with imatinib or second-generation TKIs. Although long-term survival data are not yet available, asciminib was approved for first-line treatment in the USA, and depending on price, could be a promising choice in other countries.

Before imatinib was introduced, interferon alpha (IFN) was the best available treatment for CML patients for whom stem cell transplantation was not an option. Several combinations of IFN with a TKI have been evaluated in clinical studies but results did not show a benefit to adding IFN to a TKI.

The approved TKI starting daily dose is: imatinib 400 mg, dasatinib 100 mg, bosutinib 400 mg, and nilotinib 600 mg (in two doses). Some doctors have recently tried starting TKI treatment with lower-than-standard doses in clinical studies. However, these approaches are experimental and have not been officially approved. The aim is to reduce side effects, improve compliance and lower treatment discontinuation while maintaining a good response. Studies with dasatinib and bosutinib have shown that patients might benefit from lower doses at the start of treatment. The dose can be increased depending on the response to treatment.

**Which TKI for first-line treatment?** ELN emphasize that the decision should be individualized and shared between doctor and patient considering the following points:

- What are your treatment goals – overall survival or TFR?  
For some older patients' survival might be the main treatment goal. For younger patients with life-long treatment achieving and maintaining TFR might be the desired goal. Quality of life data showed treatment discontinuation provided greater benefit to patients under 60 years at time of stopping than to those over 60.
- What are your prognostic factors at diagnosis?  
Patients with high ELTS scores may benefit from a more potent TKI.
- Do you have other medical conditions at diagnosis that may influence the choice of treatment?
  - Patients with lung disease should not use dasatinib.
  - Patients with problems of the stomach, intestine, kidneys or liver may prefer other TKIs over bosutinib.
  - Patients with diabetes mellitus, high or very high cardiovascular risk including past blockages of the blood vessels or inflammation of the pancreas should avoid nilotinib.
- Which TKIs are available and affordable?  
The choice of the right TKI also depends on their availability and cost. Generic drugs are cost-effective initial treatments for chronic phase CML.

## **Second-line treatment**

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Second-line treatment is treatment for a disease or condition after the initial treatment (first-line treatment). You and your doctor may decide to switch your initial first-line TKI to a second-line TKI. This happens in about 30–40% of patients because of intolerance or resistance.

Studies show that patients in at least MMR experiencing adverse events may benefit from a dose reduction rather than TKI switching. Imatinib can be reduced from 400 mg to 100–300 mg daily; dasatinib from 100 mg daily to 20–50 mg daily and nilotinib from 300 mg twice daily to 150–200 mg twice daily or even 150–200 mg once daily. Importantly, patients must not reduce the dose without consulting their doctor. Any dose reduction must be agreed with the doctor and assessed on an individual basis. After dose reduction, close monitoring of the response level is recommended.

A TKI switch is necessary, however, if certain serious side effects occur. These include water building up around the lungs (pleural effusions) despite dose reductions, high blood pressure in the lung vessels (pulmonary hypertension), blockages of the veins or arteries (venous or arterial occlusive events), inflammation of the small and large intestine (enterocolitis), serious conditions of the nervous system (e.g. dementia, Parkinsonism) and inflammation of the heart muscle (myocarditis), liver (hepatitis) or kidneys (nephritis) caused by the immune system. You should discuss with your doctor which TKI is best for you.

Dasatinib, nilotinib, bosutinib and in some countries asciminib can be used as second-line treatments after first-line imatinib. The same treatment response definitions are also used. There are no studies comparing the TKIs with each other and the choice of TKI is patient-related. Therefore, the ELN does not recommend the use of any specific TKI in second line unless patients have a *BCR::ABL1* mutation.

For treatment of resistance to a first-line second-generation TKI in patients without specific *BCR::ABL1* mutations, an early switch to ponatinib or asciminib (where approved for second-line treatment) should be considered. Both TKIs are described in more detail in the next section.

## **Treatment beyond second line**

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Treatment possibilities are available for patients who are no longer benefiting from first and second-lines. Patients who are intolerant to two or more previous TKIs can try using a different second generation TKI and possibly start with a lower dose that can be increased if needed.

For patients who are resistant to their second-line TKI, asciminib or ponatinib are the preferred treatments. Both asciminib and ponatinib have stronger action than first and second generation TKIs. The choice depends on the patient's *BCR::ABL1* mutations and other medical conditions.

**Ponatinib (Iclusig®)** is a third-generation TKI, that you may receive as third-line treatment if you do not respond to two other TKIs. You may also be given ponatinib if you have the genetic mutation called T315I or other mutations. The T315I mutation may cause resistance to other drugs. However, you and your doctor might consider that ponatinib is not suitable for you if you have any cardiovascular problems.

The approved starting dose of ponatinib is 45 mg once daily. Starting treatment at a lower dose of 30 mg or 15 mg may be advisable if patients have other medical conditions, especially cardiovascular risks. In patients with a *BCR::ABL1* mutation, particularly T315I, or for those with *BCR::ABL1<sup>IS</sup>* >10%, ponatinib should be started at 45 mg. Once patients have achieved a treatment response, the daily dose can be reduced to 15 mg.

**Asciminib (Scemblix®)** is a novel (new) TKI that targets a different site on the *BCR::ABL1* protein than the other TKIs. This novel mechanism leads to higher response rates and better tolerability compared to traditional TKIs.

Asciminib may be given to you in third-line if you did not tolerate or respond to treatment with one or two or more previous TKIs. Like ponatinib, asciminib can be given to patients with or without T315I mutation.

The approved starting dose of asciminib is 40 mg twice daily. Some patients received doses up to 200 mg twice daily in clinical trials and achieved good response rates. Asciminib was generally well tolerated. The most common serious side effects included high blood pressure and abnormalities of enzymes associated with the function of the pancreas (amylase and lipase).

In patients who are resistant to ponatinib and/or asciminib, stem cell transplantation should be considered as a treatment possibility.

Olverembatinib is approved for third and later treatment lines and/or for patients with T315I mutations only in China.

An overview of the choice of TKI for CML in chronic phase is shown in Table 4.

**Table 4.**

Line of treatment	Which patients?	Which treatment?
1 <sup>st</sup> line (first treatment after diagnosis)	All patients	<ul style="list-style-type: none"> <li>• <b>Imatinib</b> 400 mg once daily or lower if MMR achieved 300 mg once daily if poorly tolerated</li> <li>• <b>Dasatinib</b> 100 mg once daily or on 5 days a week, possibly a dose as low as 50 mg once daily or even lower in patients 70 years and older.</li> <li>• <b>Nilotinib</b> 300 mg twice daily</li> <li>• <b>Bosutinib</b> 400 mg once daily or lower dose if not tolerated</li> <li>• <b>Radotinib</b> 300 mg twice daily (only in South Korea)</li> <li>• <b>Asciminib</b> 80 mg once daily or 40 mg twice daily (only in some countries)</li> </ul>
2 <sup>nd</sup> line (previously treated with one TKI)	Patients with intolerance and side effects	<ul style="list-style-type: none"> <li>• <b>Any 2<sup>nd</sup> generation TKI</b> not used 1<sup>st</sup> line, choice depends on patient and treatment response. Doses may need to be adapted.</li> <li>• <b>Dose reduction rather than TKI switching</b> in patients with at least MMR. Certain side effects require TKI switch.</li> </ul>
	Patients with resistance to imatinib	<ul style="list-style-type: none"> <li>• <b>Any 2<sup>nd</sup> generation TKI</b> in patients without specific <i>BCR::ABL1</i> mutations. For patients with mutations choose the appropriate TKI.</li> </ul>
	Patients with resistance to second generation TKIs	<ul style="list-style-type: none"> <li>• <b>Ponatinib</b> or <b>asciminib</b> (if available for 2<sup>nd</sup> line) in patients who do not respond to 2<sup>nd</sup> generation TKI in 1<sup>st</sup> line</li> </ul>
3 <sup>rd</sup> line and later lines (previously treated with two or more TKIs)	Patients with intolerance	<ul style="list-style-type: none"> <li>• <b>Any 2<sup>nd</sup> generation TKI</b> not used 1<sup>st</sup> or 2<sup>nd</sup> line, possibly at a lower dose that can be increased</li> </ul>
	Patients with resistance to second generation TKIs	<ul style="list-style-type: none"> <li>• Depending on other medical conditions and <i>BCR::ABL1</i> mutations: <b>ponatinib</b> 45 mg once daily or lower dose if needed; lower dose after initial response, or <b>asciminib</b> 40 mg twice daily or 200 mg twice daily if T315I is detected</li> <li>• <b>Olverembatinib</b> in patients with T315I mutation (only in China)</li> <li>• Consider stem cell transplantation</li> </ul>
	Patients with intolerance to all available TKIs and/or with resistance to ponatinib and/or asciminib	<ul style="list-style-type: none"> <li>• Consider stem cell transplantation</li> </ul>

## **Resistance and *BCR::ABL1* mutations**

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Experience with first-line treatment in CML shows that 15–20% of patients have an unfavorable response to their first TKI treatment. In later treatment lines, an unfavorable response is seen in up to 50% of patients. Lack of response may also occur because patients do not take their drugs as prescribed. The presence of specific *BCR::ABL1* mutations may also be a reason why patients do not respond to the TKI.

Mutation testing should be done in patients who are resistant or show signs of becoming resistant to one or more TKIs, or who progress to or are in blast phase. Mutation testing is also recommended in some patients who relapse after stem cell transplantation. *BCR::ABL1* mutations are very rarely detected at diagnosis in chronic phase which is why testing is not needed then.

The best way to look for *BCR::ABL1* mutations is with a test called Next Generation Sequencing (NGS). If this test is not available, another method called Sanger sequencing can be used instead. In some cases, special PCR tests may also be done to check for certain mutations.

If a *BCR::ABL1* mutation is found, then the TKI should be switched. TKIs that are unlikely to be effective will not be used. Your doctor can discuss treatment choices with you.

## **Treatment of advanced-phase CML**

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Very few patients progress to advanced phase CML in countries with high diagnostic standards. In countries where diagnosis is limited, however, advanced phase CML is more common. Your doctor may use the ELN or the WHO classification to define your disease phase. Both classifications recognize signs of high-risk of progression to advanced phase in patients with chronic phase CML.

It is important to identify patients who are in or progressing to advanced phase CML as they will be treated differently to those in chronic phase. Patients who are in advanced phase at diagnosis seem to have a better prognosis than those who progress from chronic phase.

The ELN experts recommend that patients in blast phase should receive intensive combination chemotherapy with a TKI, preferably dasatinib or ponatinib, if possible. This should be followed by stem cell transplantation when possible. Other novel treatments are currently being studied.

## **Stem cell transplantation**

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If none of the drugs recommended for CML is effective or available, your doctor may suggest that you receive stem cells from a healthy donor. This procedure is called allogeneic stem cell transplantation (allo-SCT) and may offer a cure.

Stem cell transplantation is also a possibility for CML patients in chronic phase who do not achieve long-term disease control with TKI treatment, or who are intolerant to all available TKIs. Stem cell transplantation also remains a possibility for patients in or progressing to blast phase.

Thanks to advances in medicine, stem cell transplantation has become safer and can be offered to more patients, including older people or those with other diseases. In addition, a wider range of people can now be considered as donors.

Whenever possible, a stem cell transplantation should be performed in chronic phase since the chances of success are much better than in advanced phases. In resistant blast phase, stem cell transplantation is not recommended outside clinical studies.

## Treatment-free remission

Patients who have responded well to treatment with TKIs and who have maintained a deep molecular response (DMR) over a long period of time may no longer need TKI treatment. Some of these patients may be eligible to attempt discontinuing treatment under supervision by their doctor. Stopping treatment in this manner is known as treatment-free remission (TFR). Attempting TFR is usually safe if patients meet certain criteria and have access to high-quality molecular monitoring. TFR without monitoring and supervision of an experienced clinical team should not be attempted. Importantly, some patients who are eligible for TFR prefer to continue treatment.

**Table 5.**

Guidance for attempting treatment discontinuation
<p>According to ELN recommendations, the following <b>criteria must be met</b> before stopping treatment:</p> <ul style="list-style-type: none"> <li>• Patient is in first chronic phase of CML.</li> <li>• Patient is motivated to stop treatment and communicates well.</li> <li>• Patient has access to high-quality molecular monitoring with test results rapidly available.</li> <li>• Patient agrees to more frequent monitoring after stopping treatment.</li> </ul>
<p>A stop is allowed if the following <b>minimal</b> criteria are also met:</p> <ul style="list-style-type: none"> <li>• Patient is taking current TKI in first line or second line if the reasons for switch were intolerance or resistance due to a mutation sensitive to another TKI.</li> <li>• Patient has received TKI for more than 5 years (or more than 4 years with a second-generation TKI).</li> <li>• Patient has been in DMR (MR<sup>4</sup> or better) for more than 2 years.</li> </ul>
<p>Stopping treatment can be considered if the following <b>optimal</b> criteria are met:</p> <ul style="list-style-type: none"> <li>• Patient has received TKI treatment for more than 5 years.</li> <li>• Patient has been in DMR for more than 3 years if MR<sup>4</sup>.</li> <li>• Patient has been in DMR for more than 2 years if MR<sup>4.5</sup></li> </ul>
<p><b>Procedures after stopping:</b></p> <ul style="list-style-type: none"> <li>• Molecular monitoring every 6 to 8 weeks for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter. Monitoring may be needed more often if the number of <i>BCR::ABL1</i> transcripts increases.</li> <li>• Restart TKI treatment if MMR is lost.</li> <li>• If TKI treatment is restarted monitor every 4 to 6 weeks until MMR is regained and then every 3 months until MR<sup>4</sup> is regained.</li> </ul>

Some highly motivated patients may have a strong desire to attempt TFR although they are not yet in DMR. This may be the case with younger patients or women planning to have a child. These patients can consider switching treatment to a more effective TKI. However, there are no data showing that this approach provides better TFR results.

Not all patients are able to maintain TFR after stopping treatment, even if all the above-mentioned criteria are met. In clinical studies, the disease recurred in about 50–60% of patients following TKI stop, mostly within the first 6–8 months. This is why frequent molecular testing is very important in the first year after stopping treatment. In up to 14% of patients, CML comes back after more than 2 years in TFR. Patients should therefore be monitored every 3 months for life to prevent the disease progressing unnoticed. Patients with disease recurrence can usually restart TKI treatment. Most of these patients (90–95%) then achieve undetectable levels of disease again. The risk of CML recurring directly into blast phase is very low (less than 0.1%).

Patients with a first unsuccessful attempt to stop can try a second time. Patients with unusual junctions between BCR and ABL1 on chromosome 22, which are known as atypical *BCR::ABL1* transcripts, may consider discontinuing treatment if they have access to laboratories that can reliably measure the lowest amounts of transcripts.

Talk to your doctor if you consider attempting TFR. Your doctor should review the risks and benefits with you. The final decision to stop TKI treatment should be made jointly by you and your doctor.

## **Parenting**

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You may be at a stage where you are planning to have a family. And you may want to know how your disease and treatment might affect these plans. More information about pregnancy and parenting during treatment has become available, but is still limited.

### **Male patients**

So far, there is no clear evidence that men taking TKIs are less fertile, or that TKIs affect their partner's pregnancy or the health of their children. Therefore, men planning to father a child should continue taking their TKI.

### **Female patients**

Depending on the TKI, different amounts of drug can cross the placenta and may harm a developing child, especially between weeks 2 to 16 of pregnancy when organs are forming. This is why manufacturers of all TKIs used in CML continue to recommend treatment discontinuation during pregnancy. Similar birth defects have been seen in children of women taking imatinib, dasatinib or nilotinib. Little data are available for other TKIs. In recent years, overall fewer birth defects have been reported in relation to TKI use. This may be because patients and doctors are more aware of the risks and can better manage pregnancies.

Experience of women with CML who present to their doctors during pregnancy is limited. Management depends on the blood counts at diagnosis and the risk score. For patients with low-risk disease, CML is unlikely to progress during the pregnancy. These women might not need any treatment. Other women receive IFN through pregnancy. TKIs can be started after week 16 of pregnancy if necessary. For patients with very high white cell counts at diagnosis, a mechanical procedure to reduce white cell numbers, known as leucapheresis, can be used.

Patients already taking TKIs who wish to become pregnant should not use TKIs during the pregnancy. IFN is the safest treatment to manage pregnancy in women with CML. For patients in chronic phase whose CML is difficult to control or who are unable to maintain a good response, TKI discontinuation could cause harm to child and mother. Therefore, TKIs can be continued until pregnancy is confirmed by a positive pregnancy test 4 weeks after the last period. Doctors may recommend to continue/restart treatment with imatinib or nilotinib after 16 weeks of pregnancy. Dasatinib should not be used during pregnancy.

Women should not take TKIs while breast-feeding because small amounts pass into breast milk.

In advanced disease, women may need prompt treatment with high-dose chemotherapy or stem cell transplantation. If these patients become pregnant then the options should be carefully discussed with their doctor. The wishes of the patient and her family should always be respected.

Detailed guidance is now available for women with CML planning to have a child, for managing pregnancy in women with established CML, and for women who are pregnant and CML is confirmed when seeing their doctor.

## Adverse events

Most people with CML will take TKIs for many years. Today, there is a wider choice of TKIs, and doctors now have a better understanding of the safety of these drugs. Preventing and/or reducing side effects and helping patients have the best possible quality of life play an important part in patient care.

Like all drugs, treatment with TKIs can lead to side effects and complications otherwise known as adverse events. Unlike side effects that are directly caused by a drug (so-called toxicities), adverse events may be related to other health conditions, other medications, or aging. Some side effects may only appear after years of use, even if the drug has been considered very safe. Some can affect your health or impair your quality of life. That is why regular checkups and tests are important before and during TKI treatment. You may also have other conditions, apart from CML, and these should also be treated.

When choosing a TKI for you, your doctor will carefully review your medical history, current medications, and overall health. The goal is to choose a TKI that works well and is safe for you.

Certain side effects are serious and may require you to take another TKI. Your doctor can discuss the best choice with you. A preferred option may be to lower the dose if side effects occur, rather than switch TKIs. If your CML no longer responds to treatment then another more effective drug might be considered by you and your doctor. Generally, you should share any health problems with your doctor and discuss your CML treatment with your healthcare team.

Table 6 shows some important side effects that may occur more frequently with TKIs that are approved in different countries.

**Table 6.**

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
<b>Side effects affecting the blood vessels</b>						
Blood clots in the arteries (arterial thrombotic events)	0	(+)	+	0	++	0
High blood pressure in the arteries (arterial hypertension)	0	(+)	+	0	++	(+)
<b>Other side-effects</b>						
Skin inflammation (dermatitis)	+	+	++	+	+	(+)
Water building up around the lungs (pleural effusion)*	(+)	++	(+)	+	(+)	(+)
Puffy eyes (periorbital edema)	++	0	0	0	0	0
Diarrhea	+	(+)	0	+++**	0	0
Muscle cramps	++	0	0	0	0	0

This list includes some but not all side effects occurring with TKI treatment of CML. Many more, like headache, nausea, constipation and muscle pain (myalgia), are similarly common.

0 very rare or not described, (+) rare, + not infrequent ++ frequent, +++ very frequent.

\* Can occur late.

\*\* Often short term.

In summary, the present update emphasizes the need to tailor CML treatment to each individual patient. Any decision on choice or change of treatment should be carried out with your doctor and other healthcare professionals.

## Glossary

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**Accelerated phase (AP)** = A stage of development of CML between chronic phase and blast phase. If left untreated, the disease might progress to a more advanced stage.

**Additional chromosome abnormalities (ACA)** = Genetic changes beyond the Philadelphia chromosome that occur as the disease progresses. Additional chromosome abnormalities, also called additional chromosomal aberrations, are often linked to high risk.

**Additional chromosome aberrations** = See Additional chromosome abnormalities.

**Allogeneic stem cell transplantation** = A treatment in which a patient receives stem cells from a healthy donor to replace damaged or destroyed stem cells with healthy ones. Allogeneic stem cell transplantation can offer people with blood cancer the chance for a cure.

**BCR::ABL1** = The abnormal fusion gene that is typically present in people with CML. It is created when part of a gene called ABL1 that is normally found on chromosome 9 joins to part of a gene called BCR on chromosome 22. The result is a leukemia-causing fusion gene called *BCR::ABL1* on chromosome 22.

**Blast cells** = See Blasts.

**Blasts** = Immature blood cells that are formed in the bone marrow. Also called blast cells.

**Blast phase** = The stage of development of CML after chronic phase and accelerated phase. It is characterized by the presence of increasing numbers of immature blood cells called blasts in the blood and bone marrow. The disease worsens and the patient generally feels unwell.

**Bone marrow aspiration** = A procedure in which a liquid sample of bone marrow is removed from inside a bone using a hollow needle.

**Bone marrow biopsy** = A procedure in which a small piece of bone containing bone marrow is removed using a hollow needle.

**Chromosomes** = Thread-like structures inside cells that carry the genetic information (DNA) that determines traits and instructs the body how to grow and develop. A chromosome contains hundreds to thousands of genes. Normal human cells have 23 pairs of chromosomes.

**Chromosome banding analysis (CBA)** = A method of cytogenetic testing. A microscope is used to detect the Philadelphia chromosome and additional chromosome abnormalities in bone marrow cells.

**Chronic phase** = The initial, most stable stage of CML. If symptoms appear, they are likely to be mild and easily missed.

**Complete hematologic remission (CHR)** = See Complete hematologic response (CHR).

**Complete hematologic response (CHR)** = Blood cell count has returned to normal. Blood tests do not show any immature white blood cells. Also, if initially enlarged, the spleen has returned to normal size.

**Complete cytogenetic remission (CCyR)** = See Complete cytogenetic response (CHR).

**Complete cytogenetic response (CCyR)** = Analysis of bone marrow cells does not show any cells carrying the Philadelphia chromosome.

**Cytogenetic testing** = Testing that focuses on studying the structure and number of chromosomes in cells. Cytogenetic testing can be used to check if abnormal changes have occurred in the chromosomes of leukemia cells, such as the Philadelphia chromosome.

**Deep molecular remission (DMR)** = See deep molecular response.

**Deep molecular response (DMR)** = Cancer cells have greatly decreased following treatment but highly-sensitive tests can still detect *BCR::ABL1* at very low levels. A level of *BCR::ABL1*  $\leq 0.01\%$  is often referred to as MR4, *BCR::ABL1*  $\leq 0.0032\%$  as MR4.5, and *BCR::ABL1*  $\leq 0.001$  as MR5. Achieving and maintaining deep molecular response is a condition for stopping treatment.

**Drug intolerance** = Drug intolerance.

**Drug resistance** = See Resistance.

**European LeukemiaNet (ELN)** = An international not-for-profit research network of excellence for cooperative research on leukemia.

**EUTOS long-time survival (ELTS) score** = The preferred score to predict the risk of progression and the probability of dying from CML. The ELTS score is calculated using age, spleen size, blast percentage, and platelet count at diagnosis. The resulting risk score then indicates whether a patient has a low, intermediate or a high risk of progressing to blast phase.

**Favorable response** = A milestone of response. Favorable response means that treatment leads to a reduction in the amount of *BCR::ABL1*  $\leq 10\%$  at 3 months,  $\leq 1\%$  at 6 months,  $\leq 0.1\%$  at 12 months, or  $\leq 0.1\%$  at any time. The development of resistance is unlikely. Treatment can be continued.

**First-line treatment** = The initial treatment given to previously untreated patients.

**Fluorescence in-situ hybridization (FISH)** = A cytogenetic testing method used to detect abnormal chromosomes, such as the Philadelphia chromosome.

**Gene** = Segments of deoxyribonucleic acid (DNA) that are located inside every human cell and contain the information needed to determine physical and biological traits. Genes are contained in chromosomes.

**Gene transcripts** = Gene copies.

**Generic drug** = A drug that is developed to be the same as a brand-name drug that has already been authorized. The generic drug is a less expensive option and works in exactly the same way.

**International Scale (IS)** = A standardized method to measure *BCR::ABL1* in CML patients.

**Intolerance** = Inability of the body to tolerate adverse reactions to a medication.

**Major molecular remission (MMR)** = See Major molecular response (MMR).

**Major molecular response (MMR)** = Cells containing *BCR::ABL1* can still be detected but at a level  $\leq 0.1\%$ . This is considered an excellent response. Major molecular response is often called MR3.

**Molecular testing** = Testing to look for specific genetic changes in leukemia cells. These tests can help guide diagnosis and treatment and can provide information on disease risk. A common method for molecular testing is polymerase chain reaction (PCR).

**Mutation** = A spontaneous change in the structure of a gene or chromosome.

**Myeloid cells** = Blood cells that are formed in the bone marrow. These cells develop into red blood cells, platelets and various white blood cells.

**Next Generation Sequencing (NGS)** = Modern technology that can be used to detect genetic mutations such as *BCR::ABL1* and other abnormalities rapidly.

**Philadelphia (Ph) chromosome** = An abnormality in chromosome 22 found in almost all people with CML. It is formed when parts of chromosomes 9 and 22 break off and change location following an error in cell division. Part of chromosome 9 joins to chromosome 22, and part of chromosome 22 joins to chromosome 9.

**Polymerase chain reaction (PCR)** = A highly-sensitive test that is used to detect the presence or absence of *BCR::ABL1*. PCR can find even a very small number of cancer cells and accurately measure their amount in blood or tissue samples. It is recommended at the time of CML diagnosis, and is the most reliable way to monitor response to treatment and detect any signs of progression.

**Prognosis** = The likely outcome or course of a disease.

**Remission** = A decrease in or disappearance of the signs and symptoms of a disease, usually after treatment. Importantly, being in remission is not the same as being cured. Even if tests cannot find any trace of cancer in a patient's blood cells, the disease may return. This is why on-going treatment and regular monitoring are very important.

**Resistance** = The ability of cancer cells to survive, continue to grow, or spread even after treatment. Resistance occurs when cancer cells don't respond or stop responding to drugs intended to kill them or prevent them from growing.

**Response** = A reaction, change or improvement in a patient's condition that is related to treatment.

**Sanger sequencing** = A widely used method for detecting genetic mutations. Sanger sequencing can be used to check for *BCR::ABL1* mutations when next generation sequencing is not available.

**Second-line treatment** = Treatment given when the initial treatment doesn't work or stops working, for instance when treatment has caused side effects or when patients have developed resistance.

**Somatic mutations** = Genetic changes that are not inherited but occur after conception. In CML, these are changes in genes other than *BCR::ABL1*. They occur more commonly in advanced phase CML. These genetic changes may be associated with disease progression and poorer treatment response, but have not been shown to influence overall survival.

**Stem cell transplantation** = See allogeneic stem cell transplantation.

**Third-line treatment** = Treatment given when both initial (first-line) treatment and subsequent (second-line) treatment don't work or stop working, for instance when treatment has caused side effects or when patients have developed resistance.

**Toxicities** = Side effects that are directly caused by a drug.

**Transcripts** = See Gene transcripts.

**Translocation** = A genetic abnormality in which a part of a chromosome breaks off and joins to a different chromosome, meaning the chromosome part changes location.

**Treatment-free remission (TFR)** = The ability to maintain a deep molecular response and control the disease over a longer period of time after stopping treatment.

**Tyrosine kinase** = An enzyme that normally helps cells to grow and divide. In CML, an abnormal tyrosine kinase made by the *BCR::ABL1* gene stimulates the growth of leukemia cells.

**Tyrosine kinase inhibitor (TKI)** = A type of drug that blocks the action of tyrosine kinases. This stops the bone marrow from making more leukemia cells.

**Unfavorable response** = A milestone of response. Unfavorable response means that treatment is unlikely to be effective. The development of resistance is highly likely. This is why careful monitoring is very important. A treatment switch should be discussed.

**Warning** = A milestone of response. Warnings are signs that the disease is not responding to treatment favorably. However, good responses may still be achieved with time. The development of resistance is possible. Patients need to be monitored carefully and a treatment switch may become necessary.

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