Dasatinib dose-optimization study in chronic phase CML: 3 year follow-up with dasatinib 100 mg/day

The recommended dosing regimen of dasatinib for CML-CP is now 100 mg once daily (QD) (previously 70 mg twice daily [BID]), based upon a phase III dose-optimization study (CA180-034) that enrolled patients (pts) with CML-CP with resistance, intolerance, or suboptimal response to imatinib. While therapeutic milestones have been established for pts with CML-CP treated with imatinib, they have not been well established for pts treated with second-line TKIs.

Methods: Pts were randomized using a 2 × 2 factorial design to one of four treatment arms: 100 mg QD (n = 167), 70 mg BID (n = 168), 140 mg QD (n = 167), or 50 mg BID (n = 168). Details of study design and endpoints have been described previously.

Results: After a minimum of 24 months of follow-up, the 24-month PFS rate with 100 mg QD was 80% (vs. 75%-76% in other arms) and the overall survival rate was 91% (vs. 88%-94%). In all arms, high response rates were achieved in pts with or without a baseline BCR-ABL mutation. Dasatinib 100 mg QD was well tolerated and rates of key side effects showed only a minimal increment from 12 to 24 months. Among the four treatment arms, significant differences were observed in rates of drug-related pleural effusion (all grades: p = 0.049) and cytopenia (p = 0.003 for grade 3/4 thrombocytopenia), with lowest rates observed for 100 mg QD. Dasatinib 100 mg QD treatment resulted in the lowest rates of treatment interruption, reduction, and discontinuation. In addition to providing 36-month follow-up, the likelihood of achieving long-term endpoints based on cytogenetic status at 6, 12, and/or 18 months will be presented.

Conclusions: Dasatinib 100 mg once daily remains the optimal dosing schedule for pts with CML-CP. The landmark analyses to be presented should provide useful information to clinicians treating imatinib-resistant, -suboptimally responding, or -intolerant CML-CP pts with dasatinib 100 mg once daily based on cytogenetic response at key intervals.


Subcutaneous OMA in resistant CML patients with T315I: phase II/III trial.

Background: Omacetaxine (OM), a first-in-class cetaxine shows clinical activity against Ph+ CML with a mechanism independent of tyrosine kinase inhibition. Currently available tyrosine kinase inhibitors (TKIs) have no activity against T315I. Methods: Adult Pts with T315I+ CML following TKI failure received OM induction at 1.25 mg/m² subcutaneous (SC) twice daily (BID) for 14 days every 28 days followed by maintenance at 1.25 mg/m² SC BID for 7 days every 28 days (maintenance after at least one induction cycle and achievement of hematologic response). Results: 66 pts (39 chronic [CP], 16 accelerated [AP] and 11 blast phase [BP]) have been enrolled. All had failed prior imatinib and 80% failed ≥2 prior TKIs. Median age is 58 yrs. Median disease duration is 58 mos. OM is well tolerated with transient myelosuppression as the primary toxicity. Grade 3/4 non-hematologic events are diarrhea (2%) and fatigue (4%). Efficacy data are available for 44 Pts. In CP Pts, the median number of cycles is 4 (1-22) with 39% having...
received 6 cycles of therapy; 64% of pts have had the T315I clone reduced to below detection limits; the 2-year progression free survival is 70%. Conclusions: Omacetaxine in T315I+ CML pts results in de-selection of the T315I clone and induces hematologic and cytogenetic responses. 

Nilotinib in chronic phase CML: Follow-up results of a phase II study

Background: Nilotinib is a potent and highly selective BCR-ABL inhibitor approved for the treatment of Ph+ CML patients (pts) in CP or accelerated phase who are resistant or intolerant to prior therapy including IM. This study evaluated the efficacy and safety of nilotinib (400 mg bid) in CML-CP pts resistant or intolerant to IM.

Methods: Primary endpoint was major cytogenetic response (MCyR). Secondary endpoints included complete cytogenetic response (CCyR), complete hematological response (CHR), MCyR duration, overall survival (OS), and safety.

Results: CML-CP pts (n = 321, 70% IM-resistant, 30% IM-intolerant with resistance) with a minimum follow-up of 19 months (mos) were evaluated; 72% were treated with ≥600 mg/day IM prior to enrollment. Median duration of prior IM treatment was 32 (<1-94) mos. Median dose intensity of nilotinib (790 mg/day; range 151-1,110 mg/day) closely approximated the planned dose. Nilotinib led to rapid and durable CHR and MCyR. CHR was observed in 94% of pts. 59% achieved an MCyR (2.8 mos median time to MCyR; 56% in IM-resistant, and 65% in IM-intolerant pts), including 73% of pts with a baseline CHR and 44% achieved a CCyR (41% in IM-resistant; 51% in IM-intolerant pts). Responses were durable, with 78% pts maintaining MCyR at 24 mos. Estimated OS rate was 88% at 24 mos. Safety profile did not change with longer follow-up. Most frequent grade (gr) 3/4 biochemical laboratory abnormalities were elevated lipase (17%), hypophosphataemia (16%), hyperglycemia (12%), and total bilirubin (8%) which were transient and clinically asymptomatic. Gr 3/4 non-hematologic AEs were infrequent: rash, headache, and diarrhea occurred in 2% of pts. Most common gr 3/4 hematological laboratory abnormalities were neutropenia (31%), thrombocytopenia (31%), and anemia (10%). Brief dose interruptions were successful in management of most AEs. Pleural or pericardial effusions (gr 3/4) were uncommon (< 1%).

Conclusions: These results demonstrate that nilotinib was highly effective, with rapid and durable responses in CML-CP pts failing prior therapy due to resistance or intolerance. Nilotinib was well tolerated with favorable risk/benefit.


Update of the SPIRIT Phase-III Study with Imatinib and Imatinib-Interferon-Combination

Imatinib 400mg daily is the front-line treatment of CP CML, but provides only 50% major molecular responses (MMR) at 18 months (Mo). We designed a phase III randomized multicenter open-label prospective trial comparing IM 400 mg/d (n=159) with 3 experimental arms: IM 600 mg/d (n=160), IM 400 mg/d + s/c cytarabine (Ara-C), (20

The CML Advocates Network – www.cmladvocates.net
mg/m²/d, d15-28 of 28-day cycles) (n=158) and IM 400 mg/d + s/c Peg-IFN2a (90 µg/wk) (n=159).

Pts were allocated at a 1.1.1.1 ratio, stratified by Sokal risk groups. Molecular assessments were centralized and blinded. An interim analysis of 636 pts was planned based on an IS BCR-ABL/ABL ratio <0.01% (Optimal Molecular Response, OMR) at 1 year (?=0.85%, ?=10%).

Results: 636 pts were recruited between 9/2003 and 10/2007, median age 51 (18-78) yrs, 62% males, median follow-up for alive pts 36 (12-62) Mo. At 3 Mo, 88% of pts achieved complete hematologic response. Complete cytogenetic response (CCyR), MMR and OMR rates are presented (Table). MMR rates at 6 and 12 Mo were higher for IM-PegIFN as compared to IM-400 (p<10⁻³). At 18 Mo the cumulative OMR rates were 22% (IM-400), 28% (IM-600), 25% (IM-Ara-C), 43% (IM-PegIFN). Grade 3/4 neutropenia and/or thrombocytopenia occurred during the first year in 8% IM-400, 14% IM-600, 41% IM-Ara-C and 40% IM-PegIFN arms respectively. Grade 3/4 non-hematological toxicities occurred in 19% IM-400 (edemas, muscle cramps), 30% IM-600, 27% IM-Ara-C (diarrhea) and 31% IM-PegIFN pts (skin rashes, asthenia). Within the first 12 Mo, discontinuation of experimental treatment occurred in 8% IM-600, 39% Ara-C and 45% PegIFN pts.

Conclusions: Although a significant number of pts reduced or stopped PegIFN within the first year, significant improvements in molecular response rates were observed in the IM-Peg IFN arm and may translate into survival benefit.

Source: ASCO Abstract 7058: A phase III study exploring various doses of imatinib (IM) or IM in combination for newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML) patients (pts): Results of an interim analysis of the SPIRIT trial of French CML group. E. Nicolini, F. X. Mahon, J. Guilhot et al

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CCyR, MMR, and OMR rates

**Nilotinib 800 mg/day as first-line treatment of CML: Results of phase II GIMEMA trial**

Nilotinib has a higher binding affinity and selectivity for Abl with respect to imatinib (IM). To investigate the efficacy and the safety of nilotinib 400 mg BID in untreated, early chronic phase (ECP) CML patients (pts), the GIMEMA CML WP is conducting a
multicentric, phase II study trial (ClinicalTrials.gov NCT00481052). 73 pts have been enrolled between June 2007 and February 2008.

All 73 pts and 48/73 (66%) completed 3 and 6 months on treatment, respectively. Response at 3 and 6 months (ITT): CHR rate was 100% and 98%, CcGGR rate 78% and 96%, respectively. A MMR was achieved by 3% after 1 month on treatment, but this proportion rapidly increased to 22% after 2 months, 59% after 3 months and 74% after 6 months. One patient progressed at 6 months to accelerated-blastic phase with the T315I mutation. The median daily average dose was close to the intended dose, 789 mg (range 261 - 800); 34/73 pts (47%) interrupted nilotinib at least once, with a median interruption of 15 days (range 2-98). The dose of nilotinib at the last visit was 400 mg BID for 52 pts (71%), 400 mg daily for 20 pts (27%), and 200 mg daily for 1 patient (1%). AEs (grade 3/4) were manageable with appropriate dose adaptations: hematologic toxicity was recorded so far in 4 pts (5%); the most frequent biochemical laboratory abnormalities (grade 3) were total bilirubin increase (15%), GOT/GPT increase (11%), and lipase increase (4%). Only 1 episode of grade 4 lipase increase was recorded.

It is noteworthy, considering the 48 cases with at least 6 months of follow-up, that the incidence of any grade 2 and 3 non-hematologic adverse event, decreased from 50% and 8% (first 3 months) to 23% and 6% (second trimester), respectively. In 16 pts (22%), transient and not clinically relevant ECG abnormalities have been recorded; 2 more pts (3%) revealed a transient and uneventful QTc prolongation (>450 but <499 msec).

Conclusions: In ECP Ph-positive CML pts both cytogenetic and molecular responses to nilotinib are substantially faster than the responses to IM.


Inadequate BCR-ABL monitoring in imatinib-treated CML

Recommendations for baseline and quarterly measurement of the BCR-ABL fusion transcript to monitor imatinib response in patients with CML were formally introduced in October 2006, and have been incorporated into nationally recognized treatment guidelines. To assess BCR-ABL testing rates, we conducted a retrospective cohort analysis using a >10 million-member health plan database comprised of integrated pharmacy and medical claims.

The study cohort was defined as patients with an index imatinib pharmacy claim from July 1, 2006, to December 31, 2006, who had a CML diagnosis (ICD-9 205.1X; N = 504), and a minimum of 3 months continuous follow-up by claims history (N = 465). Over a period of up to four quarters from the index imatinib prescription date, BCR-ABL testing in each quarter was assessed by the presence of any of a set of 19 CPT-4 codes. BCR-ABL testing rates in each individual quarter and in consecutive quarters were measured.

Results: The overall study cohort was 57% male; mean (±SD) age was 52±14 y/o, with 26% 19-44 y/o, 57% 45-64 y/o, and 15% ?65 y/o. Median duration of f/u was 559 days (interquartile range 302-628 days), and a cohort of 359 patients had 4 quarters of f/u. At least one BCR-ABL test was recorded in 60% of patients. The rate of first quarter BCR-ABL testing was 40%, and remained at 42%-43% in quarters 2 thru 4. Consecutive quarterly testing rates were 24% through the second quarter, 18% through the third quarter, and 14% through the fourth quarter.
Patient Education Material

Conclusions: In this retrospective claims database analysis, only 14% of a large cohort of CML patients treated with imatinib had BCR-ABL testing recorded in each of 4 consecutive quarters. Inadequate compliance with recommended BCR-ABL testing can delay treatment decisions, and may be associated with poor clinical outcome.

Source: Abstract No: 7077: Inadequate BCR-ABL monitoring in imatinib-treated patients with chronic myelogenous leukemia. E. Stanek, R. E. Aubert, C. Sanders, F. W. Frueh, J. Yao, R. S. Epstein

Phase I study with dasatinib and MK-0457 in refractory Ph+ CML and ALL

Background: MK-0457 is a pan-aurora kinase inhibitor with activity against wild-type and mutated BCR-ABL, including the T315I form, FLT3, and JAK-2. Methods: We conducted an innovative Phase I clinical study of sequential and concomitant treatment with dasatinib, previously administered for 3 months, and MK-0457. This combined activity suggests that MK-0457, in association with dasatinib, would suppress the emergence of T315I and other resistant clone, improving upon the response rate for dasatinib and the durability of response. The trial investigated two schedules of therapy: patients who achieved and maintained a major hematologic response (MHR) after 3 months of therapy with dasatinib (70 mg twice daily) received a 6-hour biweekly infusion of MK-0457 at 64 mg/m2/hr, whereas patients who failed to achieve a MHR received a 5-days continuous infusion of MK-0457 at 10 mg/m2/hr, every 4 weeks. Results: Two patients with Ph+ ALL and one patient with CML in myeloid blast crisis, previously unsuccessfully treated with imatinib, were enrolled. The first two patients, both in hemalogic response after three months of treatment with dasatinib, subsequently received the 6-hour biweekly schedule, maintaining the hematological response. No hematological toxicity was described. The third patient, in progression disease, received the 5 days MK-0457 schedule. His peripheral blood count showed a severe pancytopenia, and his bad clinical conditions were compromised by a severe hemorrhagic pleural effusion. After one cycle of MK-0457, a complete recovery of the pulmonary disease and a complete hematologic response were obtained. Conclusions: The sequential and concomitant administration of dasatinib and MK-0457 represents a promising therapeutic strategy for refractory Ph+ CML and ALL.


Imatinib in breast milk

To our knowledge, not much is known about imatinib (IM) treatment and pregnancy, child birth, and breast feeding. Pye and colleagues recently investigated the treatment, pregnancy, and fetal outcomes of 180 women exposed to imatinib during pregnancy. There were a total of 12 infants in whom abnormalities were identified. It appeared that, although most pregnancies exposed to imatinib are likely to have a successful outcome, an element of risk remains for exposure to result in serious fetal malformations [1]. We should like to share the results of measuring imatinib levels in the breast milk of a woman treated with imatinib, even though our findings are related to neonatal rather than fetal drug exposure.

A 34-year-old woman was diagnosed with chronic myeloid leukemia (CML) in chronic phase in 2001 and started on interferon (IFN) alpha of three million units per day at a regional hospital. IFN was well tolerated and the patient achieved complete
hematological remission but no major cytogenetic response. In February 2004, the patient was referred to our institution because Bcr-Abl was detectable in 75% of peripheral blood cells by fluorescence in situ hybridization analysis. The patient was started on imatinib of 400 mg/day. Between February and May 2004, molecular monitoring yielded a 1-log decrease in Bcr-Abl messenger RNA (mRNA). In June 2004, the patient reported that she was pregnant. Imatinib was discontinued. As the molecular monitoring in July showed a further 1-log decrease in Bcr-Abl mRNA, no further CML treatment was given during pregnancy. Bcr-Abl transcripts increased up to the May 2004 level only towards the end of pregnancy. A healthy child was born at term. No malformations were detectable. After delivery, imatinib was immediately restarted at 400mg/day. The infant received bottle feeding from the start. However, we asked the mother to defer ablation until 171 h of imatinib treatment in order to obtain measurements of IM and its active metabolite Ndesmethyl-imatinib (N-DesM-IM, CGP74588) in plasma and breast milk. Drug levels were measured repeatedly (see Table 1). We found that the level of imatinib in breast milk was about half the plasma level. The active metabolite NDesM-IM accumulated about threefold in breast milk as compared to plasma levels. A pseudo-steady-state level was reached in the breast milk after about 2 days of imatinib treatment.

According to our results, breastfeeding cannot be recommended during treatment with imatinib.


Discontinuing imatinib in CML: don't try this at home

The use of the tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, and nilotinib has revolutionised the care of patients with CML. We now have more than 6 years of follow-up data on the IRIS study, and the frontline use of imatinib has been shown to be both highly efficacious and generally well-tolerated. The large majority of newly diagnosed patients treated for CML in chronic phase achieve a complete cytogenetic remission (CCyR), and over time, most of these eventually achieve major molecular responses (MMR) and even complete molecular responses (CMR). However, cure has not yet been proven, and life-long therapy with imatinib is still the consensus recommendation.

Nevertheless, there are situations when cessation or temporary interruption of TKI therapy for patients who have had a good clinical response would be desirable. For instance, even relatively minor grade 1 or 2 side effects such as fluid retention, rash, muscle cramps or mild fatigue can, over the period of many months to years, become more than annoying and sometimes even debilitating to a patient who requires lifelong therapy. A brief drug holiday can provide a welcome respite, but this is often balanced against the anxiety of a quick relapse. The cost of continuous therapy can also prove to be a burden. Finally, there are situations such as pregnancy, elective surgical procedures or intercurrent illnesses for which interrupting treatment for a short period could be considered. The paper by Goh et al. in this issue of Leukemia and Lymphoma adds to the growing body of data about the clinical outcomes for patients with CML in remission who, for various reasons, have discontinued TKI therapy while in remission.

We place these new results in the context of prospective imatinib discontinuation studies reported on recently by Australian and French investigators.

Goh et al. in Korea followed the clinical outcomes of 26 patients with Philadelphia chromosome positive CML who discontinued imatinib after achieving a CCyR or CMR. The patients in this study stopped imatinib for a variety of reasons that included toxicity,
pregnancy, cost or other patient-specific factors. In contrast to the studies described below, the design of the Korean study did not include a pre-planned discontinuation schema. A heterogeneous group of 26 patients were studied, including 11 who had previously had an allogeneic stem cell transplant and seven who had been in accelerated phase at the time imatinib was started. Twelve had previously received interferon, and only seven had received imatinib as their initial therapy for CML. Of the 26 patients included, 11 stopped imatinib after achieving CCyR and 15 stopped treatment after achieving CMR. Importantly, the median remission duration prior to drug discontinuation was only 7 months for each cohort. Several discontinued imatinib within 1–4 months after achieving a response. Patients were monitored every month for hematologic relapse and every 3 months for cytogenetic or molecular relapse. Twenty-four patients experienced a relapse from their deepest remission state within a median of 7 months (range, 4–48 months) after discontinuing imatinib. When imatinib was resumed, 23 patients regained their best previous response, but one patient, previously in CCyR, died from progression of CML. Up to 28 months were required after resuming imatinib for some patients to regain their previous best response, but no additional progression events were reported. Median followup after resumption of imatinib therapy has been 44 months.

In contrast, Australian investigators are conducting a prospective imatinib discontinuation trial for patients who were previously in CMR for greater than 24 months. Interim results presented at the 2008 American Society of Hematology (ASH) meeting reported on 13 patients who had received imatinib after prior interferon treatment and five patients who had received only imatinib. Ten of 13 interferon/imatinib patients and three of five imatinib only patients remained in CMR at last follow up. All five of the molecular relapses occurred within 5 months of discontinuing treatment, and all five patients regained CMR after restarting imatinib. No patients experienced hematologic relapse or were found to have acquired an ABL kinase domain mutation.

The most mature data have been published by the French group led by F-X Mahon. They first conducted a pilot study to evaluate the feasibility of imatinib discontinuation in patients who had been in CMR for more than 24 months. After imatinib was discontinued, patients were monitored by quantitative RT-PCR (Q-PCR) monthly for the first 6 months and then every other month thereafter. The investigators enrolled 12 patients who had been in CMR for a median of 32 months after receiving imatinib for a median of 45 months. Ten of 12 patients had had previous treatment with interferon. After stopping imatinib, six patients experienced molecular relapse; all events occurred within 5 months of drug discontinuation. After restarting imatinib, two patients regained CMR, and the other four had decreasing transcript levels at the time of publication. Six patients remained in CMR with a median follow-up of 18 months at the time of reporting, and some for as long as 24 months.

Guided by these results, the French group initiated the multicenter Stop Imatinib (STIM) study in July 2007. Study enrollment required at least 36 months of imatinib therapy and at least 24 months with CMR documented on several occasions. This trial enrolled 50 patients, 25 of whom had received prior interferon. At the time of the abstract presentation at the 2008 ASH meeting, 34 patients had been followed for longer than 6 months after imatinib was stopped. Nineteen patients (56%) had already experienced a molecular relapse, with all but one relapse occurring within 6 months of imatinib discontinuation. Fifteen patients (44%) remained in CMR with monthly monitoring by Q-PCR, but only three patients had been followed for longer than 12 months. Of note, the observed relapse rate was similar for patients who had previously received interferon when compared with those who had received only imatinib. Thus, a small but growing body of evidence suggests that a subset of patients treated for CML in chronic phase who are in a prolonged CMR on imatinib therapy may be able to discontinue their TKI therapy safely. However, this strategy requires further validation and much longer follow-up. As
yet, there appear to be no patient or disease characteristics that would identify in advance those who can safely discontinue their imatinib. Thus, such patients should be observed extremely closely and within the context of a well-designed clinical trial. Monthly monitoring with a sensitive and reliable Q-PCR method appears mandatory as well as a commitment for restarting imatinib at the first sign of molecular relapse. Fortunately, most patients can be rescued after relapse. It remains to be determined whether patients who received interferon prior to imatinib have lower relapse rates than those patients who receive imatinib alone. Future studies may consider using both agents, either sequentially as in the past or concurrently, as a strategy for CML eradication with the ultimate goal of avoiding long-term TKI exposure.

For now, clinical practice should be guided by a conservative approach. Continuous daily imatinib therapy and the timely achievement of therapeutic milestones such as early hematologic response, CCyR and MMR are critical for ensuring that the excellent published outcomes in CML are replicated in widespread practice. No patient in a prolonged molecular remission, or with any depth of remission, should attempt to stop therapy on his or her own. In addition, treating clinicians should not apply these early findings to individual patients by stopping an effective therapy before the evidence base is larger and more mature.