First-line treatment for chronic myeloid leukemia: dasatinib, nilotinib, or imatinib

Guoqing Wei¹,², Shamudheen Rafiyath², Delong Liu²*

Abstract
Imatinib, a tyrosine kinase inhibitor (TKI) of BCR-ABL, was the standard first-line therapy for chronic myeloid leukemia (CML) for almost 10 years. Dasatinib and nilotinib, two newer drugs with higher potency than imatinib against BCR-ABL and activity against most imatinib-resistant BCR-ABL mutations, have each shown superior efficacy compared with imatinib for first-line treatment of chronic-phase CML in randomized phase 3 trials. With 14 months follow-up time, available data suggest no obvious differences in efficacy between dasatinib and nilotinib. Compared with imatinib, dasatinib is associated with higher rates of pleural effusion and thrombocytopenia, but lower rates of edema, gastrointestinal AEs, musculoskeletal AEs, and rash. Nilotinib is associated with higher rates of dermatologic toxicity, headache, and biochemical abnormalities associated with hepatic and pancreatic toxicity compared with imatinib, but lower rates of edema, gastrointestinal AEs, muscle spasm, and neutropenia. Several studies have shown that poor adherence to imatinib detrimentally affects responses and should be considered in patients with a suboptimal response. The different dosing requirements of dasatinib (once daily with or without food) and nilotinib (twice daily with fasting) may be an additional factor in selecting frontline agents. This review compares and contrasts the three FDA approved first line TKI agents.

Introduction
Imatinib, which inhibits the tyrosine kinase activity of BCR-ABL, was introduced as a first-line treatment for chronic myeloid leukemia (CML) almost 10 years ago and radically improved the outcome of patients with CML. Imatinib has been the standard therapy for CML due to its remarkable activity and mild toxicity. In the IRIS study (International randomized study of interferon vs STI571) of first-line treatment with imatinib or interferon and cytarabine in patients with newly diagnosed chronic phase (CP)-CML, patients in the imatinib arm had an 8-year overall survival rate of 85% and freedom from progression to advanced disease was 92% [1]. Imatinib was also generally well tolerated during long-term treatment.

Despite the responses observed with imatinib, a proportion of patients develops resistance to imatinib or cannot tolerate its side effects. This led to the development of newer tyrosine kinase inhibitors (TKIs) of BCR-ABL, including dasatinib, nilotinib, and bosutinib, that were initially tested in clinical studies of patients with prior imatinib therapy [2-5]. Dasatinib, nilotinib and bosutinib, respectively, have 325-fold, 20-30-fold, and 30-fold increased potency over imatinib against BCR-ABL kinase in vitro [6-9]. Nilotinib has a similar chemical structure to imatinib but has an improved topographical fit in the ABL kinase pocket [6,7,9]. Dasatinib has a completely different chemical structure to imatinib and, unlike imatinib and nilotinib, binds BCR-ABL in the active conformation [10,11]. Bosutinib binds to an intermediate form of BCR-ABL [8]. All three TKIs have activity against most of the mutated forms of BCR-ABL kinase that have been associated with clinical resistance to imatinib [6,9]. Dasatinib 100 mg once daily (QD) and nilotinib 400 mg twice daily (BID) have been approved in the US and Europe as treatments for patients with CML who are resistant or intolerant to imatinib (dasatinib for all phases of CML, nilotinib for CP and accelerated phase [AP]). Dasatinib 100 mg QD and nilotinib 300 mg BID were recently approved in the US for patients with newly diagnosed CP-CML. Bosutinib is still undergoing clinical trials.

Clinical trials assessing the newer TKIs (dasatinib, nilotinib, and bosutinib) as first-line therapies in newly diagnosed CP-CML are ongoing and results from trials of
dasatinib and nilotinib have recently been reported. For dasatinib, published clinical trials in newly diagnosed CP-CML comprise: (i) DASISION (Dasatinib versus imatinib study in treatment-naive CML patients), an international, multicenter, randomized phase 3 trial of dasatinib 100 mg QD vs imatinib 400 mg QD (n = 519) [12]; and (ii) a single-arm phase 2 trial of dasatinib 100 mg QD or 50 mg BID performed by M D Anderson Cancer Center (MDACC), Houston, TX (n = 62) [13]. For nilotinib, published clinical trials in newly diagnosed CP-CML comprise: (i) ENESTnd (Evaluating nilotinib efficacy and safety in clinical trials - newly diagnosed patients), an international, multicenter, randomized phase 3 trial of nilotinib 300 mg BID vs nilotinib 400 mg BID vs imatinib 400 mg QD (n = 846) [14]; (ii) a single-arm phase 2 trial of nilotinib 400 mg BID performed by MDACC (n = 61) [15]; and (iii) a second single-arm phase 2 trial of nilotinib 400 mg BID performed by the Italian GIMEMA (Gruppo Italiano malattie e matologiche dell’adulto) group (n = 73) [4]. No data have been published from an international, multicenter, randomized trial of bosutinib vs imatinib (NCT00574873).

In this review, recent data for first-line treatment with dasatinib or nilotinib will be discussed, with a specific focus on safety and tolerability.

**Efficacy of dasatinib and nilotinib compared with imatinib in the first-line setting**

In randomized trials, both dasatinib and nilotinib have shown superior efficacy compared with imatinib as first-line treatment for patients with CP-CML (Tables 1 and 2). In the DASISION trial, responses were more frequent with dasatinib vs imatinib treatment, including higher 12-month rates of complete cytogenetic response (CCyR; 83% vs 72%; P = 0.001) and major molecular response (MMR; 46% vs 28%; P < 0.0001). Dasatinib also showed superiority over imatinib in the primary trial endpoint, the rate of confirmed CCyR (CCyR detected in two consecutive assessments), with 12-month rates of 77% vs 66%, respectively (P = 0.007). CCyR and MMR both occurred faster with dasatinib compared with imatinib. After a median 14 months of treatment, 1.9% of patients had progressed to AP/BP phase with dasatinib compared with 3.5% with imatinib. No patient in whom a MMR was achieved progressed to AP/BP [12]. In the ENESTnd trial, the primary endpoint was the rate of MMR at 12 months, and both nilotinib arms (300 mg and 400 mg) had significantly higher rates compared with the imatinib arm (43-44% vs 22%; P < 0.001). Rates of CCyR achieved by 12 months were also significantly higher for nilotinib vs imatinib (78-80% vs 65%; P < 0.001), and CCyR and MMR occurred faster in the nilotinib arms. After a median 14 months of treatment, fewer nilotinib-treated patients had progressed to AP/BP phase compared with imatinib-treated patients (< 1% vs 4%; P ≤ 0.01 in an analysis of time to progression). Similar to DASISION, no patient who had a MMR had progression to AP/BP [14]. Five-year follow-up is planned in both trials. Because available data suggest that both dasatinib and nilotinib have broadly similar efficacy in terms of their superiority over imatinib, it is likely that safety and tolerability considerations for these agents will become increasingly important when selecting first-line treatment for CML.

**The importance of adherence**

Across various chronic diseases requiring long-term treatment, poor adherence is associated with worse outcomes [16]. Similarly, recent studies have shown that

| Table 1 Rates of complete cytogenetic response (CCyR) and major molecular response (MMR) to imatinib and dasatinib in the DASISION trial |
|---|
| % of patients |
| **CCyR** |
| Imatinib 400 mg QD | Dasatinib 100 mg QD |
| 3 months | 31 | 54 |
| 6 months | 59 | 73 |
| 9 months | 67 | 78 |
| 12 months | 72 | 83 |
| **MMR** |
| 3 months | 04 | 8 |
| 6 months | 8 | 27 |
| 9 months | 18 | 39 |
| 12 months | 28 | 46 |
| Progression to AP/BP | 3.5 | 1.9 |

AP: accelerated phase; BP: blast phase; QD: once daily.
lack of adherence to imatinib treatment results in significantly lower response rates in patients with CP-CML. In a prospective observational study (Adherence assessment with Glivec: indicators and outcomes; ADAGIO), adherence to imatinib treatment was analyzed in 169 patients with CML during a 90-day period and correlated with overall responses to treatment. Only 14% of patients were found to be perfectly adherent based on pill counts (100% of imatinib taken), with 71% of patients taking less imatinib than prescribed and 15% taking more imatinib than prescribed. Importantly, worse adherence was associated with worse treatment responses; patients who had a suboptimal response to imatinib had significant higher mean percentage of imatinib not taken than those with an optimal response (23% vs 7%; P = 0.005). Similarly, patients who failed to achieve a CCyR on imatinib had a higher mean percentage of pills not taken than patients who achieved a CCyR (24% vs 9%; P = 0.012) [17]. In another prospective observational study performed at a single institution, 87 patients with CP-CML who had achieved a CCyR (24% vs 9%; P = 0.012) [17]. In another prospective observational study performed at a single institution, 87 patients with CP-CML who had achieved a CCyR on imatinib were monitored for adherence for 90 days using a microelectronic monitoring device. The adherence rate was ≤ 90% in 26% and ≤ 80% in 14%. There was a strong correlation between adherence to imatinib and probabilities of MMR and CMR; patients with ≤ 90% adherence had a lower 6-year rate of MMR than patients with > 90% adherence (14% vs 94%; P = 0.002), no patient with ≤ 90% adherence achieved a CMR, and no patient with ≤ 80% adherence achieved a MMR. Significantly worse adherence rates were found in patients with various adverse events (AEs), including asthenia, nausea, muscle cramps, and bone or joint pains, and also in patients who took imatinib independently of meals. Patients who had their imatinib dose increased had significantly worse adherence than patients who remained on imatinib 400 mg QD (86% vs 99%; P = 0.021) [18]. In a retrospective analysis of imatinib treatment in clinical practice using US administrative claims data, adherence to imatinib in 267 patients was calculated using the medication possession rate (MPR), ie, the total days supply of imatinib in a 1-year period divided by 365. Overall, the mean MPR was 78% and 31% of patients had a treatment interruption of at least 30 consecutive days. Among the study population, nonadherence was higher in patients with higher numbers of concomitant medications, women, patients with more complex disease, and patients with a higher starting dose of imatinib (≥ 600 mg/d). Although the reasons for worse adherence in women were not examined, the authors suggested that women may be more concerned than men with AEs characteristic of imatinib treatment, such as rash, edema, and weight gain [19].

The importance of adherence to imatinib in response to treatment is further illustrated by the results of a phase 3 randomized trial of imatinib 400 mg QD vs 800 mg/d (400 mg BID) in patients with newly diagnosed CP-CML (Tyrosine kinase inhibitor optimization and selectivity [TOPS]). Rates of MMR and CCyR at 12 months were similar between the two arms. However, treatment responses in patients from the 800 mg/d arm correlated with the dose of imatinib that could be tolerated, with higher MMR rates achieved in patients with an average dose intensity of 600 mg/d or higher (62-63%) compared with 400-599 mg/d (38%) or < 400 mg/d (21%). In the 400 vs 800 mg arms, 18% vs 61% of patients had a dose reduction, 52% vs 73% reported at least one day with zero dose, 38% vs 67% had dose interruption lasting longer than 5 days, and 16% vs 20% discontinued treatment. The main reason for dose reduction in the 800 mg/d arm, but not the 400 mg/d arm, was AEs or laboratory abnormalities. These data suggest that the higher number of days off medication (ie, lower adherence) in the high-dose imatinib arm counteracted any positive effect of higher dosing [20].

Nonadherence is a possible cause for reduced response to imatinib and should be considered in patients with suboptimal response to imatinib [17]. The AE profiles and tolerability of newer treatments are therefore important considerations for clinical practice in the first-line setting in terms of both efficacy and safety.

Safety and tolerability of dasatinib and nilotinib compared with imatinib in the first-line setting
Although dasatinib and nilotinib have been available for use in therapy of CML in the second-line settings for several years, new studies have provided the first direct comparison with imatinib in the first-line setting. In general, imatinib, dasatinib, and nilotinib are associated with broadly similar types of AEs, although the relative occurrence of different AEs varies between agents and some AEs are specific to one drug (Tables 3 and 4). For best management of CML patients receiving TKI therapy, knowledge of potential toxicities, how to avoid them, how to deal with them should they arise, and how they may affect response and outcome, are important factors. In general, BCR-ABL inhibitors are well tolerated and result in a limited number of higher-grade toxicities (grades 3-4). Experience with imatinib in the IRIS trial and with dasatinib and nilotinib in the second-line setting suggest that AEs tend to occur early during the course of treatment and late-onset toxicity is uncommon [21-23]. Longer-term follow-up is needed to confirm that the same is true for dasatinib and nilotinib during first-line treatment. In general, most AEs
occurring during BCR-ABL inhibitor therapy can be managed with dose interruption and reduction and/or supportive care.

**Cytopenias**

Cytopenias such as neutropenia, thrombocytopenia, and anemia are the most common grade 3-4 AEs observed in patients receiving imatinib, dasatinib, or nilotinib. In the DASISION trial, grade 3-4 cytopenia with dasatinib vs imatinib included similar rates of neutropenia (20% vs 21%) and anemia (10% vs 7%), whereas thrombocytopenia was more common with dasatinib than with imatinib (19% vs 10%) [12]. Few patients discontinued treatment due to cytopenia (1.5% with dasatinib and 1.2% with imatinib) [12]. In the MDACC study of dasatinib, grade 3-4 neutropenia, thrombocytopenia, and anemia occurred in 21%, 10%, and 6% of patients, respectively [13]. In the ENESTnd trial, grade 3-4 neutropenia was less common in the nilotinib 300 or 400 mg BID arms (12% and 10%, respectively) compared with the imatinib arm (20%), whereas grade 3-4 thrombocytopenia (10% vs 12% vs 9%) and anemia (3% vs 3% vs 5%) were similar between treatment arms [14]. In the MDACC study of nilotinib, grade 3-4 neutropenia, thrombocytopenia, and anemia occurred in 12%, 11%, and 5% of patients, respectively [15], whereas low rates (4%, 2%, and 0%) were reported in the GIMEMA study [4].

**Table 3** Drug-related nonhematologic adverse events, that occurred in ≥ 10% of patients in any treatment arm, hematologic adverse events, and biochemical abnormalities, during the DASISION trial

| Adverse event    | Imatinib 400 mg QD | Dasatinib 100 mg QD |
|------------------|--------------------|---------------------|
| Nonhematologic   |                    |                     |
| Nausea           | 20 (0)             | 8 (0)               |
| Diarrhea         | 17 (1)             | 17 (< 1)            |
| Vomiting         | 10 (0)             | 5 (0)               |
| Rash             | 17 (1)             | 11 (0)              |
| Headache         | 10 (0)             | 12 (0)              |
| Fatigue          | 10 (0)             | 8 (< 1)             |
| Musculoskeletal pain | 14 (< 1)     | 11 (0)              |
| Muscle inflammation | 17 (< 1)      | 4 (0)               |
| Fluid retention  | 42 (1)             | 19 (1)              |
| Superficial edema | 36 (< 1)         | 9 (0)               |
| Pleural effusion | 0 (0)              | 10 (0)              |
| Other            | 8 (< 1)            | 5 (1)               |
| Hematologic      |                    |                     |
| Neutropenia      | 58 (20)            | 65 (21)             |
| Thrombocytopenia | 62 (10)            | 70 (19)             |
| Anemia           | 84 (7)             | 90 (10)             |
| Biochemical abnormalities |        |                     |
| Elevated AST     | NL (1)             | NL (< 1)            |
| Elevated ALT     | NL (1)             | NL (< 1)            |
| Elevated bilirubin | NL (0)         | NL (0)              |
| Elevated lipase  | NL (0)             | NL (0)              |
| Hyperglycemia    | NL (0)             | NL (0)              |
| Elevated amylase | NL (0)             | NL (0)              |
| Decreased phosphorus | 21 (2)       | NL (4)              |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; NL: not listed; QD: once daily.

**Table 4** Drug-related nonhematologic adverse events, that occurred in ≥ 10% of patients in any treatment arm, hematologic adverse events, and biochemical abnormalities, during the ENESTnd trial

| Adverse event    | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID |
|------------------|--------------------|----------------------|----------------------|
| Nonhematologic   |                    |                      |                      |
| Nausea           | 31 (0)             | 11 (< 1)             | 19 (1)               |
| Diarrhea         | 21 (1)             | 8 (1)                | 6 (0)                |
| Vomiting         | 14 (0)             | 5 (0)                | 9 (1)                |
| Rash             | 11 (1)             | 31 (< 1)             | 36 (3)               |
| Pruritus         | 5 (0)              | 15 (< 1)             | 13 (< 1)             |
| Alopecia         | 4 (0)              | 8 (0)                | 13 (0)               |
| Headache         | 8 (0)              | 14 (1)               | 21 (1)               |
| Fatigue          | 8 (< 1)            | 11 (0)               | 9 (1)                |
| Muscle spasm     | 24 (1)             | 7 (0)                | 6 (1)                |
| Myalgia          | 10 (0)             | 10 (< 1)             | 10 (0)               |
| Peripheral edema | 14 (0)             | 5 (0)                | 5 (0)                |
| Eyelid edema     | 13 (< 1)           | 1 (0)                | 2 (< 1)              |
| Periorbital edema| 12 (0)             | < 1 (0)              | 1 (0)                |
| Hematologic      |                    |                      |                      |
| Neutropenia      | 68 (20)            | 43 (12)              | 38 (10)              |
| Thrombocytopenia | 56 (9)             | 48 (10)              | 49 (12)              |
| Anemia           | 47 (5)             | 38 (3)               | 38 (3)               |
| Biochemical abnormalities |        |                      |                      |
| Elevated AST     | 23 (1)             | 40 (1)               | 48 (3)               |
| Elevated ALT     | 20 (2)             | 66 (4)               | 73 (9)               |
| Elevated bilirubin | 10 (< 1)       | 53 (4)               | 62 (8)               |
| Elevated lipase  | 11 (3)             | 24 (6)               | 29 (6)               |
| Hyperglycemia    | 20 (0)             | 36 (6)               | 41 (4)               |
| Elevated creatinine | 13 (< 1)   | 5 (0)                | 5 (0)                |
| Elevated amylase | 12 (1)             | 15 (< 1)             | 18 (1)               |
| Elevated alkaline phosphatase | 33 (< 1) | 21 (0)               | 27 (0)               |
| Decreased phosphorus | 45 (8)         | 32 (5)               | 34 (5)               |

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; QD: once daily.
Dermatologic toxicity

Rash was one of the most common nonhematologic AEs [24,25]. In the IRIS study, rash occurred in 34%, although grade 3-4 rash was infrequent (2%). Pruritus (7%) and alopecia (4%) were also noted in smaller numbers of patients [25]. In the DASISION trial, first-line dasatinib treatment resulted in fewer cases of rash compared with imatinib treatment (11% vs 17%), with grade 3-4 rash occurring in 0% vs 1%, respectively. No rates were provided for pruritis or alopecia, suggesting that the frequencies were < 10% in both arms [12]. In the MDACC study, 58% of patients experienced “skin toxicity” (grouped term) with dasatinib, which was grade 3-4 in 2%. In addition, 8% experienced pruritus of which 2% was grade 3-4 [13]. Dermatologic toxicity seems to be more common with nilotinib than imatinib. In the ENESTnd trial, rash occurred in 31% taking nilotinib 300 mg BID, 36% taking nilotinib 400 mg BID, and 11% taking imatinib (grade 3-4 in < 1% vs 3% vs 1%, respectively). Pruritus was also more common in both nilotinib arms (15% with 300 mg BID and 13% with 400 mg BID) compared with imatinib (5%), as was alopecia (8% with nilotinib 300 mg BID, 13% with nilotinib 400 mg BID, and 4% with imatinib) [14]. In single-arm trials of first-line nilotinib 400 mg BID, rash occurred in 49% (2% grade 3-4) of patients in the MDACC trial [15] and in 42% (5% grade 3) in the GIMEMA trial [4]. Pruritus also occurred in 21% of patients in the GIMEMA trial (4% grade 3).

Gastrointestinal symptoms

Nausea, diarrhea, and vomiting are common in patients receiving BCR-ABL inhibitor therapy, although recent data indicate that gastrointestinal (GI) disturbances occur less often in patients receiving dasatinib or nilotinib compared with those receiving imatinib. In the DASISION trial, nausea (8% vs 20%) and vomiting (5% vs 10%) both occurred less frequently with dasatinib compared with imatinib, whereas rates of diarrhea were similar (17% in both arms). Grade 3-4 diarrhea was reported in < 1-1%, and no patients in either arm experienced grade 3-4 nausea or vomiting [12]. In the MDACC trial of dasatinib, higher rates of GI AEs were reported, including diarrhea in 53% (2% grade 3-4), nausea in 45% (0% grade 3-4), and vomiting in 21% (0% grade 3-4) [13]. In the ENESTnd trial, rates of GI AEs were lower with nilotinib 300 mg and 400 mg vs imatinib, including nausea (11% vs 19% vs 31%), diarrhea (8% vs 6% vs 21%), and vomiting (5% vs 9% vs 14%), of which 0-1% were grade 3-4 cases in all arms [14]. In the MDACC study of first-line nilotinib, nausea and diarrhea were reported in 38% and 21% of patients, respectively, (no grade 3-4), and diarrhea occurred in 7% (2% grade 3-4) [15]. In the GIMEMA study, 11% of patients experienced nausea/vomiting (1% grade 3-4) and 7% had diarrhea (2% grade 3) [4].

Edema

Fluid retention is common with imatinib, as shown by 56% of patients receiving imatinib in the IRIS trial experiencing superficial edema and 13% having weight gain [25]. First-line dasatinib and nilotinib treatment are associated with lower rates of edema. In the DASISION, superficial edema (grouped term) was much less frequent with dasatinib (9%) compared with imatinib (36%), and rates of grade 3-4 superficial edema were low (0% vs < 1%, respectively) [12]. In the MDACC study of dasatinib, edema was reported in 32% of patients (no grade 3-4) [13]. In the ENESTnd trial, different types of edema were reported separately. In the nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib arms, peripheral edema occurred in 5% vs 5% vs 14%, eyelid edema occurred in 1% vs 2% vs 13%, and periorbital edema occurred in < 1% vs 1% vs 12% [14]. In the GIMEMA trial, peripheral edema was reported in 4% of patients receiving nilotinib and all cases were grade 1-2 [4]. Data for edema were not reported in the MDACC study of nilotinib [15].

Pleural effusion

Pleural effusion is rare with nilotinib and imatinib but is a more prominent side effect of dasatinib treatment [26,27]. In the DASISION trial, 10% of patients in the dasatinib arm had a pleural effusion whereas no patient receiving imatinib reported this AE. Dasatinib-associated pleural effusion was grade 1 in 2% and grade 2 in 8% of patients, with no pleural effusion grade 3 or above. The occurrence of pleural effusion did not affect the efficacy of dasatinib, as shown by CCyR being achieved in 24/26 patients (92%) who had a pleural effusion. In the DASISION trial, pleural effusion was managed using dose adjustments and/or medical intervention, including dose interruption in 19 patients, diuretics in 12 patients, dose reduction in eight patients, corticosteroids in seven patients, and therapeutic thoracentesis in one patient. Discontinuation due to pleural effusion occurred in three patients (1% of the dasatinib arm) [12]. In the MDACC study of first-line dasatinib, the rate of pleural effusion (13%) was similar to DASISION, and one case of grade 3/4 pleural effusion was reported. Pleural effusion occurred less frequently in patients who received dasatinib 100 mg QD (6%) compared with 50 mg BID (19%), and two patients (3%) discontinued treatment due to pleural effusion [13]. In the ENESTnd study, pleural effusion occurred in a small number (< 1%) of nilotinib-treated patients [28] and was not reported in the single-arm studies of nilotinib.
Cardiac toxicity
In 2006, a report was published describing ten individuals who developed severe congestive heart failure (CHF) on imatinib treatment. Based on laboratory studies, the authors suggested that this effect could occur as a result of inhibition of physiologic ABL activity in cardiac tissue [29]. Subsequent retrospective analyses estimated that the frequency of CHF or left ventricular dysfunction during imatinib therapy for CML was 0.5-1.1% [30-32].

In TKI studies, instances of QT prolongation were reported [33-37]. In particular, in studies of nilotinib in patients with imatinib resistance or intolerance, sudden death was reported in 0.6% of patients, with a similar rate of occurrence in an expanded-access program. The timing of sudden death relative to initiation of nilotinib suggested that ventricular repolarization abnormalities may have contributed to their occurrence [34]. In recent TKI trials, patients with significant cardiac disease were excluded from participating.

In randomized trials of nilotinib or dasatinib vs imatinib, close monitoring for QT prolongation and changes in left ventricular ejection fraction was performed. During nilotinib or imatinib treatment in the ENESTnd study, no patient had a QTc interval of > 500 msec and no decrease from the baseline in the mean left ventricular ejection fraction was observed at any time. Eleven patients across all three study arms had an ischemic heart disease event, although no further details were provided regarding relative frequency between arms [14]. In the MDACC study of front-line nilotinib, there were two instances of hypertension and one instance of QTc prolongation (all classed as grade 1-2) [15]. In the GIMEMA study of nilotinib, 584 electrocardiograms from 73 patients were reviewed. In addition to transient/reversible abnormalities noted in 22% of patients, QTc interval prolongation to > 450 msec was noted in 2 cases [4]. In the DASISON trial, 2% vs 4% of dasatinib and imatinib arms had QTc intervals between 450-500 msec, and one patient (0.4%) in each group had a QTc interval of > 500 msec. Median changes in QTc interval from baseline were 3 msec in the dasatinib group and 8 msec in the imatinib group [12].

Bleeding
Bleeding was noted in studies of dasatinib in the second-line setting, mostly in patients with severe thrombocytopenia and more commonly in patients with advanced disease [38]. In vitro data suggest that dasatinib reversibly inhibits platelet activation [39]. In the DASISON trial, GI bleeding or other bleeding events occurred at a similar frequency in both treatment arms (5%). One patient in the dasatinib group and two patients in the imatinib group reported a grade 3-4 bleeding event [12].

Other nonhematologic AEs
Mild to moderate nonhematologic AEs such as headache, fatigue, muscle pains/cramps, and joint pain are commonly seen with BCR-ABL inhibitor treatment. These effects are usually easily managed without dose reduction and rarely cause dose interruptions. Recent data suggest that some of these AEs occur at different rates with dasatinib or nilotinib compared with imatinib. In the DASISON study, musculoskeletal AEs were less common with dasatinib compared with the imatinib arm, including myalgia (6% vs 12%), muscle inflammation (4% vs 17%), and musculoskeletal pain (11% vs 14%). Rates of fatigue (8% vs 10%) and headache (12% vs 10%) were similar in both arms. With each of these AEs, ≤ 1% of patients had a grade 3-4 event [12]. In the MDACC study of dasatinib, pain in joint/muscle (combined grouping; 74%), fatigue (73%), and headache (56%) were reported at high rates (grade 3-4 in 6%, 6%, and 2%, respectively) [13]. In the ENESTnd trial, muscle spasm occurred at a lower frequency in the nilotinib arms (6-7%) compared with the imatinib arm (24%). Myalgia occurred at a similar rate across all three arms (10%), as did fatigue (8-11%). However, headache occurred at a higher frequency in the nilotinib 300 mg BID (14%) and 400 mg BID (21%) treatment groups than in the imatinib treatment group (8%). Rates of grade 3-4 events with these AEs were ≤ 1% [14]. Similar to the MDACC study of dasatinib, the study of nilotinib at the same institution reported substantially higher rates of fatigue (67%; grade 3-4 in 3%) and headache (39%; no grade 3-4) than in the randomized study. Musculoskeletal AEs were reported as separate categories; 10% of patients experienced muscle cramp (0% grade 3-4) and 10% experienced joint pain (3% grade 3-4) [15]. In the GIMEMA study, 41% of patients taking nilotinib experienced bone/muscle/joint pain (combined grouping), of which 4% were grade 3. In addition, 30% experienced headache and 22% experienced fatigue (no grade 3-4 in each case) [4].

Biochemical abnormalities
Rates of biochemical abnormalities vary in patients receiving different BCR-ABL inhibitors and seem to be most common during nilotinib treatment. In the DASISION trial, grade 3-4 hypophosphatemia occurred in 4% of patients treated with dasatinib compared with 21% of the patients treated with imatinib. Rates of other grade 3-4 biochemical abnormalities were low in both treatment arms, including markers of hepatic toxicity (elevated alanine aminotransferase [ALT] or aspartate

[464x351]≤
expression due to polymorphisms is associated with liver disease or overt hemolysis). Reduced UGT1A1 promoter polymorphism has been found to increase the risk of nilotinib-induced bilirubin elevation [43].

Dose adjustments and discontinuations due to toxicity

The rate of discontinuations because of drug toxicity provides a measure of the frequency of the most problematic AEs. In the DASISION trial, discontinuations following study drug toxicity occurred in 5.0% of the dasatinib arm and 4.3% of the imatinib arm. Of these, hematologic toxicity led to discontinuation in 1.6% vs 1.2%, and nonhematologic toxicity led to discontinuation in 3.5% vs 3.1%, respectively. Median doses of drug delivered were 99 mg/d in the dasatinib 100 mg QD arm vs 400 mg/d in the imatinib 400 mg QD arm. Data for dose interruptions and reductions have not been reported [12]. In the ENESTnd trial, discontinuations due to AEs occurred in 5% with nilotinib 300 mg BID, 9% with nilotinib 400 mg BID, and 7% with imatinib. Median doses of drug delivered were 592 mg/d in the nilotinib 300 mg BID arm, 779 mg/d in the nilotinib 400 mg BID arm, and 400 mg in the imatinib 400 mg QD arm. Respective rates of dose reduction/interruption were 59%, 66%, and 52%. Median cumulative durations of interruptions due to AEs or biochemical abnormalities were 19 days, 22 days, and 15 days, respectively [14].

Future directions with BCR-ABL inhibitors

Bosutinib

Data are awaited from the randomized phase 3 trial of bosutinib vs imatinib for first-line treatment for newly diagnosed CML [37]. However, data have been reported for the efficacy and safety of bosutinib in patients with CP-CML who had prior imatinib treatment. Response rates with bosutinib were comparable to those seen in trials of dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%, respectively. Responses were similar in patients with or without BCR-ABL mutations. Safety data indicate that bosutinib has a distinct safety profile compared with currently approved BCR-ABL inhibitors. AE rates should be interpreted with caution based on previous observations with dasatinib and nilotinib in the second-line setting, including CCyR in 50% and MMR in 52% of evaluated patients, of which 32% were complete. At 24 months, rates of progression-free and overall survival were 80% and 95%
rash (9% grade 3-4), 21% had abdominal pain (1% grade 3-4), 21% had fatigue (1% grade 3-4), 14% had headache (no grade 3-4), and 13% had joint pain (< 1% grade 3-4). Rates of fluid retention AEs were not reported, indicating a frequency of < 10%. Of grade 3-4 biochemical abnormalities, elevated ALT occurred in 10% of patients, elevated AST in 5%, elevated lipase in 7%, elevated glucose in 3%, decreased phosphate in 8%, and hypermagnesemia in 12%. In addition, 19% of patients receiving bosutinib in this study discontinued treatment due to AEs and 45% had a dose reduction due to AEs. The median dose of bosutinib was 454 mg/d (starting dose was 500 mg/d) [44]. Overall, preliminary data from this phase 1/2 trial indicate that bosutinib is an active agent for patients with CP-CML who have failed on prior imatinib treatment, with activity against a range of BCR-ABL mutations, and an acceptable toxicity profile.

**Inhibitors for T315I mutant**

Resistance to imatinib or relapse in patients with CML arises most frequently because of point mutations within the BCR-ABL coding sequence [45-48]. In vitro data has shown that dasatinib, nilotinib, and bosutinib effectively inhibit the majority of mutated forms of BCR-ABL that have been associated with imatinib resistance in the clinic [6,9,49]. However, the T315I point mutation confers resistance to imatinib, dasatinib, nilotinib, and bosutinib [50,51]. Although data are not yet available to indicate how frequently T315I will cause resistance to the newer agents, this mutation represents an “Achilles’ heel” for CML therapy.

Several TKIs that are active against the T315I-mutated form of BCR-ABL are being developed. MK-0457, a potent inhibitor of BCR-ABL and aurora kinases, was the first agent to show clinical activity against the T315I mutation; however, development of this drug was halted due to cardiac toxicity [52]. Other BCR-ABL/aurora kinases inhibitors with activity against T315I are in clinical development, including XL228, PHA-739358 (danusertib), and AT9283 [53-57]. Ponatinib (AP24534) is a multitargeted BCR-ABL/SRC kinase inhibitor with potent in vitro activity against all tested mutants of BCR-ABL including T315I, and clinical activity has been reported in patients with a T315I mutation [58-60]. Further clinical studies of ponatinib are ongoing, most notably a single-arm phase 2 study in patients with CML or Ph+ acute lymphoblastic leukemia (ALL) who either are resistant or intolerant to either dasatinib or nilotinib, or who harbor the T315I mutation (Ponatinib Ph+ ALL and CML evaluation [PACE]; NCT01207440). Switch pocket kinase inhibitors, such as DCC-2036 and DCC-2157, target the sites involved in controlling the conformation of BCR-ABL, which ultimately controls the activity state of the kinase. These agents are active against cells expressing a variety of BCR-ABL mutations, including T135I. A phase 1 study of DCC-2036 in patients with T315I or failure on two different TKIs is underway (NCT00827138) [61,62]. Omacetaxine (previously homoharringtonine) is a naturally occurring alkaloid derived from evergreen trees that induces apoptosis in leukemic cells, including those harbouring the T315I mutation [63-65]. In a phase 2/3 trial in patients with CML and a T315I mutation, omacetaxine treatment in the subset of patients with CP-CML resulted in a CCyR in 10% and a MMR in 15% [66]. The underlying mechanism for omacetaxine inhibitory effects on leukemic cells is still unknown. Studies of omacetaxine in patients with CML, either alone or in combination with other treatments, are ongoing.

**Acknowledgements**

This study was partly supported by the Research Fund for the Doctoral Program of Higher Education of China (GW, No.20070747) and by New York Medical College Blood Diseases Fund (DL). The authors take full responsibility for the content of this article. StemScientific, funded by Bristol-Myers Squibb, were involved partially in professional writing and editing support. The authors did not receive financial compensation for authoring or publishing the article.

**Author details**

1 Bone Marrow Transplantation Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, PR China. 2 Division of Hematology and Oncology, New York Medical College and Westchester Medical Center, Valhalla, NY 10595, USA.

**Authors’ contributions**

GW, SR and DL involved in concept design, coordination, drafting and critically revising the manuscript.

**Received**: 19 November 2010 **Accepted**: 26 November 2010

**References**

1. Deininger M, O’Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, Radich JP, Hatfield AK, Mone M, Filian J, Reynolds J, Gathmann I, Larson RA, Druker BJ. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib. Blood 2009, 114(Suppl 1):462, (abstract 1126).

2. Agrawal M, Garg RJ, Cortes J, Quntas-Cardama A. Tyrosine kinase inhibitors: the first decade. *Curr Hematol Malig Rep* 2010, 5:70-80.

3. le Coutre P, Schwarz M, Kim TD. New developments in tyrosine kinase inhibitor therapy for newly diagnosed chronic myeloid leukemia. *Clin Cancer Res* 2010, 16:1771-1780.

4. Rosti G, Palandri F, Castagnetti F, Breccia M, Levato L, Giugliotta G, Capucci A, Cedrone M, Fava C, Intermesoli T, Cambrin GR, Stagno F, Tiribelli M, Amabile M, Luatti S, Poerio A, Soverini S, Testoni N, Martinelli G, Alimena G, Pane G, Saglio G, Baccarani M. Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. *Blood* 2009, 114:4933-4938.

5. Saglio G, Baccarani M. First-line therapy for chronic myeloid leukemia: new horizons and an update. *Clin Lymphoma Myeloma Leuk* 2010, 10:169-176.

6. O’Hare T, Walters D, SToffregen EP, Jia T, Manley PW, Mestan J, Cowan-Jacob SW, Lee FY, Heinrich MC, Deininger MW, Druker BJ. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res* 2005, 65:6500-6505.

7. Weissberg E, Manley PW, Breitenstein W, Bruggen J, Cowan-Jacob SW, Ray A, Huntly B, Fabbro D, Fendtch G, Hall-Meyers E, Kung AL, Mestan J,
Daley GQ, Callahan L, Catley L, Cavaizza C, Azam M, Neuberg D, Wright RD, Gilliland DG, Griffin JD: Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005, 7:129-141.

8. Putrini M, Coluccia AM, Boscelli F, Cleris L, Marchesi E, Donella-Deana A, Ahmed S, Redaelli S, Piazza R, Magistrini V, Andreoni F, Scapozza L, Formelli F, Gambacorti-Passerini C: In vitro and in vivo activity of SKI-506, a novel Src-Abl inhibitor, against imatinib-resistant Bcr-Abl+ neoplastic cells. Cancer Res 2006, 66:11314-11322.

9. Redaelli S, Piazza R, Rostagno R, Magistrini V, Perini M, Vaerega M, Gambacorti-Passerini C, Boscelli F: Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR-ABL mutants. J Clin Oncol 2009, 27:469-471.

10. Tokarski JS, Newitt JA, Chang CY, Cheng JD, Wittekind M, Kiefer SE, Kish K, Lee FY, Borrillenni R, Lombardo LJ, Xie D, Zhang Y, Klei HE: The structure of dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib-resistant ABL mutants. Cancer Res 2006, 66:5790-5797.

11. Vajpai N, Strauss A, Gowan-Jacob SW, Cowan-Jacob SW, Manley PW, Grzesiek S, Formelli F, Gambacorti-Passerini C, Boscelli F: Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR-ABL mutants. J Clin Oncol 2009, 27:469-471.

12. Kantarjian HM, Giles FJ, Bhatta KN, Pinilla-Ibarz J, Larson RA, Gattermann N, Ottmann OG, Hochhaus A, Radich JP, Saglio G, Hughes TP, Martelli G, Kim DW, Shyu Y, Gallagher NJ, Wang J, Cortes-Franco J, Baccarani M, Coutre PD: Update on imatinib-resistant chronic myeloid leukemia patients in chronic phase on nilotinib therapy at 24 months: clinical response, safety, and long-term outcomes. Blood 2009, 114(Suppl), abstract 1129.

13. Shah NP, Cortes JE, Schiffer CA, le Coutre P, Bahoci E, Lambert A, Saglio G: Four-year follow-up of patients with chronic-phase chronic myeloid leukemia receiving 100 mg of dasatinib once daily. J Clin Oncol 2010, 28(Suppl), abstract 6512.

14. Huang X, Patel S, Ahmed N, Seier K, Liu D: Severe toxicity of skin rash, fever, and diarrhea associated with imatinibcase report and review of skin toxicities associated with tyrosine kinase inhibitors. Drug Design, Development and Therapy 2008, 2:215-219.

15. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen J, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003, 348:994-1004.

16. Vignali DA, Gorospe G, Yang AS: The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib. J Hematol Oncol 2009, 2:46.

17. Wong SF: New dosing schedules of dasatinib for CML and adverse event management. J Hematol Oncol 2009, 2:10.

18. Larson RA, Le Coutre PD, Reiffers J, Hughes TP, Saglio G, Edrich P, Hoeckopp A, Gallagher NJ, Kantarjian H, Hochhaus A: Comparison of nilotinib and imatinib in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): ENESTnd beyond one year. J Clin Oncol 2010, 28(Suppl), abstract 6501.

19. Kerkela R, Gazetze L, Yacobi R, Ilescu C, Patten R, Beaum H, Walters B, Sevtsou S, Pansat S, Ollivier J, Rosenwax J, Salomon RN, Van Etten RA, Alroy J, Durand JB, Force T: Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med 2006, 12:908-916.

20. Hatfield A, Owen S, Pilot PR: In reply to ‘Cardiotoxicity of the cancer therapeutic agent imatinib mesylate’. Nat Med 2007, 13:13-16.

21. Atallah E, Durand JB, Kantarjian H, Cortes J: Congestive heart failure is a rare event in patients receiving imatinib therapy. Blood 2007, 110:1233-1237.

22. Breccia M, Cannella F, Frustaci A, Stefani Z, Levi A, Alimena G: Cardiac events in imatinib mesylate-treated chronic myeloid leukemia patients: A single institution experience. Leuk Res 2008, 32:835-836.

23. Brotol-Meyer Squibb: SPRYCEL® prescribing information (US), revised October 2010.

24. Novartis: Tasigna (nilotinib) US prescribing information, revised June 2010.

25. Kantarjian H, Giles F, Wunderle L, Bhatta K, O'Brien S, Wassmann B, Tanaka C, Manley P, Ferebee W, Bochnik S, Hochhaus A, Griffin JD, Hoelzer D, Albitar M, Dugan M, Cortes J, Alland L, Ottmann OG: Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 2006, 354:2542-2551.

26. Xu Z, Cang S, Yang T, Liu D: Cardiotoxicity of tyrosine kinase inhibitors in chronic myelogenous leukemia. Hematology Reviews 2009, 1:44.

27. Gambacorti-Passerini C, Kim DW, Kantarjian HM, Brummedford TH, Dyayl I, Grinkevicsi L, Malhotra H, Goh YT, Wang JY, Gogat K, Cortes J: An Ongoing Phase 3 Study of Bosutinib (SKI-606) Versus Imatinib in Patients with Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia. Blood 2010, 116(Suppl)

28. Quintas-Cardama A, Kantarjian H, Ravigi F, O'Brien S, Thomas D, Vidal-Senmache G, Wierda W, Kommblau C, Cortes J: Bleeding diathesis in patients with chronic myelogenous leukemia receiving dasatinib therapy. Cancer 2009, 115:2462-2470.

29. Gratzac MP, Martin V, Valera MC, Alland S, Garcia C, Sie P, Recher C, Payratte B: The new tyrosine-kinase inhibitor and anticancer drug dasatinib reversibly affects platelet activation in vitro and in vivo. Blood 2009, 114:1884-1892.

30. Hatfield A, Owen S, Pilot PR: In reply to ‘Cardiotoxicity of the cancer therapeutic agent imatinib mesylate’. Nat Med 2007, 13:13-16.
Danusertib (formerly PHA-739358) 11

Models of Chronic Myeloid Leukemia (CML). 23

A phase 1 trial of oral AP24534 in patients with refractory chronic myeloid leukemia and T315I mutation.

Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. Haematologica 2007, 92:401-404

Resistance to tyrosine kinase inhibitors in Philadelphia chromosome-positive leukemias: which mutations matter? Clin Leukemia 2008, 1:223-228

Characteristics and outcomes of patients with chronic myeloid leukemia and T315I mutation following failure of imatinib therapy. Blood 2008, 112:53-55

Clinical outcome of 27 imatinib mesylate-resistant chronic myelogenous leukemia patients harboring a T315I BCR-ABL mutation. Haematologica 2007, 92:1238-1241

A novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphoplastic leukemia with the T315I BCR-ABL mutation. Blood 2007, 109:500-502

A phase III clinical trial of the BCR-ABL inhibitor XL228 in drug-resistant Ph + leukemias. J Clin Oncol 2009, 27:Suppl

Aurora Kinase Inhibitor, Induces Clinical Responses in Chronic Myeloid Leukemia Harboring T315I Mutations of BCR-ABL. Blood 2007, 110(Suppl)

A novel combined pan-Aurora kinases and third generation Bcr-Ab1 tyrosine kinase inhibitor. Recent Results Cancer Res 2010, 184:199-214

Aurora Kinase Inhibitor, Induces Clinical Responses in Chronic Myeloid Leukemia Harboring T315I Mutations of BCR-ABL. Blood 2007, 110(Suppl)

Danusertib (formerly PHA-739358)–a novel combined pan-Aurora kinases and third generation Bcr-Ab1 tyrosine kinase inhibitor. Recent Results Cancer Res 2010, 184:199-214

Danusertib (formerly PHA-739358) is effective against imatinib-resistant BCR-ABL mutations including T315I. Blood 2008, 111:4355-4364

Potent Antitumor Activity of AP24534, an Orally Active Inhibitor of Bcr-Ab1 Variants Including T315I, in vivo and in vitro Models of Chronic Myeloid Leukemia (CML). Blood 2007, 110(Suppl)

Van Etten RA, Chan WW, Zaleskas VM, Evangelista P, Lazarides K, Peng C, Li S, Wise SC, Petillo P, Flynn DL. DCC-2036: A Novel Switch Pocket Inhibitor of ABL Tyrosine Kinase with Therapeutic Efficacy Against BCR-ABL T315I In Vitro and in a CML Mouse Model. Blood 2007, 110(Suppl)

Van Etten RA, Chan WW, Zaleskas VM, Walz C, Evangelista P, Lazarides K, Betancur M, Wise S, Petillo PA, Flynn DL. Switch Pocket Inhibitors of the ABL Tyrosine Kinase: Distinct Kinome Inhibition Profiles and in vivo Efficacy in Mouse Models of CML and B-Lymphoblastic Leukemia Induced by BCR-ABL T315I. Blood 2008, 112(Suppl)

Chen Y, Hu Y, Michaels S, Segal D, Brown D, Li S. Inhibitory effects of omacetaxine on leukemic stem cells and BCR-ABL-induced chronic myeloid leukemia and acute lymphoblastic leukemia in mice. Leukemia 2009, 23:1446-1454

Quntas-Cardama A, Cortes J. Omacetaxine mepesuccinate—a semisynthetic formulation of the natural antitumoral alkaloid homoharringtonine, for chronic myelocytic leukemia and other myeloid malignancies. Drugs 2008, 11:356-372

Chen Y, Peng C, Sullivan C, Li D, Li S. Novel therapeutic agents against cancer stem cells of chronic myeloid leukemia. Anticancer Agents Med Chem 2010, 10:111-115

Cortes JE, Khoury HJ, Corm S, Nicolinii F, Scherk T, Jones D, Hochhaus A, Craig AR, Humphris S, Kantarjian H, Study Group: Subcutaneous omacetaxine mepesuccinate in imatinib-resistant chronic myeloid leukemia patients with the T315I mutation: data from an ongoing phase III trial. J Clin Oncol 2009, 27(Suppl)

doi:10.1186/1756-8722-3-47

Cite this article as: Wei et al. First-line treatment for chronic myeloid leukemia: dasatinib, nilotinib, or imatinib. Journal of Hematology & Oncology 2010 3:47