

A Focus on Chronic Myelogenous Leukemia



ASHP Advantage E-Newsletter

September 2010

The Future of Chronic Myelogenous Leukemia: New Treatments on the Horizon

Imatinib revolutionized the treatment of chronic myelogenous leukemia (CML), improving the prognosis to such an extent that the malignancy is a chronic disease for many patients.¹ However, problems with imatinib resistance and intolerance are common. Second-generation tyrosine kinase inhibitors (TKIs) were developed to overcome these problems, but treatment failure can occur with these agents, especially in patients with highly-resistant mutations (e.g., T315I). Therefore, research has continued to develop therapies with greater efficacy in patients with CML.

Response to treatment may be monitored using various blood and bone marrow tests and outcome measures, including hematologic response, cytogenetic response, and molecular response. Hematologic response is defined as complete normalization of the peripheral blood counts. A complete hematologic response (CHR) reflects a normal peripheral complete blood count and differential and the absence of immature cells (i.e., blasts) in the blood.^{2,3} A partial hematologic response reflects the presence of immature cells or a platelet count less than 50% of the value prior to therapy, although greater than 450,000 cells/mm³. A partial hematologic response also reflects continuing splenomegaly. Major hematologic response (MHR) is defined as CHR or no evidence of leukemia (immature cells) in the setting of peripheral blood counts that have not normalized.

A complete cytogenetic response (CCyR) reflects the absence of cells with the Philadelphia chromosome in the blood and bone marrow. The presence of up to 34% of cells with the Philadelphia chromosome is considered a partial cytogenetic response, and the presence of 35% to 90% of cells with the Philadelphia chromosome is a minor cytogenetic response (MiCyR). A major cytogenetic response (MCyR) represents a complete or partial cytogenetic response. Cytogenetic monitoring is the most commonly-used method for assessing response to CML therapy. A standard goal of therapy for CML is to achieve a CCyR within 18 months after initiation of therapy.

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A complete molecular response (CMR) reflects the absence of BCR-ABL chimeric mRNA, the aberrant tyrosine kinase protein that causes rapid proliferation of CML cells, using a polymerase chain reaction blood test. A major molecular response (MMR) reflects the presence of a very low amount (at least 3-log reduction) of BCR-ABL in the blood.

Bosutinib

Bosutinib (formerly known as SKI-606) is an oral TKI with activity against multiple BCR-ABL tyrosine kinase mutations (excluding T315I) and src kinases.¹ Overexpression of src kinases is associated with resistance to TKIs. The results of three phase I/II studies of the safety and efficacy of bosutinib 500 mg/day in patients with CML were presented at the American Society of Clinical Oncology (ASCO) 46th Annual Meeting in June 2010.

The first study involved 299 patients with chronic-phase CML, 72% of whom were imatinib-resistant and 28% of whom were imatinib-intolerant.⁴ The median duration of bosutinib therapy was 16.5 months.

Bosutinib toxicities were similar to those associated with currently available TKIs.⁴ Nineteen percent of patients discontinued bosutinib therapy because of toxicity. The most common adverse events involved the gastrointestinal tract (diarrhea, nausea, and vomiting) and usually were grade 1 or 2 in severity, transient, and manageable. The most common grade 3 or 4 hematologic abnormalities were thrombocytopenia (23%), neutropenia (14%), and anemia (9%). Hypermagnesemia (11%) and increased alanine aminotransferase levels (10%) were common grade 3 or 4 laboratory abnormalities.

The CHR rate was 78% in 132 patients evaluable for hematologic response.⁴ Of 192 patients evaluable for cytogenetic response, 111 (58%) patients achieved an MCyR, including 89 (46%) patients with a CCyR. Of 156 patients evaluable for molecular response, 76 (49%) achieved an MMR, including 47 (30%) patients with a CMR. All response rates were higher in patients with imatinib intolerance than in patients with imatinib resistance.

Twenty different mutations were found at baseline in 45 (45%) of 99 patients.⁴ The CHR rate was 78% in patients with mutations and 89% in patients without mutations, and the MCyR rate was 60% in patients with mutations and 54% in patients without mutations.

A second study addressed the third-line use of bosutinib in 88 patients with chronic-phase CML and dasatinib resistance or intolerance, most of whom also were imatinib resistant or intolerant.⁵ The median duration of treatment was 6.1 months.⁶ The tolerability profile of bosutinib was similar to that in the first study, with 22% of patients discontinuing therapy because of toxicity. Thirty two (36%) patients required dosage reductions; the median daily dosage was 454 mg for dasatinib-resistant patients and 393 mg for dasatinib-intolerant patients. In evaluable patients with and without mutations, the CHR rate was 86% and 95%, respectively, and the MCyR rate was 42% and 44%, respectively.

In a third study, 134 imatinib-resistant or intolerant patients with advanced leukemia, including 63 patients with accelerated-phase CML and 48 patients with blast-phase CML, were followed for a median of 8.3 months.⁷ Some patients also had received interferon, dasatinib, or nilotinib or undergone stem cell transplantation prior to study enrollment.

As in the two studies of patients with chronic-phase CML, bosutinib was well tolerated in patients with advanced CML.⁷ Twenty seven (20%) patients required dosage reduction; the median daily dosage was 477 mg. A CHR was observed in 20 (61%) patients with accelerated-phase CML and 7 (32%) patients with blast-phase CML. An MCyR was achieved in 13 (48%) patients with accelerated-phase CML and 11 (52%) patients with blast-phase CML.

Sixteen different BCR-ABL mutations were found in 40 of 66 patients for whom baseline sequencing analysis was performed.⁷ In evaluable patients with and without mutations, the CHR rate was 50% and 47%, respectively, and the MCyR rate was 47% and 54%, respectively. Nine of ten patients with the T315I mutation were resistant to bosutinib.

The data from these three studies of second- and third-line use of bosutinib in patients with CML appear promising, although the lack of activity in patients with the T315I mutation may limit the usefulness of the drug. Additional clinical research is needed to determine the place in therapy for bosutinib. A phase III open-label study comparing the drug with imatinib as first-line therapy in patients with newly-diagnosed chronic-phase CML is under way.⁸

Danusertib

Danusertib is an aurora kinase inhibitor formerly known as PHA-739358 with activity against the T315I mutation.¹ It binds with high affinity to both unmutated BCR-ABL and BCR-ABL with the T315I mutation in *in vitro* assays.

Results of research into the likelihood of and possible mechanisms for the emergence of resistance to danusertib was presented by Brümmendorf and colleagues at the American Society of Hematology (ASH) Annual Meeting in December 2009.⁹ In primary CD34⁺ CML cells, combination therapy with imatinib and danusertib provided synergistic anti-proliferative activity that affected immature CD34⁺38⁻ cells. In a murine cell model, the emergence of resistant clones was less common with danusertib treatment than with imatinib treatment. Danusertib-resistant cells did not have mutations in BCR-ABL or aurora kinase domains, and the cells remained sensitive to imatinib. Resistance to danusertib was attributed to overexpression of the Abcg2 efflux transporter (i.e., a different mechanism from imatinib resistance). The investigators concluded that the combination of danusertib and imatinib helped to significantly reduce the emergence of drug resistance by modulating the efflux pump drug transporters most often involved in the development of resistance. These findings suggest a potential role for danusertib in patients with CML and imatinib resistance. A possible clinical role for combination TKI therapy in patients with CML also is suggested.

Preliminary results of a phase I open-label study of danusertib in 23 patients with advanced leukemia and resistance or intolerance to imatinib, a second-generation TKI, or both were reported at the ASH Annual Meeting.¹⁰ Four of the patients had accelerated-phase CML and 8 of the patients had blast-phase CML. The drug was given as a daily 3-hour intravenous infusion for 7 consecutive days every 2 weeks using five different doses ranging from 90 to 200 mg/m². A more aggressive treatment schedule is planned for the second of part of this two-part study, which had not yet begun.

The T315I mutation was confirmed in 15 (65%) of the 23 patients.¹⁰ A response occurred in 6 (43%) of 14 patients, including 3 patients with cytogenetic responses (1 complete, 1 partial, and 1 minimal), 5 patients with a hematologic response, and 1 patient with clinical improvement. Many patients with responses had been heavily pretreated (e.g., with dasatinib, nilotinib, bosutinib, or stem cell transplantation as well as imatinib).

An acceptable tolerability profile was observed.¹⁰ Diarrhea was the most commonly-reported adverse event, affecting 57% of patients. Significant but transient reductions in the white blood cell count and the peripheral blood blast count were observed in 8 (62%) of 13 patients and 3 (23%) of 13 patients, respectively.

Additional clinical experience with danusertib in patients with CML is needed to clarify its role in therapy. A phase II study of patients with CML who relapsed after imatinib or second-generation TKI therapy is under way.¹¹

Omacetaxine Mepesuccinate

Omacetaxine mepesuccinate (also known as homoharringtonine) is the first agent in a new class of drugs, cetaxines, with a mechanism of action independent of tyrosine kinase inhibition. The drug binds to and inhibits translation of short-lived oncoproteins that are upregulated in leukemic cells. Preliminary results of a study of the safety and efficacy of omacetaxine mepesuccinate in 90 patients with CML in the chronic, accelerated, or blast phase and a confirmed BCR-ABL T315I mutation and imatinib resistance were reported at the ASH Annual Meeting in December 2009.¹² A 1.25-mg/m² dose of the drug was given by subcutaneous (s.c.) injection twice daily as induction therapy for 14 days every 28 days until a hematologic response was observed, followed by maintenance therapy using 1.25 mg/m² s.c. twice daily for 7 days every 28 days. Available data were reported for 66 patients, including 40 patients in the chronic phase, 16 patients in the accelerated phase, and 10 patients in the blast phase. All patients had failed prior imatinib therapy, and 79% of patients had failed two or more prior TKIs. The median follow-up time was 6.4 months (a relatively short time frame that is adequate for observation of an initial response but probably insufficient to ascertain whether the response is durable).

In the 40 patients in the chronic phase, the CHR rate was 85%.¹² Six (15%) patients exhibited an MCyR, and an MMR was observed in 6 (15%) patients. In the 16 patients in the accelerated phase, a hematologic response was achieved in 6 (37.5%) patients, including 5 patients with a CHR and 1 patient with a return to the chronic phase. One patient in the accelerated phase achieved a CCyR. In the 10 patients in the blast phase, a hematologic response was achieved in 3 (30%) patients, including 2 patients with a CHR and 1 patient with a return to chronic phase.

Grade 3 or 4 adverse events occurred in 45 (68%) of the 66 patients.¹² The most commonly-reported events were thrombocytopenia (58%), anemia (36%), and neutropenia (33%). Non-hematologic toxicities were primarily grade 1 or 2 in severity, with diarrhea the most frequently reported non-hematologic event (44%).

Safety data from two long-term phase II studies of omacetaxine mepesuccinate in 170 patients with CML in the chronic, accelerated, or blast phase who were resistant to or intolerant of TKIs were presented at the June 2010 ASCO Annual Meeting.¹³ One study (CML-202) included 81 patients with the T315I mutation who had failed imatinib, and the other study (CML-203) included 89 patients who had failed two or more TKIs. The median follow-up time of the combined studies was 5.3 months.

At least one grade 3 or 4 treatment-emergent adverse event was reported by 136 (80%) of the 170 patients.¹³ Most of these events reflected myelosuppression. Grade 3 or 4 thrombocytopenia, neutropenia, and anemia occurred in 49%, 34%, and 30% of the 170 patients, respectively. In a subset of 93 patients in the chronic phase, the incidence of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was 62%, 47%, and 38%, respectively. In many chronic-phase patients, grade 3 or 4 myelosuppression was managed by reducing the number of days of drug administration during later treatment cycles compared with initial cycles.

Grade 3 or 4 non-hematologic treatment-emergent adverse events were uncommon.¹³ Gastrointestinal events (14%) and infections (14%) were the most commonly-reported of these events.

Clinical trials of omacetaxine mepesuccinate in various CML patient populations continue. The indication proposed to the Food and Drug Administration when the agency reviews the drug probably will be for the treatment of CML patients who have failed two or more TKIs, regardless of their mutation status.¹⁴

AP24534

Preliminary results of a phase I dose-escalating study of the safety of AP24534, an oral inhibitor of BCR-ABL and src kinases with activity against the T315I mutation, were reported at the June 2010 ASCO Annual Meeting.¹⁵ Data were available for 48 patients with leukemia, including 31 patients with chronic-phase CML, 6 patients with accelerated-phase CML, and 5 patients with blast-phase CML. Prior therapies in patients with CML included imatinib (100% of patients), dasatinib (88%), and nilotinib (65%). Single daily doses ranging from 2 mg to 60 mg were given for a median duration of 61 days.

Sixteen (33%) patients discontinued therapy, including 7 (15%) patients for progressive disease, 6 (13%) patients based on an investigator's decision, 2 (4%) patients for unrelated death, and 1 (2%) patient for toxicity (pancreatitis).¹⁵ The incidence of grade 3 or 4 neutropenia and thrombocytopenia was 43% and 40%, respectively. Four of 12 patients developed grade 3 or 4 elevations in amylase or lipase with the 60-mg dose, and two of 12 patients experienced grade 2 reversible pancreatitis. Other common treatment-related adverse events included nausea (20%), fatigue (15%), and vomiting (15%).

In evaluable patients with CML, 11 (85%) of 13 patients achieved a CHR, 7 (33%) of 21 patients achieved a CCyR, and 10 (48%) of 21 patients achieved an MCyR.¹⁵ All 7 (100%) evaluable patients with chronic-phase CML and the T315I mutation had a CHR, 4 (57%) patients had a CCyR, and 1 (14%) patient had an MiCyR.

Of 11 evaluable patients with CML in the accelerated phase or blast phase or Philadelphia chromosome-positive (Ph+) acute lymphocytic leukemia (ALL), 4 (36%) patients had an MHR and 1 (9%) patient had a CCyR.¹⁵ In a subset of 8 patients with the T315I mutation, 3 (38%) patients had an MHR and 1 (13%) patient had a CCyR. These findings suggest that AP24534 has activity in patients with CML resistant to imatinib and second generation TKIs, including patients with the T315I mutation, and the drug has an acceptable safety profile. The study and patient recruitment are ongoing.

New Clinical Insight: Imatinib in Renal and Hepatic Dysfunction

Imatinib remains the standard of care for treating chronic myelogenous leukemia (CML) until new therapies with greater safety and efficacy become available. High-dose therapy (i.e., 800 mg/day) has been used instead of standard-dose therapy (400 mg/day) to improve response rates, although myelosuppression is more common with high-dose therapy than standard-dose therapy.¹⁷

The use of high-dose imatinib therapy in patients with renal or hepatic dysfunction is a concern. Imatinib is eliminated primarily through metabolism by hepatic microsomal enzymes with excretion into the bile, although the kidneys also play a role in elimination of the drug. Renal impairment increases exposure to imatinib.¹⁸ The drug also can cause renal and hepatic toxicity. Imatinib dosage reductions are recommended by the manufacturer for patients with renal dysfunction and severe hepatic dysfunction, raising concerns about compromised efficacy in these patient populations.¹⁸

An analysis of data from three consecutive studies of the safety and efficacy of standard and high-dose imatinib in 259 patients with early chronic-phase CML, including 11 patients with renal dysfunction and 38 patients with liver dysfunction, was published in the July 1, 2010 issue of *Cancer*.¹⁹ Imatinib therapy was initiated using 400 mg once daily (the standard dose) in 50 patients and 400 mg twice daily (high-dose therapy) in 209 patients. Dosage reductions were made for severe, persistent, or recurrent hematologic or non-hematologic toxicity, with 300 mg/day as the minimum dosage.

Worsening of renal function occurred in 9 (18%) of the 50 patients treated with standard-dose imatinib and 33 (16%) of the 209 patients receiving high-dose imatinib. Liver toxicity developed in 15 (30%)

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Bafetinib

Bafetinib (formerly known as INNO-406) is an oral dual inhibitor of BCR-ABL and Lyn kinases. Results of a phase I dose-escalation study in 56 patients with Ph+ CML or ALL and imatinib resistance (40 patients) or intolerance (16 patients) were reported in the June 1, 2010 issue of *Cancer*.¹⁶ Forty seven patients had CML, including 31 patients in the chronic phase, 9 patients in the accelerated phase, and 7 patients in the blast phase. Many enrollees also had failed dasatinib (26), nilotinib (20), or both (9). Mutations present at the time of enrollment included Y253H, G250E, T315I, and F317L. A dosage of 30 mg once daily was used initially, with subsequent dosage increases made after at least 3 patients received each dosage until a maximum tolerated dosage was reached. The median duration of treatment was 3.7 months (4.4 months for the 31 patients with CML in the chronic phase).

Six (11%) of the 56 study participants experienced an MCyR to bafetinib.¹⁶ All 6 patients had CML in the chronic phase. The rate of MCyR in the 31 patients with CML in the chronic phase was 19%. Four of the 6 patients with an MCyR had received bafetinib 240 mg twice daily or a larger dosage. No responses were observed in patients with CML in the accelerated phase or blast phase or Ph+ ALL.

Transaminase elevations and thrombocytopenia were dose-limiting toxicities at a bafetinib dosage of 480 mg twice daily.¹⁶ Transaminase elevations also were observed at dosages of 360 mg and 240 mg twice daily. The elevations were less severe with 240 mg twice daily than larger dosages, and the elevation resolved when drug administration was temporarily interrupted and therapy was resumed using a lower dosage. Therefore, a dosage of 240 mg twice daily was recommended for phase II studies. Bafetinib may prove useful in patients with imatinib-resistant chronic-phase CML.

patients receiving standard-dose imatinib therapy and 36 (17%) patients during high-dose therapy.

Imatinib dosage reductions were required in 91 (43%) of 210 patients with normal renal and hepatic function, including 6 (15%) of 39 in the standard-dose group and 85 (50%) of 171 in the high-dose group. Eight (73%) of 11 patients with renal dysfunction, including 2 (50%) of 4 in the standard-dose group and 6 (86%) of 7 in the high-dose group, required dosage reductions. Nineteen (50%) of 38 patients with hepatic dysfunction, including 2 (29%) of 7 in the standard-dose group and 17 (55%) of 31 in the high-dose group, required dosage reductions. After the 48-month follow up, 3 (11%) patients with normal organ function in the standard-dose group, 3 (3%) patients with normal organ function in the high-dose group, and 1 (17%) patient with renal dysfunction in the high-dose group were receiving imatinib 300 mg/day. All other patients received 400 mg/day or more.

Grade 3 or 4 hematologic toxicity (anemia, neutropenia, and thrombocytopenia) was more common in patients with renal dysfunction receiving high-dose imatinib therapy than in patients without renal dysfunction receiving high- or standard-dose therapy. Rates of CCyR, event-free survival, and overall survival were similar in patients with and without organ dysfunction. The study was not powered to compare the efficacy of high-dose and standard-dose therapy in the three subsets of patients based on organ function. The study findings suggest that although imatinib dosage reduction may be needed to prevent or ameliorate hematologic toxicity in some patients with early chronic-phase CML and renal dysfunction, the success of therapy is not compromised. The investigators concluded that most patients with renal or hepatic dysfunction may receive standard-dose therapy without risk of substantial toxicity.

Making an Impact

A live educational activity, *Chronic Myelogenous Leukemia: Considerations for Selecting and Managing Therapy*, was conducted by ASHP Advantage with the support of Novartis Oncology this spring. The activity will be repeated at various locations throughout the United States in cooperation with ASHP state affiliates in the coming months (for a list of locations, dates, and times, go to <http://onlinece.ashpadvantagemedia.com/cml/activities.html>). The program also has been archived as a web-based activity that may be completed at any time (go to <http://www.ashpmedia.org/symposia/cml/>). A group of nationally-recognized oncology experts developed the activity. One hour (0.1 CEU) of continuing pharmacy education credit is offered for both the live and web-based activity. The activity content is as follows:

- 1) Introduction
 - a) Epidemiology
 - b) Natural history
 - c) Molecular pathophysiology
 - d) Historical treatment options (busulfan, hydroxyurea, stem cell transplantation)
- 2) Imatinib
 - a) Molecular pharmacology
 - b) Toxicity profile
 - c) Drug-drug interactions
 - d) Clinical trial data (IRIS trial) for newly diagnosed patients
 - e) Data in accelerated phase/chronic phase
- 3) Second-generation tyrosine kinase inhibitors (dasatinib and nilotinib)
 - a) Pharmacodynamics compared with imatinib
 - b) Toxicity profile compared with imatinib
 - c) Drug-drug interactions
 - d) Data in chronic phase, accelerated phase/blast crisis (second-line use)
 - e) Role as a third-line agent
 - f) Comparative costs of dasatinib, nilotinib, and imatinib
- 4) Stem cell transplantation (brief overview of how its role has changed)
- 5) Future directions

Many participants in the live educational activity responding to a survey have already made changes at their practice sites based on information obtained during the program. Examples of these changes include:

- Optimized therapeutic recommendations for patients with chronic myelogenous leukemia (CML) based on disease phase,
- Improved drug therapy monitoring and treatment of side effects from therapy,
- Increased awareness of the potential for and options for managing drug interactions,
- Formulary recommendations for a stepped approach to use of first- and second generation tyrosine kinase inhibitors, and
- Provision of medications for indigent patients through a pharmacy assistance program.

Register for an upcoming live activity or complete the web-based activity today and make an impact on the care of patients with CML at your institution!

CE Information



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1 hour (0.1 CEU) of continuing pharmacy education credit (ACPE Activity #204-000-10-426-L01P and 204-000-10-426-H01P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP Learning Center (<http://ce.ashp.org/>) following the activity.

For complete information on the educational activities included in this initiative and to sign up to receive updates, visit www.ashpadvantage.com/cml. There is no fee for participation in these activities. Please share this e-Newsletter with colleagues who might be interested in this topic.

Planned and conducted by ASHP Advantage and supported by an educational grant from Novartis Oncology.



References

1. Agrawal M, Garg TJ, Kantarjian H et al. Chronic myeloid leukemia in the tyrosine kinase inhibitor era: what is the "best" therapy? *Curr Oncol Rep.* 2010; 12:302-13.
2. Radich JP. How I monitor residual disease in chronic myeloid leukemia. *Blood.* 2009; 114:3376-81.
3. American Cancer Society. Leukemia—chronic myeloid (myelogenous): treating chronic myeloid leukemia by phase. <http://www.cancer.org/Cancer/Leukemia-ChronicMyeloidCML/DetailedGuide/leukemia--chronic-myeloid--myelogenous--treating-treating-by-phase> (accessed 2010 Aug 18).
4. Cortes JE, Kantarjian H, Brümmendorf T et al. Safety and efficacy of bosutinib (SKI-606) in patients (pts) with chronic phase (CP) chronic myeloid leukemia (CML) following resistance or intolerance to imatinib (IM). Presented at the American Society of Clinical Oncology 46th Annual Meeting. Chicago, IL: June 4-8, 2010. *J Clin Oncol.* 2010; 28(15 suppl):abstract 6502. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=52917 (accessed 2010 Aug 13).
5. Khoury HJ, Kim D, Zaritsky A et al. Safety and efficacy of third-line bosutinib in imatinib (IM) and dasatinib (DAS) resistant or intolerant chronic phase (CP) chronic myeloid leukemia (CML). Presented at the American Society of Clinical Oncology 46th Annual Meeting. Chicago, IL: June 4-8, 2010. *J Clin Oncol.* 2010; 28(15 suppl):abstract 6514. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=52695 (accessed 2010 Aug 13).
6. Nelson R. Bosutinib effective as second- and third-line therapy in CML. <http://www.medscape.com/viewarticle/723465> (accessed 2010 Aug 14).
7. 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. Presented at the American Society of Clinical Oncology 46th Annual Meeting. Chicago, IL: June 4-8, 2010. *J Clin Oncol.* 2010; 28(15 suppl):abstract 6509. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=42904 (accessed 2010 Aug 13).
8. U.S. National Institutes of Health ClinicalTrials.gov database. Compare bosutinib to imatinib in subjects with newly diagnosed chronic phase Philadelphia chromosome positive CML. <http://www.clinicaltrials.gov/ct2/show/NCT00574873?term=bosutinib+AND+>

chronic+myelogenous+leukemia&rank=1 (accessed 2010 Aug 14).

9. Brümmendorf TH, Gontarewicz A, Keller G et al. Resistance to danusertib (formerly PHA-739358) in BCR-ABL-positive cells is mediated by upregulation of the drug transporter Abcg2 and can be suppressed in vitro by combination treatment with imatinib. Presented at the American Society of Hematology Annual Meeting. New Orleans, LA: December 5-8, 2009. *Blood*. 2009; 114:abstract 1724. <http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/1724?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=danusertib&searchid=1&FIRSTINDEX=0&volume=114&issue=22&resourcetype=HWCIT> (accessed 2010 Aug 13).
10. Cortes-Franco J, Dombret H, Schafhausen P et al. Danusertib hydrochloride (PHA-739358), a multi-kinase aurora inhibitor, elicits clinical benefit in advanced chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia. Presented at the American Society of Hematology Annual Meeting. New Orleans, LA: December 5-8, 2009. *Blood*. 2009; 114: abstract 864. <http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/864?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=danusertib&searchid=1&FIRSTINDEX=0&volume=114&issue=22&resourcetype=HWCIT> (accessed 2010 Aug 13).
11. U.S. National Institutes of Health ClinicalTrials.gov database. PHA-739358 in treating patients with chronic myelogenous leukemia that relapsed after imatinib mesylate or c-ABL therapy. <http://www.clinicaltrials.gov/ct2/show/NCT00335868?term=PHA-739358+AND+chronic+myelogenous+leukemia&rank=1> (accessed 2010 Aug 14).
12. Cortes-Franco J, Khoury HJ, Nicolini FE et al. Safety and efficacy of subcutaneous-administered omacetaxine mepesuccinate in imatinib-resistant chronic myeloid leukemia (CML) patients who harbor the Bcr-Abl T315I mutation—results of an ongoing multi-center phase 2/3 study. Presented at the American Society of Hematology Annual Meeting. New Orleans, LA: December 5-8, 2009. *Blood*. 2009; 114:abstract 644. <http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/644?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=omacetaxine&searchid=1&FIRSTINDEX=0&volume=114&issue=22&resourcetype=HWCIT> (accessed 2010 Aug 13).
13. Lipton JH, Wetzler M, Nicolini F et al. Safety of omacetaxine mepesuccinate (OM) subcutaneous (SQ) injection for the treatment of chronic myeloid leukemia (CML) patients (pts) resistant or intolerant to tyrosine kinase inhibitors (TKIs): analysis of two phase II studies. Presented at the American Society of Clinical Oncology 46th Annual Meeting. Chicago, IL: June 4-8, 2010. *J Clin Oncol*. 2010; 28(15 suppl):abstract 6568. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=54142 (accessed 2010 Aug 13).
14. ChemGenex Pharmaceuticals Limited. ChemGenex and U.S. FDA agree on potential regulatory pathway for OMAPRO™. <http://www.chemgenex.com/2010/07/us-fda-agree-on-potential-regulatory-pathway/> (accessed 2010 Aug 14).
15. Talpaz M, Cortes JE, Deininger MW et al. Phase I trial of AP24534 in patients with refractory chronic myeloid leukemia (CML) and hematologic malignancies. Presented at the American Society of Clinical Oncology 46th Annual Meeting. Chicago, IL: June 4-8, 2010. *J Clin Oncol*. 2010; 28(15 suppl):abstract 6511. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=53232 (accessed 2010 Aug 13).
16. Kantarjian H, le Coutre P, Cortes J et al. Phase 1 study of INNO-406, a dual Abl/Lyn kinase inhibitor, in Philadelphia chromosome-positive leukemias after imatinib resistance or intolerance. *Cancer*. 2010; 116:2665-72.
17. Kantarjian H, Talpaz M, O'Brien S et al. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. *Blood*. 2004; 103(8):2873-8.
18. Gleevec package insert. East Hanover, NJ: Novartis Pharmaceuticals; 2009 May.
19. Tong WG, Kantarjian H, O'Brien S et al. Imatinib front-line therapy is safe and effective in patients with chronic myelogenous leukemia with pre-existing liver and/or renal dysfunction. *Cancer*. 2010; 116:3152-9.