

## LEUKEMIA TREATMENT REGIMENS: Chronic Myeloid Leukemia (CML) (Part 1 of 3)

**Clinical Trials:** The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

### Primary Treatment<sup>1</sup>

**Note:** All recommendations are Category 2A unless otherwise indicated.

REGIMEN	DOSING
<b>Ph positive or BCR-ABL positive<sup>2-9</sup></b>	Imatinib 400mg orally daily (Category 1) <b>OR</b> Nilotinib 300mg orally twice daily (Category 1) <b>OR</b> Dasatinib 100mg orally daily (Category 1).

### 3 Month Evaluation

<b>BCR-ABL1/ABL1&lt;10% (IS) or PCyR<sup>2-9</sup></b>	Continue current regimen.
<b>If response of BCR-ABL1 transcripts &gt;10% (IS) or less than PCyR on bone marrow cytogenetics<sup>9-12</sup></b> Evaluate patient compliance and drug-drug interactions, consider mutational analysis and bone marrow cytogenetics	<b>Primary Treatment with Imatinib</b> Change Therapy to alternate TKI <b>OR</b> Imatinib dose may be increased to a maximum of 800 mg, if tolerated <b>and</b> evaluate for hematopoietic stem cell transplantation (HSCT) depending on response to tyrosine kinase inhibitor (TKI) therapy <b>Primary Treatment with Nilotinib or Dasatinib</b> Continue same dose of nilotinib or dasatinib <b>OR</b> Change Therapy to alternate TKI (other than imatinib) <b>and</b> evaluate for HSCT depending on response to TKI therapy

### 6 Month Evaluation<sup>1</sup>

<b>BCR-ABL1/ABL1&lt;10% (IS) or PCyR<sup>2-9</sup></b>	Continue current regimen.
<b>If response of BCR-ABL1 transcripts &gt;10% (IS) or less than PCyR on bone marrow cytogenetics<sup>13</sup></b> Evaluate patient compliance and drug-drug interactions, consider mutational analysis and bone marrow cytogenetics	Change Therapy to alternate TKI (other than imatinib) and evaluate for HSCT depending on response to TKI therapy

### 12 Month Evaluation<sup>1</sup>

<b>Complete cytogenetic response<sup>2-9</sup></b>	Continue current regimen.
<b>Partial cytogenetic response<sup>10</sup></b> Evaluate patient compliance and drug-drug interactions, consider mutational analysis and bone marrow cytogenetics	Change therapy to alternate TKI (other than imatinib) <b>OR</b> Continue same dose of TKI <b>OR</b> Increase dose of imatinib to a maximum dose of 800 mg, as tolerated (if not candidate for alternate TKI or omacetaxine)
<b>Minor or no cytogenetic response<sup>10</sup></b> Evaluate patient compliance and drug-drug interactions, consider mutational analysis	Change therapy to alternate TKI (preferred) (other than imatinib) <b>and</b> evaluate for HSCT depending on response to TKI

*continued*

# LEUKEMIA TREATMENT REGIMENS: Chronic Myeloid Leukemia (CML) (Part 2 of 3)

## 12 Month Evaluation<sup>1</sup> (continued)

REGIMEN	DOSING
<b>Cytogenetic relapse<sup>10</sup></b> Evaluate patient compliance and drug-drug interactions, mutational analysis	Change therapy to alternate TKI (preferred) (other than imatinib) <b>OR</b> Increase dose of imatinib to a maximum dose of 800 mg, as tolerated (if not candidate for alternate TKI or omacetaxine) and evaluate for HSCT depending on response to TKI therapy.

## 18 Month Evaluation<sup>1</sup>

<b>Complete cytogenetic<sup>2-9</sup></b>	Continue previous regimen.
<b>Partial cytogenetic response<sup>14</sup></b> Evaluate patient compliance and drug-drug interactions, mutational analysis	Change therapy to alternate TKI (other than imatinib) <b>and</b> repeat bone marrow evaluation at 3 months to document Complete Cytogenetic Response (CCyR) <b>AND</b> Evaluation for HSCT depending on response to TKI therapy.
<b>Cytogenetic relapse<sup>14</sup></b> Evaluate patient compliance and drug-drug interactions, mutational analysis	Change therapy to alternate TKI (other than imatinib) <b>and</b> repeat bone marrow evaluation at 3 months to document Complete Cytogenetic Response (CCyR) <b>AND</b> Evaluation for HSCT depending on response to TKI therapy.

## Advanced Phase<sup>1</sup>

<b>Accelerated phase<sup>15-31</sup></b>	Imatinib 600mg orally daily <b>OR</b> Dasatinib 140mg orally daily (70mg twice daily) <b>OR</b> Nilotinib 400mg orally twice daily <b>OR</b> Bosutinib 500mg orally daily <b>OR</b> Omacetaxine 1.25mg/m <sup>2</sup> SC twice daily on days 1–14 cycled every 28 days until hematologic response, followed by omacetaxine 1.25mg/m <sup>2</sup> SC twice daily on days 1–7 cycled every 28 days until disease progression or unacceptable toxicity <b>AND</b> Consider HSCT based on response.
<b>Blast phase—lymphoid<sup>15-31</sup></b>	ALL-type induction chemotherapy, <b>plus</b> TKI followed by HSCT, if feasible <b>OR</b> TKI followed by HSCT, if feasible.
<b>Blast phase—myeloid<sup>15-31</sup></b>	AML-type induction chemotherapy, <b>plus</b> TKI followed by HSCT, if feasible. <b>OR</b> TKI followed by HSCT, if feasible.

## References

- NCCN Clinical Practice Guidelines in Oncology™. Chronic Myelogenous Leukemia. v 1.2015. Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/cml.pdf](http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf). Accessed October 29, 2014.
- Kantarjian HM, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;28:398–404.
- Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2012;119:1123–1129.
- Hochhaus A, Kim D-W, Shah NP, et al. Four-year (yr) follow-up of patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) receiving dasatinib or imatinib: efficacy based on early response [abstract]. *Blood*. 2013;122: Abstract 653.
- Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia*. 2012;26:2197–2203.
- 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*. 2014;123:1353–1360.
- O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994–1004.
- Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251–2259.
- Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol*. 2010;28:398–404.
- Hanfstain B, Muller MC, Hehlmann R, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia*. 2012;26:2096–2102.

*continued*

## LEUKEMIA TREATMENT REGIMENS: Chronic Myeloid Leukemia (CML) (Part 3 of 3)

### References (continued)

11. 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*. 2014;123:494-500.
12. Yeung DT, Osborn MP, White DL, et al. Early switch to nilotinib does not overcome the adverse outcome for CML patients failing to achieve early molecular response on imatinib, despite excellent overall outcomes in the TIDEL II trial [abstract]. *Blood*. 2012;120:Abstract 3771.
13. Kim DD, Lee H, Kamel-Reid S, Lipton JH. BCR-ABL1 transcript at 3 months predicts long-term outcomes following second generation tyrosine kinase inhibitor therapy in the patients with chronic myeloid leukaemia in chronic phase who failed imatinib. *Br J Haematol*. 2013;160:630-639.
14. Falchi L, Kantarjian HM, Wang X, et al. Significance of deeper molecular responses in patients with chronic myeloid leukemia in early chronic phase treated with tyrosine kinase inhibitors. *Am J Hematol*. 2013;88:1024-1029.
15. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood*. 2002;99:1928-1937.
16. Kantarjian HM, Cortes J, O'Brien S, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. *Blood*. 2002;99:3547-3553.
17. Kantarjian HM, O'Brien S, Cortes JE, et al. Treatment of Philadelphia chromosome-positive, accelerated-phase chronic myelogenous leukemia with imatinib mesylate. *Clin Cancer Res*. 2002;8:2167-2176.
18. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood*. 2002;99:3530-3539.
19. Palandri F, Castagnetti F, Testoni N, et al. Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up. *Haematologica*. 2008;93:1792-1796.
20. Palandri F, Castagnetti F, Alimena G, et al. The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up. *Haematologica*. 2009;94:205-212.
21. Silver RT, Cortes J, Waltzman R, et al. Sustained durability of responses and improved progression-free and overall survival with imatinib treatment for accelerated phase and blast crisis chronic myeloid leukemia: long-term follow-up of the STI571 0102 and 0109 trials. *Haematologica*. 2009;94:743-744.
22. Rea D, Etienne G, Nicolini F, et al. First-line imatinib mesylate in patients with newly diagnosed accelerated phase-chronic myeloid leukemia. *Leukemia*. 2012;26:2254-2259.
23. Ohanian M, Kantarjian HM, Quintas-Cardama A, et al. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. *Clin Lymphoma Myeloma Leuk*. 2014;14:155-162 e151.
24. Apperley JF, Cortes JE, Kim D-W, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START A trial. *J Clin Oncol*. 2009;27:3472-3479.
25. Cortes J, Kim DW, Raffoux E, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. *Leukemia*. 2008;22:2176-2183.
26. Kantarjian H, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. *Blood*. 2009;113:6322-6329.
27. Le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. *Leukemia*. 2012;26:1189-1194.
28. Giles FJ, Kantarjian HM, le Coutre PD, et al. Nilotinib is effective in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. *Leukemia*. 2012;26:959-962.
29. Gambacorti-Passerini C, Cortes JE, Khoury HJ, et al. Safety and efficacy of bosutinib in patients with AP and BP CML and ph+ ALL following resistance/intolerance to imatinib and other TKIs: Update from study SKI-200 [abstract]. *J Clin Oncol*. 2010;28(15\_suppl):Abstract 6509.
30. Sokal JE, Baccarani M, Russo D, Tura S. Staging and prognosis in chronic myelogenous leukemia. *Semin Hematol*. 1988;25:49-61.
31. Nicolini FE, Khoury HJ, Akard L, et al. Omacetaxine mepesuccinate for patients with accelerated phase chronic myeloid leukemia with resistance or intolerance to two or more tyrosine kinase inhibitors. *Haematologica*. 2013;98: e78-79.

(Revised 11/2014)

© 2014 by Haymarket Media, Inc.