Chronic Myeloid Leukemia Treatment (PDQ®)–Health Professional Version

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General Information About Chronic Myeloid Leukemia (CML)

Incidence and Mortality

Estimated new cases and deaths from CML in the United States in 2025:[1]

- New cases: 9,560.
- Deaths: 1,290.

CML is one of a group of diseases called the myeloproliferative disorders. It is also called chronic myelogenous leukemia. Other related entities include:

- Polycythemia vera.
- Myelofibrosis.
- Essential thrombocythemia.

For more information, see Myeloproliferative Neoplasms Treatment.

Molecular Genetics

CML is identified by too many myeloblasts in the blood and bone marrow, and the disease worsens as the number of myeloblasts increase.

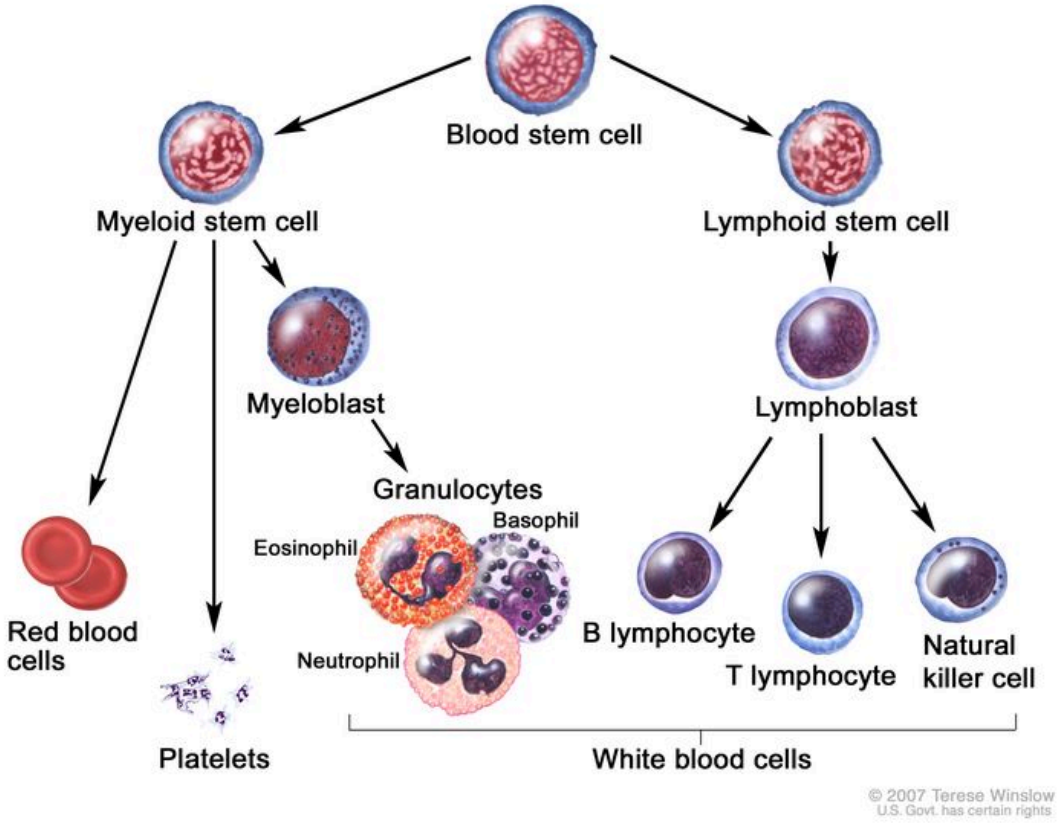

Figure 1. Hematopoietic tree, expanded lymphoid line.

CML is a clonal disorder that is easily diagnosed because the leukemic cells of more than 95% of patients have a distinctive cytogenetic abnormality, the Philadelphia chromosome (Ph).[2]

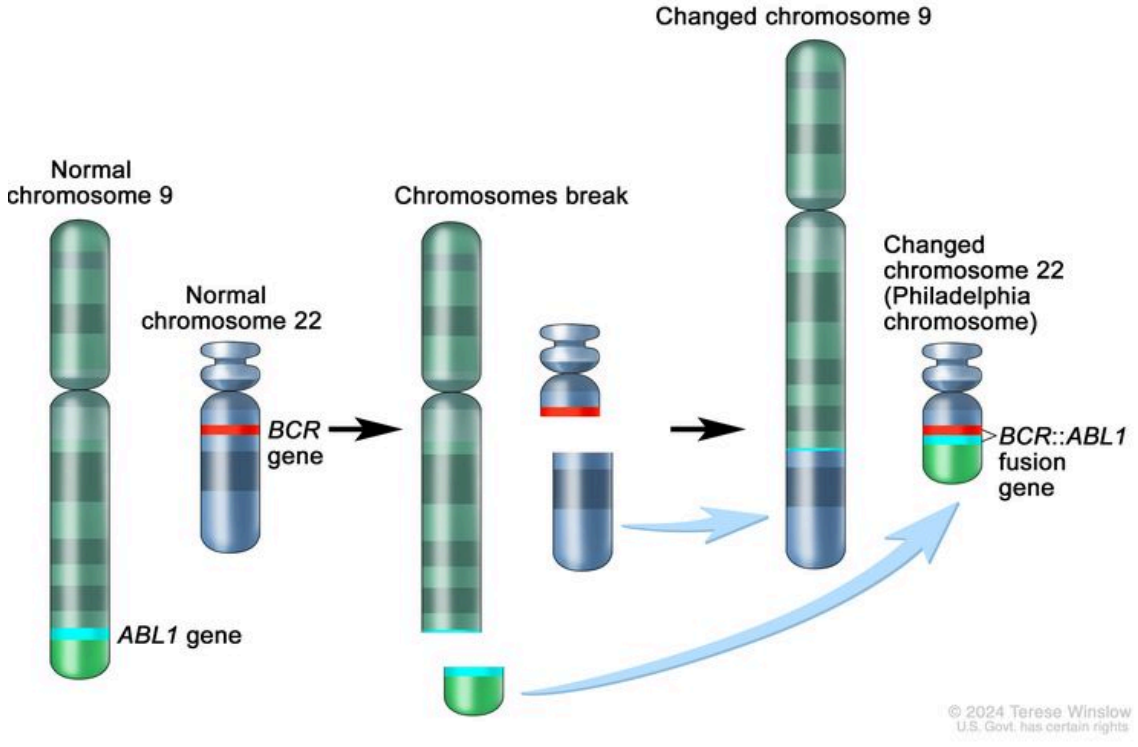

Figure 2. The Philadelphia chromosome is a translocation between the *ABL1* oncogene (on the long arm of chromosome 9) and the *BCR* gene (on the long arm of chromosome 22), resulting in the *BCR*::*ABL1* fusion gene. *BCR*::*ABL1* encodes an oncogenic protein with tyrosine kinase activity.

The Ph chromosome results from a reciprocal translocation between the long arms of chromosomes 9 and 22, and it is demonstrable in all hematopoietic precursors.[3] This translocation results in the transfer of the *ABL1* oncogene on chromosome 9 to an area of chromosome 22 termed the breakpoint cluster region (within the *BCR* gene).[3] This, in turn, results in a *BCR*::*ABL1* fusion gene and in the production of an abnormal tyrosine kinase protein that causes the disordered myelopoiesis found in CML. Using peripheral blood, molecular techniques can detect the presence of the 9;22 translocation.

Clinical Presentation

Although CML may present without symptoms, splenomegaly is the most common finding during physical examination at the time of diagnosis.[4] The spleen may be enormous, filling most of the abdomen, causing pain or a feeling of fullness and presenting a significant clinical problem, or the spleen may be only minimally enlarged. In about 10% of patients, the spleen is neither palpable nor enlarged on computed tomography (CT) scan.

Patients may also present with the following symptoms:

- Fatigue.
- Unexplained weight loss.
- Drenching night sweats.
- Fever.

Transition between the chronic, accelerated, and blastic phases may occur gradually over 1 year or more, or it may occur abruptly (blast crisis). Patients with accelerated-phase CML show signs of progression without meeting the criteria for blast crisis (acute leukemia). The following signs and symptoms indicate a change to accelerated-phase CML:

- Progressive splenomegaly.
- Increased leukocytosis and/or thrombocytosis.
- Progressive anemia.

The following signs and symptoms indicate a change to a blast crisis, in addition to the accelerated-phase CML symptoms:

- Thrombocytopenia.
- Increasing and painful splenomegaly or hepatomegaly.
- Fever.
- Bone pain.
- Development of destructive bone lesions.

In the accelerated phase, differentiated cells persist, although they often show increasing morphological abnormalities. The patient experiences increased anemia, thrombocytopenia, and marrow fibrosis.[4]

Risk Factors

Risk factors for CML include:

- Older age.
- Exposure to high-dose ionizing radiation.

Diagnostic Evaluation

In addition to a health history and physical examination, the initial workup may include:

- **Complete blood count with differential**.
- **Blood chemistry studies**.
- **Bone marrow aspiration and biopsy**. In routine presentations of CML, the utility of bone marrow aspiration and biopsy for all newly diagnosed patients is questionable outside the context of a clinical trial. Bone marrow testing is appropriate for patients with clinical signs of accelerated phase or blast crisis (fever, enlarged spleen, or >20% blasts in the peripheral blood).[5]
- **Cytogenetic analysis**.
- **Fluorescence *in situ* hybridization (FISH)**. FISH of the *BCR*::*ABL1* translocation can be performed using the bone marrow aspirate or peripheral blood of patients with CML.[4]
- **Reverse transcription–polymerase chain reaction (RT-PCR)**. A small subset of patients has the *BCR*::*ABL1* rearrangement detectable only by RT-PCR, which is the most sensitive technique currently available. Patients with RT-PCR evidence of the *BCR*::*ABL1* fusion gene appear clinically and prognostically identical to patients with a classic Ph chromosome. However, patients who are *BCR*::*ABL1*-negative by RT-PCR have a clinical course more consistent with chronic myelomonocytic leukemia, which is a distinct clinical entity related to myelodysplastic syndrome.[6-8]
- **CT scan**.

Prognosis and Survival

The median age of patients with Ph chromosome–positive CML is 67 years.[9] With the advent of the oral tyrosine kinase inhibitors (TKIs) , the median survival is projected to approach normal life expectancy for most patients.[10]

Ph chromosome–negative CML is a poorly defined entity that is less clearly distinguished from other myeloproliferative syndromes. Patients with Ph chromosome–negative CML generally have a poorer response to treatment and shorter survival than Ph chromosome–positive patients.[11] Ph chromosome–negative patients who have *BCR*::*ABL1* gene rearrangements detectable by Southern blot analysis, however, have prognoses equivalent to Ph chromosome–positive patients.[6,12]

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Histopathology and Phases of CML

Histopathological examination of the bone marrow aspirate of patients with chronic myeloid leukemia (CML) demonstrates a shift in the myeloid series to immature forms that increase in number as patients progress to the blastic phase of the disease. The marrow is hypercellular, and differential counts of both marrow and blood show a spectrum of mature and immature granulocytes like that found in normal marrow. Increased numbers of eosinophils or basophils are often present, and monocytosis is sometimes seen. Increased megakaryocytes are often found in the marrow, and sometimes fragments of megakaryocytic nuclei are present in the blood, especially when the platelet count is very high. The percentage of lymphocytes is reduced in both the marrow and blood compared with normal samples. The myeloid:erythroid ratio in the marrow is usually greatly elevated. The leukocyte alkaline phosphatase enzyme is either absent or markedly reduced in the neutrophils of patients with CML.[1]

Most patients do not require bone marrow examination. However, bone marrow testing is appropriate for patients with fever, malaise, rapidly enlarging splenomegaly, and more than 10% circulating blasts. In patients with CML, bone marrow sampling is performed to assess cellularity, fibrosis, and cytogenetics. Reverse transcription–polymerase chain reaction (RT-PCR) or fluorescence

in situ hybridization (FISH) analyses using blood or marrow aspirates demonstrate the 9;22 translocation.[1]

Chronic-Phase CML

Chronic-phase CML is characterized by bone marrow and cytogenetic findings as listed below with less than 10% blasts and promyelocytes in the peripheral blood and bone marrow.[2] The following factors are predictive of a shorter chronic phase after treatment with tyrosine kinase inhibitors:

- Older age.[3]
- Cytogenetic abnormalities in addition to the Philadelphia chromosome.[3,4]
- A higher proportion of marrow or peripheral blood blasts.[3]
- Anemia.[3]

Predictive models using multivariate analysis have been derived.[5-7]

The rate of progression from chronic phase to blast crisis is 5% to 10% in the first 2 years and 20% in subsequent years.[5]

For more information, see the Treatment of Chronic-Phase CML section.

Accelerated-Phase CML

Accelerated-phase CML is characterized by 10% to 19% blasts in either the peripheral blood or bone marrow.[2]

For more information, see the Treatment of Accelerated-Phase CML section.

Blastic-Phase CML

Blastic-phase CML is characterized by 20% or more blasts in the peripheral blood or bone marrow.

When 20% or more blasts are present along with fever, malaise, and progressive splenomegaly, the patient has entered blast crisis.[2]

For more information, see the Treatment of Blastic-Phase CML section.

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Treatment Option Overview for CML

Treatment of patients with chronic myeloid leukemia (CML) is usually initiated at diagnosis, which is based on the presence of an elevated white blood cell count, splenomegaly, thrombocytosis, and identification of the *BCR*::*ABL1* translocation.[1]

Table 1. Treatment Options for CML Phases

Phase	Treatment Options
Chronic-phase CML	Targeted therapy with an allosteric inhibitor of BCR::ABL1 at the ABL1 myristoyl pocket
	Targeted therapy with other BCR::ABL1 TKIs
	Allogeneic BMT or SCT
Accelerated-phase CML	Targeted therapy with TKIs
	Allogeneic SCT
Blastic-phase CML	Targeted therapy with TKIs
	Allogeneic BMT or SCT
Relapsed CML	Targeted therapy with TKIs

BMT = bone marrow transplant; CML = chronic myeloid leukemia; SCT = stem cell transplant; TKIs = tyrosine kinase inhibitors.

Targeted Therapy With Tyrosine Kinase Inhibitors (TKIs)

The optimal front-line treatment for patients with chronic-phase CML involves specific inhibitors of the BCR::ABL1 tyrosine kinase. Although imatinib mesylate has been extensively studied in patients with CML, TKIs with greater potency and selectivity for BCR::ABL1 than imatinib have also been evaluated.[1-4] Bariatric surgery may impede proper absorption of oral TKIs, resulting in suboptimal responses.[5]

Allogeneic Bone Marrow Transplant (BMT) or Stem Cell Transplant (SCT)

Allogeneic BMT or SCT has also been used with curative intent.[6] Long-term data beyond 10 years of therapy are available, and most long-term survivors show no evidence of the *BCR*::*ABL1* translocation by any available test (e.g., cytogenetics, reverse transcription–polymerase chain reaction, or fluorescence *in situ* hybridization). Some patients, however, are not eligible for this approach because of age, comorbid conditions, or lack of a suitable donor. In addition, substantial morbidity and mortality result from allogeneic BMT or SCT; a 5% to 10% treatment-related mortality can be expected, depending on whether a donor is related and the presence of mismatched antigens.[6]

Evidence (allogeneic SCT vs. drug treatment):

1. In a prospective trial of 427 transplant-eligible, previously untreated patients, 166 patients were allocated to allogeneic SCT, and 261 patients were allocated to drug treatment (mostly imatinib).[6][Level of evidence C1]
    - No difference in 10-year overall survival was reported between the treatment groups.

    Similar outcomes were seen in patients who underwent allogeneic SCT because of TKI intolerance or nonadherence.[7]

Interferon Alfa

Long-term data are also available for patients treated with interferon alfa.[8-10] Approximately 10% to 20% of these patients have a complete cytogenetic response with no evidence of *BCR*::*ABL1* translocation by any available test, and most of these patients are disease free beyond 10 years. Maintenance therapy with interferon is required, however, and some patients experience side effects that preclude continued treatment.

Hydroxyurea

Hydroxyurea is superior to busulfan in the chronic phase of CML, with significantly longer median survival and significantly fewer severe adverse effects.[11] A dose of 40 mg/kg per day is often used initially, and frequently results in a rapid reduction of the white blood cell (WBC) count. When the WBC count drops below 20×10^9/L, the hydroxyurea dose is often reduced and titrated to maintain a WBC count between 5×10^9/L and 20×10^9/L.

Hydroxyurea is used primarily to stabilize patients with hyperleukocytosis or as palliative therapy for patients who have not responded to other therapies.

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Treatment of Chronic-Phase CML

Treatment Options for Chronic-Phase CML

Treatment options for chronic-phase chronic myeloid leukemia (CML) include:

1. Targeted therapy with an allosteric inhibitor of BCR::ABL1 at the ABL1 myristoyl pocket (asciminib).

2. Targeted therapy with other BCR::ABL1 tyrosine kinase inhibitors (TKIs) (nilotinib, dasatinib, bosutinib, or imatinib).
3. Allogeneic bone marrow transplant (BMT) or stem cell transplant (SCT).

The preferred initial treatment for patients with newly diagnosed chronic-phase CML could be any of the specific inhibitors of the BCR::ABL1 tyrosine kinase (including asciminib, nilotinib, dasatinib, bosutinib, or imatinib).[1] With any of these agents, the 10-year event-free survival and overall survival (OS) rates exceed 90%.[2-4]

CML response rate abbreviations used in this section include:

- DMR: Deep molecular response (previously called CMR [complete molecular response]). This means greater than 4-log reduction (BCR::ABL1 ≤ 0.01%) and is also called MR 4 (molecular response 4). MR 4.5 is designated for BCR::ABL1 ≤ 0.0032%, and MR 5 is designated for BCR::ABL1 ≤ 0.001%.
- EMR: Early molecular response. This means a greater than 1-log reduction (BCR::ABL1 ≤ 10%) at 3 months.
- MMR: Major molecular response. This means a greater than 3-log reduction (BCR::ABL1 ≤ 0.1%).

A BCR::ABL1 transcript level of 10% or less in patients after 3 months of treatment with a specific TKI (deemed EMR) is associated with the best prognosis in terms of failure-free survival, progression-free survival (PFS), and OS.[5-10] However, in a retrospective analysis, even patients with a BCR::ABL1 transcript level greater than 10% after 3 months of therapy did well when the halving time was less than 76 days.[11]

Mandating a change of therapy based on this 10% transcript level at 3 to 6 months is problematic because 75% of patients do well even with a suboptimal response.[12] After 1 year, the preferred response target is an MMR, which is defined as a BCR::ABL1 level of less than or equal to 0.1%. The optimal target is a DMR, which is defined as under 4 logs (BCR::ABL1 ≤ 0.01%) or undetectable, which is usually a BCR::ABL1 level of less than or equal to 0.001% (MR 5).[13]

Targeted therapy with an allosteric inhibitor of BCR::ABL1 at the ABL1 myristoyl pocket

Evidence (targeted therapy with an allosteric inhibitor of BCR::ABL1 at the ABL1 myristoyl pocket):

1. A prospective study (NCT04971226) included 405 patients with newly diagnosed CML. Patients were randomly assigned to receive asciminib (n = 201) (an allosteric inhibitor of BCR::ABL1 at the ABL1 myristoyl pocket, a site unique from those used by other TKIs) or either imatinib mesylate (n = 102) or nilotinib, dasatinib, or bosutinib (n = 102).[14]
    - With a median follow-up of 16.3 months, the 48-week MMR rate was 67.7% for patients who received asciminib and 49% for patients who received imatinib, nilotinib, dasatinib, or bosutinib ($P < .002$).[14][Level of evidence B3]
    - Patients who received asciminib had fewer grade 3 or greater adverse events (38%) compared with imatinib (44%) and the other TKIs (55%). The rate of discontinuation due to

adverse events was lower for patients who received asciminib (5%) compared with patients who received imatinib (11%) or the other TKIs (10%).

- Asciminib showed improved efficacy in this early reporting of the trial, and it also showed better tolerability based on adverse events and discontinuations. On this basis, the U.S. Food and Drug Administration approved the use of asciminib as first-line therapy. Use of asciminib will pose significant financial toxicity ($260,000 per year in 2024) versus imatinib ($500 per year in 2024). The price of the other TKIs may decrease because dasatinib is available as a generic, and nilotinib, bosutinib, and ponatinib are expected to be released as generics in 2027.
- A prespecified subgroup analysis compared asciminib with the second-generation TKIs (not including imatinib). At week 48, 66.0% of patients who received asciminib had an MMR, and 57.8% of patients who received second-generation TKIs had an MMR. The 8.2% difference was not statistically significant (95% confidence interval [CI], -5.1 to 21.5). In the first year, it appears that the efficacy of asciminib is equivalent to those of second-generation TKIs. Longer follow-up is required to fully assess efficacy and toxicity outcomes.[14]

Targeted therapy with other BCR::ABL1 TKIs

Evidence (targeted therapy with other BCR::ABL1 TKIs):

1. A randomized prospective study of 846 patients compared nilotinib with imatinib.[15][Level of evidence B3]
    - The rate of MMR at 24 months was 71% and 67% for patients who received two-dose schedules of nilotinib and 44% for patients who received imatinib ($P < .0001$ for both comparisons).
    - Progression to accelerated-phase CML or blast crisis occurred in 17 patients who received imatinib (14%), but this progression only occurred in two patients who received nilotinib 300 mg twice daily (<1%, $P = .0003$) and in five patients who received nilotinib 400 mg twice daily (1.8%, $P = .0089$).
2. A randomized prospective study of 519 patients compared dasatinib with imatinib, with the following results:[16][Level of evidence B3]
    - The rate of MMR at 12 months was 46% for patients who received dasatinib and 28% for patients who received imatinib ($P < .0001$).
    - The rate of MMR at 24 months was 64% for patients who received dasatinib and 46% for patients who received imatinib ($P < .0001$).
    - At 5 years, there was no difference in PFS or OS.
    - Progression to accelerated-phase CML or blast crisis occurred in 13 patients (5%) who received imatinib and in six patients (2.3%) who received dasatinib (not statistically significant).
    - In retrospective comparative analyses, a dasatinib dose of 50 mg a day showed equal efficacy to 100 mg, but resulted in fewer pleural effusions (5% vs. 21%).[17][Level of evidence C3]

3. A randomized prospective study of 536 patients compared bosutinib with imatinib.[18][Level of evidence B3]
    - The MMR rate at 5 years was 73.9% for patients in the bosutinib arm versus 64.6% for patients in the imatinib arm (hazard ratio [HR], 1.57; 95% CI, 1.08–2.28; *P* = .0075). At 5 years, a DMR (4.5 logs) was attained by 47.4% of patients in the bosutinib arm and 36.6% of patients in the imatinib arm (HR, 1.57; 95% CI, 1.11–2.22).[18]
    - Progression to accelerated-phase CML or blast crisis occurred in four patients (1.6%) who received bosutinib and in six patients (2.5%) who received imatinib.

In randomized prospective trials, nilotinib, dasatinib, and bosutinib showed higher rates of earlier MMR compared with imatinib. It is unclear whether this will translate to improved long-term outcomes.[8,9,18][Level of evidence B3] A dose-ranging phase II study of dasatinib in patients older than 70 years showed optimal response and reduction of toxicity starting at 20 mg once daily (with dose escalation if needed), versus the standard dose of 100 mg daily.[19][Level of evidence C3]

Can TKIs be discontinued?

For patients who obtain a DMR, it is unclear if TKI therapy can be discontinued. Several nonrandomized reports are summarized as follows:[20-24][Level of evidence C3]

- Patients who have taken a TKI for more than 3 to 5 years and attained a DMR (molecular remission, 4.5; BCR::ABL1 ≤ 0.0032%) are the best candidates to consider stopping therapy.
- 50% of patients will experience a relapse of their disease if they discontinue TKI therapy. However, a retrospective analysis with a median follow-up of 3 years found that patients who were in DMR (4 to 4.5 logs) for 5 or more years had a relapse rate of approximately 10%.[25][Level of evidence C3] Another retrospective report with a median of 3 years of follow-up found three measurable factors predictive of MMR maintenance: increased duration of TKI treatment, increased duration of DMR on TKI treatment, and the absence of any peripheral blood blast cells at diagnosis.[20]
- Almost all patients who relapse based on BCR::ABL1 quantitative reverse transcription–polymerase chain reaction (RT-PCR) testing can be successfully reinduced with the previous TKI.

However, after the reinduction of a previous TKI, the duration of remissions or the depth of responses are not known. Data to recommend universal discontinuation of TKIs are insufficient, even in patients with a DMR or CMR. Follow-up (i.e., at least every 3 months initially, although the precise interval is not well-defined) is required after stopping therapy because relapses have been noted even after 2 to 3 years. A withdrawal syndrome of muscle and joint pain has been reported after discontinuing TKI therapy.[26] Quality-of-life assessments suggest improved social function, diarrhea, and fatigue after stopping TKI therapy.[27][Level of evidence C1]

Allogeneic BMT or SCT

Allogeneic BMT or SCT is the only consistently successful curative treatment for patients with CML.[28-30] Patients younger than 60 years with an identical twin or with HLA–matched siblings can consider BMT early in the chronic phase. Although the procedure is associated with considerable acute morbidity and mortality, 50% to 70% of patients who undergo transplant in the chronic phase appear to be cured. The results are better in younger patients, especially for those younger than 20 years. The outcomes of patients who undergo transplant in the accelerated and blastic phases of the disease are

progressively worse.[31,32] Most transplant series suggest improved survival when the procedure is performed within 1 year of diagnosis.[33-35][Level of evidence C1] The data supporting early transplant, however, have never been confirmed in controlled trials.

Evidence (allogeneic SCT):

1. In a randomized clinical trial, patients underwent allogeneic SCT after receiving preparative therapy with either cyclophosphamide and total-body irradiation (TBI) or busulfan and cyclophosphamide without TBI. The following results were reported:[36][Level of evidence A1]
    - Disease-free survival and OS were comparable between arms.
    - Busulfan and cyclophosphamide without TBI was associated with less graft-versus-host disease (GVHD) and fewer fevers, hospitalizations, and hospital days.
2. A retrospective review of 2,444 patients who underwent myeloablative allogeneic SCT reported the following:[37]
    - The 15-year OS rates were 88% (95% CI, 86%–90%) for sibling-matched transplant recipients and 87% (95% CI, 83%–90%) for unrelated-donor transplant recipients.
    - The cumulative incidences of relapse were 8% (95% CI, 7%–10%) for sibling-matched transplant recipients and 2% (95% CI, 1%– 4%) for unrelated-donor transplant recipients.
3. In a prospective trial of 354 patients younger than 60 years, 123 of 135 patients with a matched, related donor underwent early allogeneic SCT while the others received interferon-based therapy and imatinib at relapse. Some patients also underwent a matched unrelated-donor SCT in remission.[38][Level of evidence B4]
    - With a 9-year median follow-up, survival still favored the drug treatment arm (P = .049), but most of the benefit was early from transplant-related mortality, with the survival curves converging by 8 years.

Although most relapses occur within 5 years of transplant, relapses have occurred as late as 15 years after a BMT.[39] In a molecular analysis of 243 patients who underwent allogeneic BMT over a 20-year interval, only 15% had no detectable BCR::ABL1 transcript by PCR analysis.[40] The risk of relapse appears to be less in patients who underwent transplant early in disease and in patients who developed chronic GVHD.[32,41] In a retrospective review, patients with relapsed disease after allogeneic transplant who received TKI therapy had a 3-year OS rate of 60%.[42][Level of evidence C1]

With the introduction of asciminib, imatinib, dasatinib, bosutinib, and nilotinib therapy, the timing and sequence of allogeneic BMT or SCT has been questioned.[43] Allogeneic SCT is the preferred choice for certain patients presenting with blastic-phase disease, those with a *T315I* variant and resistance to ponatinib (an oral TKI), and for patients with complete intolerance to the pharmacological options.[44] Similar outcomes were seen in patients who underwent allogeneic SCT because of TKI intolerance or nonadherence.[45]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Accelerated-Phase CML

Treatment Options for Accelerated-Phase CML

Treatment options for accelerated-phase chronic myeloid leukemia (CML) include:

1. Targeted therapy with tyrosine kinase inhibitors (TKIs).
    - Bosutinib.
2. Allogeneic stem cell transplant (SCT).

Targeted therapy with TKIs

Bosutinib

The U.S. Food and Drug Administration approved bosutinib as a first-line treatment for patients with accelerated-phase CML. These patients were included in the initial phase I/II trial that showed improved efficacy versus imatinib, based on response rates and major molecular response at 5 years of follow-up.[1][Level of evidence C3]

Allogeneic SCT

Induction of remission using a TKI and consideration of an allogeneic SCT for patients with poor responses, when feasible, is a standard approach for patients with accelerated-phase CML.[2]

Evidence (imatinib vs. allogeneic SCT):

1. A cohort study of 132 patients with accelerated-phase CML compared imatinib with allogeneic SCT as first-line therapy, with a median follow-up of 32 months.[2][Level of evidence C1]
    - The overall survival rate was improved using allogeneic SCT for the Sokal high-risk patients (100% vs. 17.7%; $P = .008$).
    - For Sokal low- and intermediate-risk patients, there were no survival differences between the two first-line approaches.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Blastic-Phase CML

Treatment Options for Blastic-Phase CML

Treatment options for blastic-phase chronic myeloid leukemia (CML) include:

1. Targeted therapy with tyrosine kinase inhibitors (TKIs).
2. Allogeneic bone marrow transplant (BMT) or stem cell transplant (SCT).

Targeted therapy with TKIs

Bosutinib, imatinib mesylate, dasatinib, and nilotinib have demonstrated activity in patients with myeloid blast crisis and lymphoid blast crisis or Philadelphia (Ph) chromosome–positive acute lymphoblastic leukemia (ALL).[1-3]

Evidence (targeted therapy with TKIs):

1. Two trials of imatinib mesylate and one trial of dasatinib involved a total of 518 patients with blastic-phase CML.[2,4,5][Level of evidence C1]
    - The studies confirmed a hematologic response rate of 42% to 55% and a major cytogenetic response rate of 16% to 25%, but the estimated 2-year survival rate was below 28%.
2. Patients with lymphoid blastic-phase CML (as opposed to the more common myeloid blastic phase) have been given the same therapy as patients with Ph chromosome–positive ALL. In a phase II trial, 23 patients with lymphoid blastic-phase CML received hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and dasatinib. The major molecular response rate was 70%, and most patients were referred for allogeneic SCT.[6][Level of evidence C3]
3. A review of 477 patients with blastic-phase CML treated between 1997 and 2016 at a single center showed that 72% had received previous TKI therapy in chronic phase before transformation.[7][Level of evidence C3]
    - The median overall survival was 12 months.
    - The median failure-free survival was 5 months.
    - Patients who could complete an allogeneic SCT fared best, but this may have resulted from selection bias.

Allogeneic BMT or SCT

Allogeneic BMT or SCT should be considered when feasible, depending on response and durability of response.[8-12]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Relapsed CML

Treatment Options for Relapsed CML

Treatment options for relapsed chronic myeloid leukemia (CML) include:

1. Targeted therapies with tyrosine kinase inhibitors (TKIs).
    - Ponatinib.
    - Asciminib.

Relapsed CML is characterized by any evidence of progression of disease from a stable remission. This may include:

- Increasing myeloid or blast cells in the peripheral blood or bone marrow.
- Cytogenetic positivity when previously cytogenetic negative.
- Fluorescence *in situ* hybridization (FISH) positivity for *BCR*::*ABL1* translocation when previously FISH negative.

Detection of the *BCR*::*ABL1* translocation by reverse transcription–polymerase chain reaction (RT-PCR) during prolonged remissions does not constitute relapse on its own. However, exponential drops in quantitative RT-PCR measurements for 3 to 12 months correlates with the degree of cytogenetic response, just as exponential rises may be associated with quantitative RT-PCR measurements that are closely connected with clinical relapse.[1] Overt treatment failure is defined as a loss of hematologic remission or progression to accelerated-phase or blast crisis phase CML. A consistently rising quantitative RT-PCR BCR::ABL1 level suggests relapsed disease.

Targeted therapy with TKIs

In case of treatment failure or suboptimal response, patients should undergo BCR::ABL1 kinase domain mutation analysis to help guide therapy with the newer TKIs or with allogeneic transplant.[2,3]

Variants in the tyrosine kinase domain can confer resistance to imatinib mesylate. Alternative TKIs such as dasatinib, nilotinib, or bosutinib, higher doses of imatinib mesylate, and allogeneic stem cell transplant (SCT) have been studied in this setting.[4-16] In particular, the *T315I* variant marks resistance to imatinib, dasatinib, nilotinib, and bosutinib.

Ponatinib

Ponatinib is an oral TKI that has activity in patients with *T315I* variants or in patients for whom another TKI failed.[17-19] Multiple phase II studies concluded that the optimal response (≤1% BCR::ABL1) and least toxicity occurred at a 45 mg starting dose, with a decrease to 15 mg upon achieving the response.[20,21][Level of evidence C3] Ponatinib is associated with increased cardiovascular adverse

events. Patients with significant cardiovascular disease, hypertension, or diabetes mellitus have been excluded from clinical trials.[20,21]

Evidence (ponatinib):

1. Ponatinib has been studied in multiple phase II studies involving 799 patients.[17,21][Level of evidence C3]
    - Of the 799 patients with the *T315I* variant or resistance to two or more prior TKIs, 46% to 68% had an optimal response (≤1% BCR::ABL1) to ponatinib.
2. In a retrospective review of 184 patients with recurrent chronic CML and the *T315I* variant, the following was reported:[18][Level of evidence C3]
    - Patients treated with ponatinib had a higher 4-year overall survival (OS) rate than did patients treated with allogeneic SCT (73% vs. 56%; hazard ratio [HR], 0.37; 95% confidence interval [CI], 0.16–0.84; *P* = .017).
    - For patients with accelerated-phase CML, survival was equivalent; however, for patients with blast crisis-phase CML, OS was worse for those who received ponatinib (HR, 2.29; 95% CI, 1.08–4.82; *P* = .030).
3. In a retrospective review, patients with a *T315I* variant and CML that did not respond to ponatinib had a poor prognosis, with a median survival of 16 months. The outcomes for these patients were best after allogeneic SCT, but this could have resulted from selection bias.[22][Level of evidence C3]
4. A phase II trial of 282 patients was conducted to determine the lowest efficacious dose of ponatinib, because higher doses are correlated with arterial occlusive events.[20]
    - The optimal dose was found to be an initial 45 mg dose given once daily, then lowered to 15 mg upon achievement of a response (≤1% BCR::ABL1).[20]

Asciminib

Asciminib is an allosteric inhibitor of BCR::ABL1 at the ABL1 myristoyl pocket, a site unique from those used by TKIs.

Evidence (asciminib):

1. An open-label randomized clinical trial compared asciminib with bosutinib. With a median follow-up of 14.9 months, 233 patients with refractory or resistant disease were randomly assigned in a 2:1 ratio to receive either asciminib or bosutinib.[23]
    - The major molecular response (MMR) rate at week 24 was 25.5% for patients who received asciminib versus 13.2% for patients who received bosutinib. The difference in response (adjusted for major cytogenetic response at baseline) was 12.2% (95% CI, 2.19%–22.30%; *P* = .029).[23][Level of evidence B3]
    - Grade 3 or 4 adverse events were experienced by 50.6% of patients who received asciminib and 60.5% of patients who received bosutinib.
2. A phase I trial of asciminib included heavily pretreated patients who experienced resistance or unacceptable side effects after standard TKIs. Patients with a *T315I* variant and those in whom

ponatinib failed were included.[24][Level of evidence C3]

- Of 141 patients, 48% achieved an MMR by 12 months.

3. A phase II trial included 31 patients who received asciminib.[25][Level of evidence C3]
    - An MMR rate of 41% was reported by 12 months.
    - Three of nine patients with disease that failed to respond to previous ponatinib responded to asciminib.

Current Clinical Trials

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Key References for CML

These references have been identified by members of the PDQ Adult Treatment Editorial Board as significant in the field of chronic myeloid leukemia (CML) treatment. This list is provided to inform users of important studies that have helped shape the current understanding of and treatment options for CML. Listed after each reference are the sections within this summary where the reference is cited.

- Hughes TP, Saglio G, Kantarjian HM, et al.: Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. Blood 123 (9): 1353-60, 2014. [PUBMED Abstract]

  Cited in:

  - Treatment of Chronic-Phase CML

- Jabbour E, Kantarjian HM, Saglio G, et al.: Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood 123 (4): 494-500, 2014. [PUBMED Abstract]

  Cited in:

  - Treatment of Chronic-Phase CML

- Kantarjian HM, Hochhaus A, Saglio G, et al.: Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol 12 (9): 841-51, 2011. [PUBMED Abstract]

  Cited in:

  - Treatment of Chronic-Phase CML

Latest Updates to This Summary (03/13/2025)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date

above.

General Information About Chronic Myeloid Leukemia (CML)

Updated statistics with estimated new cases and deaths for 2025 (cited American Cancer Society as reference 1).

Treatment of Chronic-Phase CML

Revised text about a prospective study that included 405 patients with newly diagnosed CML. Patients were randomly assigned to receive asciminib or either imatinib mesylate or nilotinib, dasatinib, or bosutinib. A prespecified subgroup analysis compared asciminib with the second-generation tyrosine kinase inhibitors (TKIs) (not including imatinib). At week 48, 66.0% who received asciminib had a major molecular response (MMR), and 57.8% of patients who received second-generation TKIs had an MMR. The 8.2% difference was not statistically significant. In the first year, it appears that the efficacy of asciminib is equivalent to those of second-generation TKIs. Longer follow-up is required to fully assess efficacy and toxicity outcomes.

This summary is written and maintained by the PDQ Adult Treatment Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® Cancer Information for Health Professionals pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of chronic myeloid leukemia. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Adult Treatment Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Chronic Myeloid Leukemia Treatment are:

- Aaron Gerds, MD (Cleveland Clinic Taussig Cancer Institute)
- Eric J. Seifter, MD (Johns Hopkins University)

Any comments or questions about the summary content should be submitted to Cancer.gov through the NCI website's Email Us. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Adult Treatment Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

Permission to Use This Summary

The preferred citation for this PDQ summary is:

PDQ® Adult Treatment Editorial Board. PDQ Chronic Myeloid Leukemia Treatment. Bethesda, MD: National Cancer Institute. Updated <MM/DD/YYYY>. Available at: https://www.cancer.gov/types/leukemia/hp/cml-treatment-pdq. Accessed <MM/DD/YYYY>. [PMID: 26389354]

Disclaimer

Based on the strength of the available evidence, treatment options may be described as either “standard” or “under clinical evaluation.” These classifications should not be used as a basis for insurance reimbursement determinations. More information on insurance coverage is available on Cancer.gov on the Managing Cancer Care page.

Contact Us

More information about contacting us or receiving help with the Cancer.gov website can be found on our Contact Us for Help page. Questions can also be submitted to Cancer.gov through the website's Email Us.

Updated: March 13, 2025
