Dovepress

Open Access Full Text Article

PERSPECTIVES

How I Manage Patients with Chronic Myeloid Leukemia (CML): Perspectives from Clinical Practice

Guru Subramanian Guru Murthy

Division of Hematology & Oncology, Medical College of Wisconsin, Milwaukee, WI, USA

Correspondence: Guru Subramanian Guru Murthy, Division of Hematology & Oncology, Medical College of Wisconsin, Milwaukee, WI, USA, Tel +1 414-805-4600, Fax +1 414-805-6815, Email gmurthy@mcw.edu

Abstract: The management of chronic myeloid leukemia (CML) has remarkably changed in the last 20 years with the availability of tyrosine kinase inhibitors (TKI). Most patients with chronic phase CML now have a life expectancy like that of age matched controls. Understanding the practical aspects of choosing the appropriate TKI, monitoring response and side-effects are key to long term success. Currently, treatment cessation is also an option in patients achieving sustained deep molecular response. Novel agents are needed in patients with lack of response to TKI and in those with advanced disease.

Keywords: leukemia, myeloid, chronic, treatment

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of t (9, 22) leading to BCR-ABL1 gene rearrangement. In United States, it is diagnosed at a median age of 67 years with about 8450 new cases in 2020.[1] Although CML was considered as a deadly disease in the past, the availability of BCR-ABL tyrosine kinase inhibitors (TKI) have remarkably changed the outlook of this disease. Currently, CML is considered as a disease that is well manageable with oral TKI giving excellent long-term results and the option for stopping treatment in some patients. In this review, we will discuss about the practical aspects of managing CML and the common considerations given at various levels of management.

Considerations for Diagnosis

Most patients with CML present with leukocytosis and left shifted granulocytes, and/or thrombocytosis. Symptoms at presentation are variable and could include fever, night sweats, fatigue, and some patients are asymptomatic. To diagnose CML, the demonstration of the Philadelphia chromosome abnormality or the BCR-ABL gene rearrangement is important. At the cytogenetic level, CML is characterized by a reciprocal translocation in chromosomes 9 and 22.[2] This leads to the fusion of BCR and ABL1 genes. The breakpoint typically occurs in introns 13 or 14 of the BCR gene in chromosome 22 and exons 1 or 2 of ABL1 in chromosome 9. This results in the typical transcripts (e13a2 or e14a2) and major fusion protein (p210). In some patients, the break points can occur at other exon location (e1a2 with p190, e19a2 with p230, e13a3, e14a3) and should be considered if the classical major BCR is not present. Confirmation of t (9, 22) can be done using conventional karyotyping or Fluorescence-in-situ-hybridization studies and the identification and quantitation of the BCR-ABL1 fusion transcripts can be done using polymerase chain reaction (PCR). Testing can be done either from the peripheral blood or bone marrow specimens, although, obtaining a bone marrow biopsy at baseline would also assist in confirming the disease phase and provide an opportunity to assess for additional chromosomal abnormalities.

Once a diagnosis established, it is important to know the disease phase and the risk status to determine the optimal first line therapy. CML has 3 phases - chronic, accelerated and blast phase. While most of the patients diagnosed with CML are in chronic phase, some patients have higher disease risk with presentations such as accelerated or blast phase. Knowing the disease phase is important as the management and prognosis differs significantly based on this aspect. Patients with chronic phase CML now have a survival that is similar to age matched controls, but patients

1

with blast phase CML have a median survival of 7–11 months.[3,4] Chronic phase CML can be risk stratified using Sokal risk score (used more commonly in US) based on age, spleen size by clinical exam, platelet counts and peripheral blast percentage.[5] This stratification helps in understanding the prognosis and choosing the first line therapy.

Considerations for Initial Management with First Line TKI

Currently, imatinib, dasatinib, nilotinib and bosutinib are available as first line options for management of CML. Imatinib is a first generation TKI that was compared against interferon and cytarabine for newly diagnosed CML and showed significantly higher response rates (major cytogenetic response 87.1% vs 34.1%) and lower risk of transformation to accelerated or blast phase (freedom from progression 96.7% vs 91.5%).[6] Subsequently, second generation TKI such as dasatinib, nilotinib, and bosutinib were compared against imatinib in prospective clinical studies and showed encouraging efficacy[7–12] (Table 1). In general, starting treatment with second generation TKI would lead to quicker achievement of cytogenetic and molecular responses, minimizes the risk of transformation to accelerated phase or blast crisis and allows for patients to be eligible for stopping therapy after achievement of a sustained deep molecular response. However, the overall survival is not significantly different between first generation and second generation TKI and patients treated with imatinib therapy can still be candidates for treatment cessation as long as they achieve the goals (see Considerations for Stopping TKI).

In practice, the choice of TKI is guided by disease risk status, side-effect profile and financial affordability and reimbursement for patients. Given the higher risk of transformation to advanced stage disease in patients with intermediate-high risk chronic phase CML, starting treatment with second generation TKI would reduce this risk and is commonly preferred. In patients with low-risk disease, either first generation (imatinib) or second generation TKI are suitable options for frontline therapy. A careful assessment of concomitant medications is essential while administering TKI as medications such as proton pump inhibitors and H2-receptor blockers decreases the drug exposure while azole antifungals, certain antidepressants, supplements such as curcumin, green tea extract, and *Ginkgo biloba* increases the drug exposure. The side-effect profile between the TKI also play an important role in the therapy selection. Imatinib is associated with rash, fluid overload, muscle cramps and liver abnormalities. Dasatinib is associated with pleural effusions and pulmonary hypertension. Nilotinib could cause QTc prolongation, pancreatitis, hyperglycemia and peripheral arterial occlusive disease. Bosutinib could lead to diarrhea and hepatotoxicity. Hence, choosing them based on patient's comorbid conditions and preference would be reasonable. For example, imatinib, dasatinib, and bosutinib could be options for patients with arrhythmia, heart disease, pancreatitis, or hyperglycemia while imatinib, nilotinib, or bosutinib could be selected for patients with lung disease.

Dose holding and adjustments are considered in the event of toxicities from therapy. Cytopenia such as neutropenia (ANC $<1.0\times10^9$/L) and thrombocytopenia (platelets $<50\times10^9$/L) would require dose holding, growth factor support as indicated and resumption of therapy upon improvement. Similarly, grade 3–4 non-hematological toxicities such as diarrhea, transaminitis (with or without hyperbilirubinemia), QTc prolongation are addressed by dose interruption till resolution and restarting at the same or reduced dose based on the severity and time taken for recovery. Gastrointestinal upset is manageable by taking the medication with meal (if appropriate) and large glass of water. Pleural effusion associated with dasatinib can be addressed with additional measures such as diuretics, steroids, and pleural tap. In patients who develop recurrent pleural effusion or pulmonary arterial hypertension, dasatinib would be switched to another appropriate TKI.

Table 1 Outcomes of First Line Therapy with TKI

TKI Choice	Early Molecular Response	Complete Cytogenetic Response at 12 Months	Major Molecular Response at 12 Months	Accelerated/ Blast Phase Transformation	Overall Survival at 5-Years
Dasatinib vs Imatinib	84% vs 64%	83% vs 72%	46% vs 28%	4.6% vs 7.3% by 5 years	91% vs 90%
Nilotinib vs Imatinib	91% vs 67%	80% vs 65%	44% vs 22%	0.7% vs 4.2%	93.7% vs 91.7%
Bosutinib vs Imatinib	75% vs 57%	77% vs 66%	47% vs 37%	2.2% vs 2.6%	94.5% vs 94.6%

Monitoring of Response

After initiation of first line therapy, patients are periodically monitored for molecular response using PCR for BCR-ABL transcript every 3 months. Achievement of BCR-ABL1 (IS) ≤10% by 3–6 months after starting therapy is known as early molecular response and is associated with improved outcomes.[13] Major molecular response (MMR) is defined by BCR-ABL1 (IS) ≤0.1% and would be typically expected to happen within 1 year after starting therapy. Deep molecular responses with BCR-ABL1 (IS) ≤0.01—0.0032% (MR4-MR4.5) are also seen in patients responding to treatment. In patients not achieving molecular milestones at appropriate timepoints or in patients with loss of response, measures such as ensuring compliance to therapy, reviewing concomitant medications, testing for cytogenetics to look for additional cytogenetic abnormalities, performing bone marrow biopsy to reassess disease phase, and checking BCR-ABL kinase domain mutations are considered based on true lack of response versus inadequate drug delivery.

Considerations for Second Line TKI

Patients with CML may require a second line TKI either due to lack of response or intolerance to first line TKI. In case of intolerance to a first line TKI, switching to a second line TKI with non-overlapping toxicity profile is reasonable. Similarly, intolerance to a second generation TKI is mostly addressable by switching to a different TKI with non-overlapping toxicity profile. Lack of response to standard dose first line imatinib is addressed best by switching to a second generation TKI as shown in prospective clinical trials.[14–16] Achievement of major cytogenetic response was the primary endpoint in most of these trials and dasatinib (major cytogenetic response 59%, complete cytogenetic response 44%,), nilotinib (major cytogenetic response 56%, complete cytogenetic response 41%) and bosutinib (major cytogenetic response 57%, complete cytogenetic response 44%) yielded similar results. The choice between these second generation TKI can be guided further through kinase domain mutation analysis as certain mutations such as T315I are sensitive to ponatinib (Table 2).

The choice of a subsequent TKI in patients with lack of response or progression after initial second generation TKI is challenging. Mutation profiling is helpful in identifying resistance mutations to various TKI in this setting and further therapy selection. Both bosutinib and ponatinib have prospective data in this patient population and could be considered.[17,18] In patients with T315I gatekeeper mutation, ponatinib is an active agent although there is risk of arterial occlusive events with higher dose (45mg). However, the OPTIC study explored the efficacy and safety of three different doses of ponatinib (15mg, 30mg, and 45mg) and demonstrated that starting treatment with 45mg dose followed by dose reduction to 15mg upon achievement of BCR-ABL1 ≤1% yielded the optimal risk/benefit ratio.[19] This strategy is currently recommended while using ponatinib. An additional newer option for managing patients with resistance to TKIs is described later (Newer agents).

For patients treated with first line imatinib who do not achieve optimal response at 3, 6 or 12 months, switching to a second generation TKI such as dasatinib or nilotinib could improve the responses.[20,21] However, this would be a consideration only after certain important steps such as close monitoring and repeat testing to confirm suboptimal response, ensuring treatment adherence, and discussion with the patient about this option.

Considerations for Stopping TKI

Given the excellent deep responses with long term TKI therapy, studies have demonstrated the feasibility of stopping TKI therapy in patients who achieve sustained deep molecular remission. In United States, a prospective longitudinal study (LAST study) with 173 patients showed a treatment free remission rate of 60.8% and similar results have been shown in other studies[22-27] (Table 3). The current NCCN guidelines describes the eligibility for TKI cessation as patients with age ≥ 18 years, chronic phase CML, no prior history of accelerated phase/blast phase, presence of a quantifiable BCR-ABL transcript,

Table 2 BCR-ABL1 Mutation Profile

Mutation	Drug to be Avoided
V299L, G250E, F317L, T315I	Bosutinib
F317L/V/I/C, V299L, T315I	Dasatinib
Y253H, E255K/V, F359V/C/I, T315I	Nilotinib

Table 3 TKI Cessation Studies

Study	Characteristics	Treatment Free Remission/Molecular Relapse Free Survival	Trigger to Restart TKI
LAST	N= 173 TKI – imatinib, dasatinib, nilotinib, bosutinib	60% at 12 months	Loss of MMR
ENESTfreedom	N=215 TKI – nilotinib	51.6% (48 weeks)	Loss of MMR
DasFree	N=84 Dasatinib	46% (2 years)	Loss of MMR
Euro-SKI	N=821 TKI - Imatinib, nilotinib or dasatinib	50% (12 months)	Loss of MMR
Twister	N=40 TKI - imatinib	47.1% (24 months)	Loss of MMR or two consecutive positive samples at any value
STIM1	N=100 TKI- Imatinib	38% (60 months)	Loss of MMR or atleast 2 positive PCR with 1 log increase

treatment with TKI for at least 3 years with minimum 2 years of stable molecular response of MR4 (BCR-ABL1 $\leq$0.01), and access to reliable PCR monitoring during follow-up.[28] During the period after stopping TKI, close monthly monitoring with q-PCR for the first 6 months, bimonthly monitoring during months 7–12, followed by quarterly thereafter indefinitely is recommended as long as they maintain major molecular response (BCR-ABL1 $\leq$0.1%). In patients who lose MMR, prompt resolution of TKI can get most of them back to MMR. For example, in the ENESTfreedom study, 98.9% of patients who need to restart nilotinib regained MMR and 92.3% regained MR4.5.[27] Additional attempts of TKI cessation can be considered under clinical trials and referral to academic centers is recommended.

Role of Allogeneic Hematopoietic Stem Cell Transplantation (HCT)

In the current era, patients with chronic phase CML patients are not routinely considered for allogeneic HCT given excellent long-term outcomes with TKI. However, in patients with resistance to all available TKI, progression to accelerated phase or blast phase while on TKI and in those who present with accelerated or blast phase CML, early referral to allogeneic HCT is important. A recent analysis by the center for international blood and marrow transplant research (CIBMTR) showed a 5-year overall survival of 53% after allogeneic HCT with either myeloablative or reduced intensity conditioning.[29]

Role of Omacetaxine Mepesuccinate

Omacetaxine mepesuccinate is a protein synthesis inhibitor that blocks protein translocation in ribosomes and induces apoptosis of oncoproteins such as BCR-ABL1, Mcl-1, cMyc, cyclin D1 and is unaffected by BCR-ABL1 mutations. It is approved for treatment of CML patients in chronic or accelerated phase with resistance or intolerance to 2 or more TKI. Major cytogenetic response of 18–20% in chronic phase and a major hematological response of 14–27% in accelerated phase has been seen in clinical studies.[30–32] This is an option for management of progressive or TKI intolerant CML although newer agents are actively being investigated in this setting.

Newer Agents

Asciminib is an allosteric inhibitor that binds to the myristoyl pocket of the BCR-ABL1 kinase and acts independent of the ATP binding site (which is the mechanism of action for most TKI). In a Phase I study, single agent asciminib resulted in 92% hematological response, 54% complete cytogenetic response, 48% major molecular response by 12 months

4

Blood and Lymphatic Cancer: Targets and Therapy 2022:12

including those in patients with T315I mutation (28%) or resistance/intolerance to ponatinib (57%).[33] In a Phase III open label randomized study, asciminib was compared against bosutinib in CML patients after 2 or more prior TKI and showed superior MMR at 24 weeks (25.5% vs 13.2%) with a difference of 12.2% after adjusting for baseline major cytogenetic response.[34] The drug was FDA approved in October 2021 for the management of chronic phase CML with 2 or more prior TKI and those with T315I mutation. This is an exciting option given the unmet need for patients with resistance/intolerance to current available TKI and those with T315I mutations. The dose is 80 mg once daily or 40mg twice daily. In patients with T315I mutation, the dose is 200 mg twice daily. Rare complications such as asymptomatic lipase elevation and clinical pancreatitis needs to be monitored.

Conclusions

CML is a prototype disease where molecular discoveries and targeted therapies have revolutionized the clinical management and outcomes. Both continuous management with TKI as well as cessation of therapy after achievement of deep sustained molecular response are available as options for managing these patients. While the outcomes of chronic phase CML remain excellent, careful monitoring of response, management of side-effects and considering the financial burden of therapy are key aspects of management. Novel therapies are needed to address patients with disease progression after TKI and those with blast crisis.

Funding

Disclosure

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590
2. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. *Blood*. 2008;112(13):4808–4817. doi:10.1182/blood-2008-07-077958
3. Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol*. 2015;2(5):e186–93. doi:10.1016/S2352-3026(15)00048-4
4. Hehlmann R. How I treat CML blast crisis. *Blood*. 2012;120(4):737–747. doi:10.1182/blood-2012-03-380147
5. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood*. 1984;63:789–799. doi:10.1182/blood.V63.4.789.789
6. 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(11):994–1004. doi:10.1056/NEJMoa022457
7. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2260–2270. doi:10.1056/NEJMoa1002315
8. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: the Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. *J Clin Oncol*. 2016;34(20):2333–2340. doi:10.1200/JCO.2015.64.8899
9. 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. doi:10.1056/NEJMoa0912614
10. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia*. 2016;30(5):1044–1054. doi:10.1038/leu.2016.5
11. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: results from the Randomized BFORE Trial. *J Clin Oncol*. 2018;36(3):231–237. doi:10.1200/JCO.2017.74.7162
12. Brummendorf TH, Cortes JE, Milojkovic D, et al. Bosutinib (BOS) Versus Imatinib for Newly Diagnosed Chronic Phase (CP) Chronic Myeloid Leukemia (CML): final 5-Year Results from the Bfore Trial. *Blood*. 2020;136(Supplement 1):41–42. doi:10.1182/blood-2020-137393
13. Hanfstein B, Müller 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(9):2096–2102. doi:10.1038/leu.2012.85
14. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. *Am J Hematol*. 2016;91:869–874. doi:10.1002/ajh.24423
15. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a Phase II study. *Leukemia*. 2013;27:107–112. doi:10.1038/leu.2012.181
16. Gambacorti-Passerini C, Cortes JE, Lipton JH, et al. Safety and efficacy of second-line bosutinib for chronic phase chronic myeloid leukemia over a five-year period: final results of a phase I/II study. *Haematologica*. 2018;103:1298–1307. doi:10.3324/haematol.2017.171249

17. Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. *Am J Hematol*. 2016;91:1206–1214. doi:10.1002/ajh.24536

18. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A Phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369 (19):1783–1796. doi:10.1056/NEJMoa1306494

19. Cortes J, Apperley J, Lomaia E, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. *Blood*. 2021;138(21):2042–2050. doi:10.1182/blood.2021012082

20. Cortes JE, De Souza CA, Ayala M, et al. Switching to nilotinib versus imatinib dose escalation in patients with chronic myeloid leukaemia in chronic phase with suboptimal response to imatinib (LASOR): a randomised, open-label trial. *Lancet Haematol*. 2016;3(12):e581–e591. doi:10.1016/S2352-3026(16)30167-3

21. Cortes JE, Jiang Q, Wang J, et al. Dasatinib vs. imatinib in patients with chronic myeloid leukemia in chronic phase (CML-CP) who have not achieved an optimal response to 3 months of imatinib therapy: the DASCERN randomized study. *Leukemia*. 2020;34(8):2064–2073. doi:10.1038/s41375-020-0805-1

22. Atallah E, Schiffer CA, Radich JP, et al. Assessment of Outcomes After Stopping Tyrosine Kinase Inhibitors Among Patients With Chronic Myeloid Leukemia: a Nonrandomized Clinical Trial. *JAMA Oncol*. 2021;7(1):42–50. doi:10.1001/jamaoncol.2020.5774

23. Guru Murthy GS, Atallah E. Treatment-Free Remission in CML: the US Perspective. *Curr Hematol Malig Rep*. 2019;14(1):56–61. doi:10.1007/s11899-019-0496-8

24. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747–757. doi:10.1016/S1470-2045(18)30192-X

25. Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*. 2013;122(4):515–522. doi:10.1182/blood-2013-02-483750

26. Etienne G, Guilhot J, Rea D, et al. Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia. *J Clin Oncol*. 2017;35(3):298–305. doi:10.1200/JCO.2016.68.2914

27. Radich JP, Hochhaus A, Masszi T, et al. Treatment-free remission following frontline nilotinib in patients with chronic phase chronic myeloid leukemia: 5-year update of the ENESTfreedom trial. *Leukemia*. 2021;35(5):1344–1355. doi:10.1038/s41375-021-01205-5

28. Deininger MW, Shah NP, Altman JK, et al. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(10):1385–1415. doi:10.6004/jnccn.2020.0047

29. Chhabra S, Ahn KW, Hu ZH, et al. Myeloablative vs reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chronic myeloid leukemia. *Blood Adv*. 2018;2(21):2922–2936. doi:10.1182/bloodadvances.2018024844

30. Cortes JE, Nicolini FE, Wetzler M, et al. Subcutaneous omacetaxine mepesuccinate in patients with chronic-phase chronic myeloid leukemia previously treated with 2 or more tyrosine kinase inhibitors including imatinib. *Clin Lymphoma Myeloma Leuk*. 2013;13:584–591. doi:10.1016/j.clml.2013.03.020

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. doi:10.3324/haematol.2012.083006

32. Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: results with 24 months of follow-up. *Cancer*. 2015;121(10):1637–1644. doi:10.1002/cncr.29240

33. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. *N Engl J Med*. 2019;381 (24):2315–2326. doi:10.1056/NEJMoa1902328

34. Réa D, Mauro MJ, Boquimpani C, et al. A Phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood*. 2021;138(21):2031–2041. doi:10.1182/blood.2020009984