181 High and Early Rates of Cytogenetic and Molecular Response with Nilotinib 800 Mg Daily as First Line Treatment of Ph-Positive Chronic Myeloid Leukemia in Chronic Phase: Results of a Phase 2 Trial of the GIMEMA CML Working Party

Monday, December 8, 2008: 7:00 AM
Halls B and C (Moscone Center)

Gianantonio Rosti1,*, Fausto Castagnetti1,*, Angela Poerio1,*, Massimo Breccia2,*, Luciano Levato3,*, Adele Capucci3,*, Mario Tribelli5,*, Fabio Stagno5,*, Alfonso Zaccaria5,*, Tamara Intermesoli8,*, Bruno Martino9,*, Monica Bocchia10,*, Michele Cedrone11,*, Francesco Bartucci12,*, Francesca Palandri17,*, Gabriele Gugliotta17,*, Nicoletta Testoni17,*, Giuliana Alimena13,*, Giovanni Martinelli17,*, Fabrizio Pane, MD14, Giuseppe Saglio15,*, and Michele Baccarani1

1Institute of Hematology Seragnoli, Bologna, Bologna, Italy
2University of Rome – La Sapienza, Italy
3Hematology Unit, Catanzaro, Italy
4Hematology Unit, Brescia, Italy
5Chair of Hematology, Udine, Italy
6Chair of Hematology, Catania, Italy
7Ematologia-Ravenna, Italy
8Chair of Hematology, Bergamo, Italy
9Reggio Calabria Hospital
10Chair of Hematology, University of Siena, Italy
11Hematology Unit, "San Giovanni-Addolorata" Hospital, Roma, Italy
12Novartis Pharma, Origgio (VA), Italy
13Division of Hematology-Dept. of Cellular Biotechnologies and Hematology, University La Sapienza of Rome, Rome, Italy
14A.F. di Oncologia Ematologica Diagnostica, Azienda Ospedaliera, Napoli, Italy
15Internal Medicine and Hematology, Università di Torino - Ospedale San Luigi, Orbassano, Italy

Imatinib (IM) 400 mg daily is the standard treatment for chronic myeloid leukemia in early chronic phase (ECP): the results of the IRIS trial have shown a 72 months overall survival of 95%; EFS and PFS were 83% and 93%, respectively; the cumulative rate of complete cytogenetic response (CCgR) for the IM 400 mg arm was 25% at 3 months (at 6, 12, 18 and 60 months it was 51%, 69%, 76% and 87%, respectively). Nilotinib, a second generation TKI, has a higher binding affinity and selectivity for Abl with respect to IM, being 20 to 50 times more active in IM-sensitive cell lines and is highly effective in IM resistant patients, across every disease phase. To investigate the therapeutic efficacy and the safety of nilotinib 400 mg BID in untreated, ECP, Ph-pos CML patients, the italian GIMEMA CML Working Party is conducting an open-label, single stage, multicentric, phase II study trial (ClinicalTrials.gov. NCT00481052); all patients provided written informed consent. The primary endpoint is the CCgR rate at 1 year; the kinetic of molecular response is studied by Q-PCR baseline and after 1, 2, 3, 6, 9 and 12 months from treatment start. PATIENTS Seventy-three patients have been enrolled from 20 Centres between June, 2007 and February, 2008. The median age was 51 years (range 18-83), 45% low, 41% intermediate and 14% high Sokal risk. Median follow-up is currently 210 days (range 68-362). RESULTS All 73 patients and 48/73 (66%) completed 3 and 6 months on treatment, respectively. Response at 3 and 6 months (ITT): the CHR rate was 100% and 98%, the CCgR rate 78% and 96%, respectively. A MMR, defined as a BCR-ABL:ABL ratio < 0.1% according to the International Scale, was achieved by 3% of all treated patients 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. NILOTINIB DOSE AND COMPLIANCE No dose escalation was permitted in case of
resistance; the median daily average dose was close to the intended dose, 789 mg (range 261 – 800); 34/73 patients (47%) interrupted nilotinib at least once, with a median duration of dose interruption of 15 days (range 2-98). The dose of nilotinib at the last visit was 400 mg BID for 52 patients (71%), 400 mg daily for 20 patients (27%) and 200 mg daily for 1 patient (1%). ADVERSE EVENTS: AEs (grade III/IV) were manageable with appropriate dose adaptations: hematologic toxicity was recorded so far in 4 pts (5% - only 1 event grade IV neutropenia); the most frequent biochemical laboratory abnormalities (grade III) were total bilirubin increase (15%), GOT/GPT increase (11%) and lipase increase (4%). Only 1 episode of grade IV 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 II and III non-hematologic adverse event, decreased from 50% and 8% (first 3 months) to 23% and 6% (second trimester), respectively. ECG monitoring: in 16 patients (22%), transient and not clinically relevant ECG abnormalities have been recorded; 2 more patients (3%) revealed a transient and uneventful QTc prolongation (>450 but <499 msec). CONCLUSIONS: The results that have been achieved in these unselected patients and within a multicentric trial, strongly support the notion that in ECP Ph-pos CML patients both cytogenetic and molecular responses to nilotinib are substantially faster than the responses to IM.

Acknowledgements: Work supported by European LeukemiaNet

3219 Randomized Phase II Study of Proteinase 3-Derived PR1 Peptide Vaccine and GM-CSF with or without PEG-Interferon ALFA-2B to Eradicate Minimal Residual Disease in Chronic Myeloid Leukemia

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-301
Alfonso Quintás-Cardama

Alfonso Quintás-Cardama1, Hagop M. Kantarjian2, Rosa Rios1, Eric D. Wieder, Ph.D.3, Jeffrey J. Molldrem, M.D.4 and Jorge Cortes1

1Leukemia, M.D. Anderson Cancer Center, Houston, TX
2M.D. Anderson Cancer Center, Houston, TX
3Stem Cell Transplant Program, Department of Medicine, University of Miami, Miami, FL
4Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX

BACKGROUND: Complete molecular eradication of chronic myeloid leukemia (CML) cells occurs only in a minority of patients treated with imatinib (IM). The curative potential of allogeneic transplantation and donor lymphocyte infusions highlights the responsiveness of CML to T-cell-mediated immunity. The proteinase 3-derived PR1 peptide (VLQELNVTV) is a leukemia-associated antigen presented on HLA-A2 to cytotoxic T lymphocytes (CTL) that preferentially kill leukemia over normal hematopoietic progenitors.

METHODS: This phase II study was designed to evaluate the anti-leukemic effects of PR1 vaccine (2 mg) with GM-CSF (0.6 mg) and an incomplete Freund’s adjuvant (Montanide ISA-51) given subcutaneously to patients with CML on IM in complete cytogenetic response (CCyR) with stable residual molecular disease. Patients were randomized to receive the vaccine alone or in combination with pegylated interferon α (PEG-IFN-α; 0.5 μg/kg) with each vaccination. PR1 vaccination was administered on weeks 0, 3, 6, and 18. Immune responses were assessed by PR1/HLA-A2 tetramer staining and molecular responses by quantitative PCR (qPCR) in peripheral blood before study entry, prior to each vaccination, and every 3 months thereafter.
RESULTS: Five of the 20 planned HLA-A2+ patients (3 male) have been accrued. All but patient 4 (b3a2) expressed b2a2 transcripts prior to vaccination. Patients 1 (on IM 600 mg/d for 85 months), 2 (on IM 800 mg/d for 72 months) and 5 (on IM 400 mg/d for 76 months) were randomized to receive vaccine+PEG-IFN-α whereas Patients 3 and 4 (both on IM 400 mg/d, for 43 and 37 months, respectively) received PR1 vaccine alone. BCR-ABL1/ABL1 ratios prior to vaccination were 0.99, 0.79, 0.52, 0.10, and 0.44 respectively. The median follow-up from the first PR1 vaccination is 19 months (range, 4-20). All patients experienced transient mild elevations of BCR-ABL1 transcripts after the first vaccination followed by steady decline in transcript levels in Patient 1 (>1-log), and patients 2, 3, and 5 (<1-log) (Figure 1). Furthermore, patient 1 continues exhibiting an ongoing decrement of transcript levels. BCR-ABL1 transcripts have not decreased in Patient 4. Toxicity was limited to grade 1-2 injection site reactions except for Patient 2, in whom the fourth and last dose of PEG-IFN-α was not administered due to behavioral changes. Peripheral blood lymphocytes were analyzed in all 5 patients with PR1/HLA-A2 tetramer and detailed immunophenotyping (CD8, CCR7, CD45RA). Patients 1, 2 and 3 had immune responses (IR) defined as ≥2-fold increase in PR1/HLA-A2 tetramer+ cells. Patient 4 did not have an IR, but had pre-existing PR1-CTL that decreased transiently 3 weeks after the first vaccination. Patient 5 harbored pre-existing PR1-CTLs as well; follow-up analysis pending. No clear trends regarding memory T cell subsets have been identified. Immunity to control CMV-derived pp65 peptide was evident in all 5 patients but did not change after vaccination. Multiple clones of PR1-CTL could be derived from patients 1, 2 and 3 and studies are underway to analyze their TCR-ab affinity to PR1/HLA-A2.

CONCLUSION: PR1 vaccination induces specific immunologic responses and improvement of molecular response in patients with CML in CCyR with stable or rising levels of BCR-ABL1 transcripts receiving imatinib therapy.

Figure 1. Dynamics of molecular response after PR1 vaccination
Dasatinib (SPRYCEL®) is an effective BCR-ABL inhibitor that is 325-fold more potent than imatinib and 16-fold more potent than nilotinib in vitro against unmutated BCR-ABL. Across a series of phase II and III trials, dasatinib has demonstrated durable efficacy in patients with CML following resistance, suboptimal response, or intolerance to imatinib. BCR-ABL mutations are an important cause of imatinib failure and suboptimal response. Here, the efficacy of dasatinib in patients with CML-CP who had baseline BCR-ABL mutations following imatinib treatment was analyzed using data from three trials (CA180-013, -017, and -034). Mutational assessment of the BCR-ABL kinase domain was performed using RT-PCR and direct sequencing of peripheral blood cell mRNA. Hematologic, cytogenetic, and molecular response rates were reported after ≥24 mos of follow-up. Duration of response, progression-free survival (PFS), and overall survival (OS; in 013/034) were calculated using Kaplan-Meier analysis, and rates were estimated at the 24-mo time point. Of 1,150 patients with CML-CP who received dasatinib, 1,043 had a baseline mutational assessment and were analyzed further. Of these, 402 patients (39%) had a BCR-ABL mutation, including 8% of 238 imatinib-intolerant and...
48% of 805 imatinib-resistant patients. Excluding known polymorphisms, 64 different BCR-ABL mutations were detected affecting 49 amino acids, with Q250 (n=61), M351 (n=54), M244 (n=46), F359 (n=42), H396 (n=37), Y253 (n=26), and E255 (n=25) most frequently affected. Dasatinib treatment in patients with or without a baseline BCR-ABL mutation, respectively, resulted in high rates of major cytogenetic response (MCyR; 56% vs 65%), complete cytogenetic response (CCyR; 44% vs 56%), major molecular response (MMR; 33% vs 45%); PFS (70% vs 83%), and OS (89% vs 94%) (Table). After 24 mos, CCyRs in patients with or without a BCR-ABL mutation had been maintained by 84% vs 85%, respectively, of those achieving this response. Among patients with mutations who received dasatinib 100 mg once daily, which has a more favorable clinical safety profile, efficacy and durability were similar (MCyR: 55%; CCyR: 41%; MMR: 36%; PFS: 73%; OS: 90%). In general, high response rates and durable responses were observed in patients with different mutation types, including highly imatinib-resistant mutations in amino acids L248, Y253, E255, F359, and H396. When responses were analyzed according to dasatinib cellular IC_{50} for individual BCR-ABL mutations, dasatinib efficacy was observed in 44 patients who had any of 5 imatinib-resistant mutations with a dasatinib cellular IC_{50} >3 nM (Q252H, E255K/V, V299L, and F317L, excluding T315I), including MCyR in 34%, CCyR in 25%, MMR in 18%, PFS in 48%, and OS in 81%. Among patients whose mutations had a dasatinib IC_{50} <3 nM (n=254) or unknown IC_{50} (n=83), responses and durability were comparable to patients with no BCR-ABL mutation. As expected, few patients with a T315I mutation (IC_{50} >200 nM; n=21) achieved a response. Among 70 patients with >1 mutation, a MCyR was achieved in 53% and a CCyR in 37%. Among patients with mutational analysis at last follow-up (n=162), 42 (26%) retained a BCR-ABL mutation (20 retained a mutation with IC_{50} >3 nM), 42 (26%) lost a mutation (5 lost a mutation with IC_{50} >3 nM), and 44 (27%) developed a new mutation (39 developed a mutation with IC_{50} >3 nM), with some patients counted in more than one category. Overall, this analysis demonstrates that dasatinib has broad efficacy against all BCR-ABL mutations except for T315I. For patients with BCR-ABL mutations, dasatinib treatment is associated with durable responses and favorable long-term outcomes.

Table

<table>
<thead>
<tr>
<th></th>
<th>No BCR-ABL mutation</th>
<th>BCR-ABL mutation</th>
<th>BCR-ABL mutation treated with 100 mg QD</th>
<th>Analysis by dasatinib IC_{50}</th>
<th>&gt;3 nM (excl. T315I)</th>
<th>≤3 nM*</th>
<th>Unknown IC_{50}**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>641</td>
<td>402</td>
<td>49</td>
<td>44</td>
<td>254</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Response rates (≥24 mos of follow-up), %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHR</td>
<td>93</td>
<td>90</td>
<td>90</td>
<td>82</td>
<td>94</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>MCyR</td>
<td>65</td>
<td>56</td>
<td>55</td>
<td>34</td>
<td>58</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>CCyR</td>
<td>56</td>
<td>44</td>
<td>41</td>
<td>25</td>
<td>47</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>45</td>
<td>33</td>
<td>36</td>
<td>18</td>
<td>34</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Median time to MCyR, mos</td>
<td>2.8</td>
<td>2.9</td>
<td>2.8</td>
<td>5.7</td>
<td>2.9</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Median time to CCyR, mos</td>
<td>3.0</td>
<td>5.3</td>
<td>3.0</td>
<td>5.7</td>
<td>5.4</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>24-mo PFS (95% CI), %</td>
<td>83 (79.8–86.5)</td>
<td>70 (65.3–75.2)</td>
<td>73 (60.1–86.3)</td>
<td>48 (31.2–64.7)</td>
<td>73 (66.6–78.9)</td>
<td>89 (82.3–96.3)</td>
<td></td>
</tr>
</tbody>
</table>
Dasatinib (SPRYCEL®) is a potent BCR-ABL inhibitor that is 325-fold more potent than imatinib and 16-fold more potent than nilotinib in vitro against unmutated BCR-ABL. In this analysis, time to, duration, and rates of cytogenetic responses to dasatinib were determined using Kaplan-Meier analysis in patients recruited to phase II trials in imatinib-resistant or -intolerant CML-CP (START-C and -R), which have more than 2 years of follow-up. In both trials, patients received dasatinib at the previous dose of 70 mg twice daily (the approved dose in CML-CP is now 100 mg once daily following phase III dose optimization demonstrating improved tolerability). In START-C, imatinib-resistant and -intolerant patients were recruited, and separate analyses were performed for each group. In START-R, a randomized trial of dasatinib vs escalated-dose imatinib, only imatinib-resistant patients were recruited and patients from the dasatinib arm were analyzed prior to cross over. In all dasatinib trials, MCyRs and CCyRs were determined using conventional bone marrow cytogenetic assessment. Progression was defined as increasing white blood cell count, loss of complete hematologic response, loss of MCyR, transformation to accelerated or blast phase, or death. Among imatinib-resistant patients treated in START-C, a MCyR had been achieved at 3, 6, and 12 months by 29%, 40%, and 51%, and a CCyR had been achieved by 18%, 28%, and 39%, respectively (Table). At 24 months, MCyR and CCyR had been achieved by 55% and 44%, respectively. Among responding patients, median time to MCyR was 2.9 months and to CCyR was 5.5 months. In resistant patients who had achieved a MCyR, 94% and 84% had maintained this response 12 and 24 months after it had been initially achieved. For CCyR, 95% and 86% had maintained their response at 12 and 24 months, respectively. Progression-free survival (PFS) at 12 and 24 months for imatinib-resistant patients was 88% and 75%. In START-R, dasatinib response rates and durability were similar to those observed in the imatinib-resistant population of START-C, and median times to MCyR and CCyR were 2.8 and 4.1 months, respectively. Among imatinib-intolerant patients treated in START-C, MCyRs had been achieved at 3, 6, and 12 months by 62%, 74%, and 80%, and CCyRs by 44%, 65%, and 74%, respectively. Rates at 24 months had reached 82% for MCyR and 78% for CCyR. Median times to achieve MCyR and CCyR in the intolerant population were both 2.8 months. Among responding patients, 99% and 97% of intolerant patients were without loss of MCyR 12 and 24 months after responding, and 100% and 98% were without loss of CCyR, respectively. The 12- and 24-month PFS rates were 98% and 94%. In conclusion, dasatinib treatment results in high rates of durable MCyRs and CCyRs in patients with imatinib-resistant or -intolerant CML-CP, and responses are achieved rapidly in most patients.
### Table

<table>
<thead>
<tr>
<th></th>
<th>START-C</th>
<th>START-R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>(N=387)</td>
<td>(n=288)</td>
</tr>
<tr>
<td>CCyR achieved (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>6 months</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>9 months</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>12 months</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>18 months</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>24 months</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td>Median time to CCyR (months)</td>
<td>3.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Patients without loss of CCyR (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>24 months</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>PFS (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>24 months</td>
<td>80</td>
<td>75</td>
</tr>
</tbody>
</table>

---

**3236 Prevalence of T315I, Dasatinib-Specific Resistant Mutations (F317L, V299L, and T315A), and Nilotinib-Specific Resistant Mutations (P-loop and F359) at the Time of Imatinib Resistance in Chronic-Phase Chronic Myeloid Leukemia (CP-CML)**

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-318

**Michael W.N. Deininger, MD**1, Michael J. Mauro1, Yousif Matloub2*, Ritwik Sinha2*, Lynn Ploughman2*, David Liu2* and Jerald Radich3*

1Oregon Health & Science University Cancer Institute, Portland, OR
2Bristol-Myers Squibb, Wallingford, CT
3Fred Hutchinson Cancer Research Center, Seattle, WA
Mutations in the catalytic domain of ABL kinase (AKD) are a major mechanism of resistance to imatinib. Over 70 mutations in more than 50 amino acid residues have been reported to date. The ‘gatekeeper’ mutation, T315I, which causes complete resistance to all three FDA-approved tyrosine kinase inhibitors (TKIs), was reported to be not uncommon among a heterogeneous set of patients who had failed first-line imatinib therapy. In addition, the F317L, V299L, and T315A mutations were reported to convey a high degree of resistance to dasatinib, and higher frequency mutations within the P-loop (Y253H/F, E255V/K) and F359 mutations were associated with a high degree of resistance to nilotinib. We studied the prevalence of AKD mutations in the START-C phase II trial of dasatinib in patients who have failed imatinib (resistance or intolerance). Baseline mutation data were available for 95 of 99 patients with imatinib intolerance, and 274 of 288 patients with imatinib resistance. Of these patients, 13 (14%) with imatinib intolerance and 136 (50%) with imatinib resistance had AKD mutations. Of the 149 patients with mutations, only 3 (2%) had the T315I mutation. A total of 57 (38%) subjects had mutations in the P-loop (between 248-256): 13 patients with Y253H/F (9%), and 6 patients with E255V/K (4%). Four subjects (3%) had the F317L mutation, and 8 (5%) had F359 mutations. No subjects with V299L or T315A mutations were detected at baseline. The rates of complete cytogenetic response (CCyR) were 52% in patients with any mutation, 69% in patients with Y253H/F, 40% among those with E255V/K, 0% for T315I mutations, 0% for F317L mutations, and 50% for F359 mutations. Patients without mutations achieved a 55% rate of CCyR. These results confirm that select P-loop and F359 mutations are sensitive to dasatinib, while F317L and T315I mutations are resistant to dasatinib treatment. However, the overall incidence of these dasatinib-resistant mutants is low. In contrast, nilotinib-resistant mutations in the P-loop (Y253H/F, E255V/K) or at F359 are more common, representing 15% and 5% of all patients with mutations, respectively. Therefore, the likelihood of harboring a nilotinib-resistant mutation at the time of imatinib resistance appears higher than the likelihood of harboring a dasatinib-resistant mutation, and suggests mutation testing may become instrumental for choosing between the various second-line TKI inhibitors to optimize outcomes.

### 182 Efficacy of Dasatinib in Patients (pts) with Previously Untreated Chronic Myelogenous Leukemia (CML) in Early Chronic Phase (CML-CP)

**Monday, December 8, 2008: 7:15 AM**  
Halls B and C (Moscone Center)

M.D. Anderson Cancer Center, Houston, TX

**Background:** Dasatinib (BMS-354825) is a multi-targeted kinase inhibitor of BCR-ABL and SRC with significant activity in pts with CML-CP resistant to or intolerant of imatinib (IM). We initiated a phase II trial to study efficacy and safety of dasatinib in pts with previously untreated CML-CP. **Aims:** To investigate the efficacy and safety of dasatinib as initial therapy for patients with CML-CP. **Methods:** The primary objective was to estimate the proportion of pts attaining major molecular response (MMR) at 12 months (mo). Pts with previously untreated CML-CP were eligible and received dasatinib 100 mg/day, randomized to either 50 mg-twice-daily (BID) or a 100 mg-once-daily (QD). **Results:** Fifty pts have been enrolled (25 on the QD schedule, 25 BID). Median age was 45 years (yrs) (range 18–76 yrs); 75% are Sokal low risk. Median follow-up is 24 months (mo). Overall, 44/45 (98%) evaluable patients achieved complete cytogenetic response [CCyR]. The CCyR rate at 3, 6 and 12 mo compares favorably to that observed in historical controls treated with imatinib 400mg or 800 mg daily:

<table>
<thead>
<tr>
<th>Mo on therapy</th>
<th>Percent with CCyR (No. evaluable)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dasatinib</td>
<td>Imatinib 400mg</td>
</tr>
<tr>
<td>3</td>
<td>78 (45)</td>
<td>37 (49)</td>
</tr>
<tr>
<td>6</td>
<td>93 (41)</td>
<td>54 (48)</td>
</tr>
</tbody>
</table>
MMR was achieved in 12/35 (34%) at 12 mo and 12/25 (48%) at 18 mo. One of 46 (2%) evaluable pts have achieved confirmed complete molecular response, and 1 other unconfirmed (ie, only achieved on their last assessment). Grade 3-4 non-hematologic toxicity (regardless of causality) included pruritus (13%), fatigue (6%), neuropathy (4%), and memory impairment (4%). Pleural effusion occurred in 21% evaluable pts (grade 3-4 in 2%). Grade 3-4 hematologic toxicity (transient) was thrombocytopenia in 11%, neutropenia in 21%, and anemia in 9%. Twenty-seven (54%) pts required transient treatment interruption. The actual median daily dose for all pts was 100mg. There is no significant difference in grade 3-4 toxicity by treatment schedule. Four pts came off study: 1 pts choice after 1 dose, 1 for toxicity (pleural effusion, QD schedule), and 2 lost response after multiple treatment interruptions (1 myelosuppression, 1 pleural effusion, both BID schedule). Two other pts have lost response because of non-compliance. 24 month EFS (event = loss of CHR, loss of MCyR, AP/BP, death, or off because of toxicity) is 81%. Conclusion: Rapid CCyR occurs in most patients with previously untreated CML-CP treated with dasatinib frontline therapy with a favorable toxicity profile. Accrual to this trial continues.

446 Efficacy of Nilotinib (formerly AMN107) in Patients (Pts) with Newly Diagnosed, Previously Untreated Philadelphia Chromosome (Ph)-Positive Chronic Myelogenous Leukemia in Early Chronic Phase (CML-CP)

Monday, December 8, 2008: 1:45 PM
2009-2011-2022-2024 - West (Moscone Center)

Jorge Cortes1, Susan O'Brien2, Dan Jones2, Alessandra Ferrajoli2, Marina Konopleva2, Gautam Borthakur2, Guillermo Garcia-Manero2, Laurie A. Letvak3 and Hagop Kantarjian2

1M.D. Anderson Cancer Center, Houston, TX
2The University of Texas M.D. Anderson Cancer Center, Houston, TX
3Novartis Oncology, East Hanover, NJ

Background: Nilotinib is an oral tyrosine kinase inhibitor with high selectivity towards Bcr-Abl and approximately 30-fold more potent than imatinib, and is effective in patients with CML after imatinib failure. We initiated a phase II study to evaluate the efficacy of nilotinib as 1st line therapy in pts with newly diagnosed CML-CP. Aims: To investigate the efficacy and safety of nilotinib as initial therapy for patients with CML-CP. Methods: The primary objective was to estimate the proportion of pts attaining major molecular response (MMR) at 12 months (mo). Pts with untreated CML-CP (or with <1 months of therapy with imatinib) were eligible and received nilotinib 400mg twice daily. A cohort of patients with previously untreated CML in accelerated phase (AP) was also included. Results: Forty-nine pts have been treated for a median of 13 months (mo). The median age was 47 years (yrs) (range, 21 to 81); 69% are Sokal low risk. Eight (16%) had received imatinib for <1 months. Overall, 46/48 (96%) of evaluable CP pts achieved a complete cytogenetic response [CCyR]. The rate of CCyR at 3, 6 and 12 mo for pts in CP compares favorably to those observed in historical controls treated with imatinib 400mg or 800 mg daily:

<table>
<thead>
<tr>
<th>Months on therapy</th>
<th>Percent with CCyR (No. evaluable)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nilotinib</td>
<td>Imatinib 400mg</td>
</tr>
<tr>
<td>3</td>
<td>93 (45)</td>
<td>37 (49)</td>
</tr>
<tr>
<td>6</td>
<td>100 (36)</td>
<td>54 (48)</td>
</tr>
</tbody>
</table>
MMR was observed in 45% at 6 mo and 52% at 12 mo. Two of 44 (5%) evaluable pts have achieved confirmed complete molecular response, and 3 others unconfirmed (ie, only achieved on their last assessment). Grade 3-4 hematologic toxicity (transient) included thrombocytopenia in 10%, neutropenia in 12%, and anemia in 2%. Grade 3-4 non-hematologic adverse events (regardless of causality) included elevation of bilirubin in 8% and lipase in 6%. 19 (36%) pts had transient treatment interruptions and 17 (32%) had dose reductions. The actual median dose is 800mg daily. Three pts have come off study: 1 pt’s choice and 2 because of toxicity (1 liver, 1 pericardial effusion). One of them (liver toxicity) transformed to blast phase shortly after coming off study. Estimated 24 month EFS (event = loss of CHR, loss of MCyR, AP/BP, death, or off because of toxicity) is 95%.

Conclusion: Nilotinib 400 mg twice daily induces a CCyR in nearly all patients as early as 3 months after the start of therapy with a favorable toxicity profile. Accrual is ongoing.

335 A Phase III, Randomized, Open-Label Study of 400 Mg Versus 800 Mg of Imatinib Mesylate (IM) in Patients (pts) with Newly Diagnosed, Previously Untreated Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Using Molecular Endpoints: 1-Year Results of TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) Study

Monday, December 8, 2008: 12:00 PM
2009-2011-2022 - West (Moscone Center)

Jorge Cortes, MD1, Michele Baccarani, MD2*, François Guilhot, MD3, Brian J. Druker, MD4, Susan Branford, PhD5, Dong-Wook Kim, MD, PhD6, Fabrizio Pane, MD7, Marc Rudoltz, MD8, Richard Yu9, LaTonya Collins, RN, BSN10*, Tillmann Krahne, PhD10*, Jerald P. Radich, MD11*, and Timothy P Hughes, MD12

1The University of Texas MD Anderson Cancer Center, Houston, TX
2Institute of Hematology and Medical OncologySeragnoli, Bologna, Italy
3Clinical Investigational Centre INSERM 802, CHU de Poitiers, Poitiers, France
4Oregon Health & Science University, Portland, OR
5Division of Molecular Pathology, Institute of Medical & Veterinary Science, Adelaide, Australia
6Division of Hematology, St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea
7CEINGE- Biotecnologie Avanzate, University of Naples Federico II, Naples, Italy
8Novartis Pharmaceutical, Inc., Florham Park, NJ
9Novartis, East Hanover, NJ
10B&sr, Novartis Pharmaceuticals
11Fred Hutchinson Cancer Research Ctr., Seattle, WA
12Haematology, Institute of Medical and Veterinary Science, Adelaide, Australia

Background: IM 400 mg/d is the standard of care for pts with newly diagnosed CML-CP. Previous reports suggest the rate of major molecular response (MMR), defined as BCR-ABL/control gene (BAC) ratio of ≤ 0.1% on the International Scale, predicts for a benefit in long-term outcomes. Phase 2 trials demonstrated that IM 800 mg/d as initial treatment of CML-CP decreases the time to MMR and increases the depth of molecular response (MR), and may therefore improve long-term outcomes.

Methods: TOPS is a prospective, open-label, randomized (2:1) Phase 3 trial that compared IM 800 mg/d to 400 mg/d in CML-CP. Pts were stratified by Sokal risk score. The primary endpoint is MMR rate at 12 months (mo) and secondary endpoints include: rates of complete hematological response, complete cytogenetic response (CCyR), time to CCyR and MMR, progression to accelerated phase (AP) or blast crisis (BC), event-free survival (EFS), overall survival (OS), IM dose-intensity, pharmacokinetics, and safety. Rates were compared by Fisher’s exact test and time to event outcomes by log-rank test. Results: 476 pts were enrolled (800 mg/d, n=319; 400 mg/d, n=157) at
Patient Education Material

103 sites in 19 countries between 6/05 and 12/06. Median age at diagnosis was 47 yrs, and 24% of pts had high Sokal risk score. Significantly more pts receiving IM 800 mg/d achieved MMR at 3 mo and 6 mo, but not at 12 mo when compared with 400 mg/d (Table 1). Time to MMR was faster in the 800 mg/d arm compared to 400 mg/d; \( P = .0038 \).

<table>
<thead>
<tr>
<th>Table 1: MMR rate (%) over time according to randomized dose of IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR rate (%)</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Month 3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Month 6</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Month 9</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Achievement of MMR according to average dose over the first 12 mo of treatment was greatest when the intended dose intensity (DI) was achieved (Table 2).

<table>
<thead>
<tr>
<th>Table 2: MMR at 12 mo according to DI (evaluable patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Dose</td>
</tr>
<tr>
<td>400 mg (n = 133)</td>
</tr>
<tr>
<td>800 mg (n = 269)</td>
</tr>
</tbody>
</table>

CCyR occurred faster in the 800 mg/d arm, indicated by a higher response rate at 6 mo (57% vs. 45%, \( P = .0146 \)). At 12 mo rates of MMR and CCyR (ITT population) were higher for the 800 mg/d arm but were no longer significantly different (MMR 46% vs. 40%, \( P = .2035 \); CCyR 70% vs. 66%, \( P = .3470 \)). In pts with high Sokal risk scores, rates of MMR at 12 mo were 41% and 26% (\( P = .1565 \)) for the 800 mg/d and 400 mg/d arms, respectively. Exploratory analysis of MR at 3 mo and its correlation with achievement of MMR at 12 mo follow. Of the pts in the 400 mg arm with BAC ratios >0.1- ≤ 1%, >1- ≤ 10% or > 10% at 3 mo, 83%, 46%, and 11% later achieved an MMR at 12 mo. In the 800 mg arm 73%, 45% and 21% of the pts with respective BAC ratios achieved an MMR at 12 mo. Based on the BAC ratio at 6 mo, the observed MMR rate at 12 months was 52%, 11%, and 0% in the 400 mg/d arm compared to 46%, 14%, and 18% in the 800 mg/d arm. In the first year of follow-up, 6 pts had documented progression to AP/BC during treatment: 3 (1.9%) in the 400 mg/d arm and 3 (0.9%) in the 800 mg/d arm. At 12 mo, 85% of pts in the 400 mg/d arm were receiving the randomized dose compared to 62% of pts in the 800 mg/d arm. Median DI was 400 mg/d in the 400 mg arm and 750 mg/d in the 800 mg arm. Dose interruptions > 5 days occurred more frequently in the 800 mg/d arm (67% vs 38%). Earlier achievement of MMR correlated with IM plasma trough level at 1 mo for the overall TOPS cohort; pts with IM concentrations < 1165 ng/mL (lowest quartile of the aggregate group) achieved MMR slower than those with concentrations ≥ 1165 ng/mL (\( P = .0149 \)). The most common grade 3/4 nonhematologic toxicities were rash, diarrhea and myalgia occurring slightly more frequently in the 800 mg/d arm. Grade 3/4 hematologic toxicity occurred more frequently in pts receiving 800 mg/d. Conclusions: TOPS confirms the efficacy and safety of IM in newly-diagnosed CML-CP. MMR occurred earlier in pts treated with 800 mg/d and in patients with plasma IM level above the lowest quartile, reinforcing the utility of IM blood level testing to optimize treatment. DI of IM 800 mg/d was maintained and tolerability was good. Additional follow-up is required to evaluate the effect of dose and MR on long-term clinical outcomes.

334 Reduction of BCR-ABL Transcript Levels at 6, 12, and 18 Months (mo) Correlates with Long-Term Outcomes on Imatinib (IM) at 72 Mo: An Analysis from the International Randomized Study of Interferon versus STI571 (IRIS) in Patients (pts) with Chronic Phase Chronic Myeloid Leukemia (CML-CP)

Monday, December 8, 2008: 11:45 AM
Background: An exploratory endpoint of the IRIS trial was measurement of BCR-ABL transcripts over time and its correlation with long-term outcomes. BCR-ABL measured by polymerase chain reaction (PCR) was required per protocol only after achievement of a complete cytogenetic response (CCyR). However, preplanned substudies occurred at sites in Germany and Australia who conducted PCR measurements on pts at intervals from the start of treatment independent of cytogenetic response (CyR). Additionally, other IRIS investigators contributed non-protocol specified molecular assessments. This first entire PCR dataset from IRIS assesses the prognostic value of molecular response (MR) at specific time points.

Methods: 553 pts were enrolled onto the IM arm of IRIS; of these, 476 pts with at least one PCR measurement form the basis for this analysis. A major molecular response (MMR) is defined as the ratio of BCR-ABL/control gene (BAC) of \( \frac{Q}{DO} DVHZHUHFRQGXFWHGDWDQGPRUHODWLQJ BAC \) percent reduction to event free survival (EFS), where events were defined as death during study treatment, loss of complete hematologic response, loss of Major CyR (MCyR), progression to accelerated phase (AP) or blast crisis (BC), or an increasing white blood cell count to > 20 x 10^9/L.

Results: Among pts receiving first line IM for CML-CP, MMR was observed in 13% of samples available for study at 3 mo, 33% at 6 mo, 50% at 12 mo, 65% at 18 mo, 75% at 48 mo, 85% at 60 mo, and 86% at 72 mo.

Table 1. Correlation of CCyR with molecular response at 3, 6, 12 and 18 mo.

<table>
<thead>
<tr>
<th>Time point</th>
<th>Pts with CCyR and PCR samples available (n)</th>
<th>CCyR and ( \leq 0.1% ) BAC [MMR], n (%)</th>
<th>CCyR and ( \leq 1% ) BAC, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td>51</td>
<td>17 (33%)</td>
<td>38 (75%)</td>
</tr>
<tr>
<td>6 mo</td>
<td>127</td>
<td>61 (48%)</td>
<td>114 (90%)</td>
</tr>
<tr>
<td>12 mo</td>
<td>177</td>
<td>110 (62%)</td>
<td>168 (95%)</td>
</tr>
<tr>
<td>18 mo</td>
<td>163</td>
<td>127 (78%)</td>
<td>154 (94%)</td>
</tr>
</tbody>
</table>

At 6 mo, half of the pts with BAC >10% who also had a cytogenetic assessment at the same time had at least a partial cytogenetic response (PCyR) with an EFS of 91% at 72 mo, and 64% of these pts achieved MMR later. The other half of the pts with >10% BAC who did not have a PCyR at 6 mo had an EFS of 43%, and 31% later achieved MMR. A separate landmark analysis by CyR status alone showed EFS rates at 72 mo of 92% for pts in CCyR, 86% for pts in PCyR, 60% for Minor/Minimal CyR and 49% for No CyR.

At 12 mo, pts with BAC \( \leq 1\% \) had excellent long term outcomes (72 month EFS of >90%, >95% without progression to AP/BC). Those pts with BAC > 1 - \( \leq 10\% \) (n = 36) had a 67% EFS, and 44% later achieved an MMR. These molecular analyses compare similarly to cytogenetic analyses alone
Patient Education Material

(Baccarani et al; ASH 2006), with 60 mo EFS of 93% for pts in CCyR, 78% for pts in PCyR and 61%
for pts without PCyR.

At 18 mo, pts with MMR could be statistically distinguished from pts with BAC >0.1 - ≤ 1%; EFS was
98% versus 89%, p=0.0137 (with 6 events in each group). The rate without AP/BC at 72 mo was not
significantly different (with only 2 events in the >0.1 – ≤ 1% group). Baccarani et al (ASH 2006)
reported an EFS at 60 mo of 96% for pts in CCyR, 80% for pts in PCyR and 69% for pts without PCyR.

Table 2: Long-term outcomes (estimated rates at 72 mo) by MR levels at 6, 12 and 18 mo.

<table>
<thead>
<tr>
<th>BCR-ABL categories</th>
<th>≤0.1% (MMR)</th>
<th>&gt;0.1 – ≤ 1%</th>
<th>&gt;1 - ≤ 10%</th>
<th>&gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo landmark</td>
<td>N=86</td>
<td>90%</td>
<td>94%</td>
<td>88%</td>
</tr>
<tr>
<td>EFS rate at 72 mo</td>
<td>N=89</td>
<td>100%</td>
<td>95%</td>
<td>55%</td>
</tr>
<tr>
<td>Without AP/BC at 72 mo</td>
<td>N=39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo landmark</td>
<td>N=153</td>
<td>94%</td>
<td>93%</td>
<td>67%</td>
</tr>
<tr>
<td>EFS rate at 72 mo</td>
<td>N=90</td>
<td>96%</td>
<td>83%</td>
<td>46%</td>
</tr>
<tr>
<td>Without AP/BC at 72 mo</td>
<td>N=26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 mo landmark</td>
<td>N=164</td>
<td>98%</td>
<td>89%</td>
<td>67%</td>
</tr>
<tr>
<td>EFS rate at 72 mo</td>
<td>N=48</td>
<td>96%</td>
<td>83%</td>
<td>47%</td>
</tr>
<tr>
<td>Without AP/BC at 72 mo</td>
<td>N=16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P=0.0137. None of the other comparisons between MMR and > 0.1 - ≤ 1% BAC were statistically
significant.

Conclusion: In pts on first-line IM, MMR rates increase over time, and in pts who achieved an MMR
at any time point progression is rare. Achievement of a CCyR correlated well with BAC of ≤1% from 6
mo onwards. Exploratory molecular analyses show pts with BAC >10% at 6 mo have EFS rates
distinguishable by their cytogenetic status. At 12 mo, pts with a BAC > 1% or without CCyR, fare more
poorly than those with BAC ≤ 1% or those in CCyR. At 18 mo pts with BAC ≤ 1% have excellent long
term outcomes, with the best outcomes seen in those with BAC ≤ 0.1%. Molecular and cytogenetic
evaluations are recommended until at least CCyR is achieved, with molecular assessments measured
indefinitely thereafter.

186 International Randomized Study of Interferon Versus STI571 (IRIS) 7-Year Follow-up: Sustained Survival, Low Rate of Transformation and Increased Rate of Major Molecular Response (MMR) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib (IM)

Monday, December 8, 2008: 8:15 AM
Halls B and C (Moscone Center)

Stephen G O’Brien, MD, PhD1, François Guilhot, MD2, John M Goldman, DM, FRCP3*, Andreas
Hochhaus, MD4, Timothy P Hughes, MD5, Jerald P. Radich, MD6, Marc Rudoltz, MD7, Jeiry Filian7, Insa Gathmann, M.Sc.8, Brian J. Druker, MD9 and Richard A. Larson, MD10

1Department of Haematology, University of Newcastle, Newcastle, United Kingdom
2Clinical Investigational Centre INSERM 802, CHU Poitiers, Poitiers, France
3Department of Hematology, Imperial College London, Hammersmith Hospital, London, United Kingdom
4Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim, Germany
5Haematology, Institute of Medical and Veterinary Science, Adelaide, Australia
6Fred Hutchinson Cancer Research Ctr., Seattle, WA
7Oncology, Novartis Pharmaceutical, Inc., Florham Park, NJ
8Novartis Pharma AG, Basel, Switzerland
9Oregon Health & Science University Cancer Institute, Portland, OR
10University of Chicago, Chicago, IL

Background: Based on results from the IRIS trial, IM is the standard of care for pts with newly
diagnosed CML-CP. This report presents the 7 yr data update of IRIS to assess long term outcome,
Methods: 553 pts were randomly assigned to IM and evaluated for hematologic, cytogenetic and molecular responses, discontinuations/cross-over reasons, event-free survival (EFS), progression to accelerated-phase (AP) or blast crisis (BC) and OS. Events for EFS were defined as the first occurrence of any of the following during treatment: death from any cause, progression to AP/BC, loss of a complete hematologic response or major cytogenetic response (MCyR), or an increasing white blood cell count to > 20 x 10^9/L. After discontinuation of study treatment, pts were followed only for OS.

Results: At 7 yrs, the estimated EFS was 81%, freedom from progression (FFP) to AP/BC was 93%, and the estimated OS was 86%. The best observed rates for MCyR and complete cytogenetic response (CCyR) were 89% and 82%, respectively. A total of 317 (57%) of all randomized pts remained on IM per protocol and were in CCyR. The estimated rates of progression to AP/BC from yrs 1 through 7 are 1.5, 2.8, 1.6, 0.9, 0.5, 0, and 0.4%, respectively, with one pt progressing to AP/BC between yrs 6 and 7. Yearly event rates are 3.3%, 7.5%, 4.8%, 1.7%, 0.8%, 0.3% and 2% (5 events occurred in the 7th yr: 3 unconfirmed loss of MCyR, 2 deaths). Of the 456 pts who achieved CCyR, 79 (17%) subsequently lost CCyR; 25 remained on IM (19 pts regained CCyR, of whom 6 responded to an increase in IM dose; 6 pts remained in MCyR without dose escalation). A total of 15 pts (3%) who achieved CCyR on IM progressed to AP/BC during study treatment, typically during the 1st year after achievement of CCyR; 3 CCyR pts progressed to AP/BC after the 2nd year. A total of 332 (60%) pts remain on IM on protocol at the 7-yr data cut-off. Reasons for discontinuation or crossover include: 5% adverse events/safety, 15% lack of efficacy/progression, 3% bone marrow transplant, 2% death, and 15% other (protocol violation, withdrawal of consent or lack of renewal of consent, lost to follow-up, administrative) reasons. Between yrs 6 and 7, 17 pts (3%) discontinued IM for the following reasons: adverse events (n=3), death (n=2; 1 CML-related), unsatisfactory therapeutic effect (n=7; 1 progression to AP/BC, 4 unconfirmed loss of MCyR, 2 unconfirmed loss of CCyR), protocol violation (n=1), and withdrawal of consent (n=4). Molecular response (MR) assessment was required per the IRIS protocol only in pts who had achieved CCyR. However, MR was measured routinely in 98 pts treated in Australia/New Zealand and Germany (sub-study) at baseline and every 3 mo through 72 mo, and other sites contributed assessments if available. Of the total IRIS IM cohort, 476 pts had at least one PCR measurement. MMR was defined as a ratio of BCR-ABL/control transcripts of ≤ 0.1% according to the International Scale.

Table 1: MR over time: BCR-ABL/control gene transcript levels (as % of available samples)

<table>
<thead>
<tr>
<th>Time-points (mo)</th>
<th>All available samples</th>
<th>Sub-study samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>&gt;10%</td>
<td>&gt; 1.0 - ≤10%</td>
</tr>
<tr>
<td>3</td>
<td>174</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>258</td>
<td>15%</td>
</tr>
<tr>
<td>12</td>
<td>305</td>
<td>9%</td>
</tr>
<tr>
<td>18</td>
<td>253</td>
<td>8%</td>
</tr>
<tr>
<td>48</td>
<td>238</td>
<td>6%</td>
</tr>
<tr>
<td>60</td>
<td>273</td>
<td>3%</td>
</tr>
<tr>
<td>72</td>
<td>210</td>
<td>2%</td>
</tr>
</tbody>
</table>

The MMR rates at 12 and 48 mo for all available samples are consistent with the reported rates of 53% and 80%, respectively, noted in a subset of pts with CCyR (Druker et al, NEJM, 2006) and similar to the unselected sub-study data. Additionally, MMR responses at 12 mo are similar to the recently reported TOPS trial (Cortes et al, EHA 2008). Between yr 6 and 7, serious adverse events suspected to be related to IM were reported in 9 pts, resulting in treatment discontinuation in 3 pts. No new safety issues were identified.

Conclusions: Responses with IM therapy remain durable with estimated 7 yr rates of FFP to AP/BC 93%, EFS 81%, and OS 86%. Only 1 patient progressed between yrs 6 and 7. The safety profile is unchanged and confirms a favorable risk-benefit ratio in CML-CP. Long-term follow-up of pts who continue to respond to IM demonstrate an MMR rate of 85-90% at 5-6 years. These results demonstrate increasing suppression of CML over time in patients who continue to receive imatinib.
3238 Nilotinib in Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) with Imatinib Resistance or Intolerance: 2-Year Follow-up Results of a Phase 2 Study

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-320

Hagop M Kantarjian¹, Francis Giles, MD², Kapil N. Bhatta, MD², Richard A. Larson, MD³, Norbert Gattermann, MD⁴, Oliver G. Ottmann, MD⁶, Ariful Haque, M.S.⁷, Neil J. Gallagher, MD, PhD⁵, Michele Baccarani, MD⁶ and Philipp D. le Coutre, MD⁷

¹The University of Texas M. D. Anderson Cancer Center, Houston, TX
²The Institute for Drug Development, CTRC, University of Texas Health Science Center, San Antonio, TX
³H. Lee Moffitt Cancer Center, University of South Florida, Tampa, FL
⁴University of Chicago, Chicago, IL
⁵Heinrich-Heine-University, Düsseldorf, Germany
⁶Department of Medicine, Hematology/Oncology, University Hospital of Frankfurt, Frankfurt, Germany
⁷Novartis Pharmaceuticals, Florham Park, NJ
⁸Oncology, Novartis Pharma AG, Basel, Switzerland
⁹Institute of Hematology and Medical OncologySeragnoli, Bologna, Italy
¹⁰Department of Hematology and Oncology, Charité - Humboldt-Universität, Campus Virchow, Berlin, Germany

Background: Nilotinib is a potent and highly selective BCR-ABL kinase inhibitor approved for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia patients in chronic (CML-CP) or accelerated phase (CML-AP) who are resistant or intolerant to prior therapy including imatinib. Methods: This open-label, single-arm, phase 2 study was designed to evaluate the efficacy and safety of nilotinib in CML-CP patients resistant or intolerant to imatinib. Imatinib intolerant patients with prior major cytogenetic response (MCyR) on imatinib were not eligible for this trial. Nilotinib was dosed at 400 mg twice daily with the option of dose escalation to 600 mg twice daily if responses were inadequate. Rate of MCyR was the primary endpoint. Secondary endpoints included complete cytogenetic response (CCyR), complete hematological response (CHR), duration of MCyR, survival, and safety. Results: A total of 321 CML-CP patients (71% imatinib-resistant; 29% imatinib-intolerant) were evaluated. Most patients were heavily pretreated with 72% having received more than 600 mg/day of imatinib prior to study entry. Furthermore, imatinib-intolerant patients could not have achieved prior MCyR on imatinib therapy. Median duration of prior imatinib treatment was 33 months (range 0.3–95 months). Dose reductions (25%) and discontinuations (15%) due to adverse events were infrequent on nilotinib therapy and median dose intensity (788 mg/day; range 151-1112 mg/day) closely approximated the planned dose. Median duration of exposure was 465 days (15.5 months). Overall, nilotinib therapy resulted in rapid and durable hematologic and cytogenetic responses. Of all imatinib-resistant and –intolerant patients, 58% achieved MCyR (1 month median time to MCyR), with 72% of patients having a baseline CHR achieving MCyR. The MCyR rate was 63% in imatinib-intolerant and 56% in imatinib-resistant patients, respectively. Overall, 42% of patients achieved a CCyR (50% in imatinib-intolerant and 39% in imatinib-resistant patients, respectively). Responses were durable, with 84% of patients maintaining their MCyR at 18 months. Estimated overall survival (OS) rates at 12 and 18 months were 95% and 91%, respectively. Nearly half of all patients (47%) were still receiving nilotinib at the time of cut-off for data analysis. Longer follow-up has not significantly changed the safety profile of nilotinib. The most frequently reported grade 3/4 biochemical laboratory abnormalities were elevated lipase (16%), hypophosphatemia (15%), hyperglycemia (12%), and elevated total bilirubin (7%). Overall, biochemical laboratory abnormalities were transient and clinically asymptomatic. Grade 3/4 non-hematologic adverse events were infrequent with rash, headache, and diarrhea occurring in only 2% of patients. No pleural or pericardial effusions were documented during nilotinib therapy. The most common grade 3/4 hematological laboratory abnormalities included neutropenia (30%), thrombocytopenia (28%), and anemia (10%). Overall, QTcF changes greater than 60 milliseconds from baseline were infrequent, occurring in only 8 patients (2.5%), and QTcF prolongation >500 milliseconds was uncommon (<1%), occurring in only 3 patients.

The CML Advocates Network – www.cmiadvocates.net
**Patient Education Material**

Brief dose interruptions were sufficient to manage most adverse events. **Conclusions:** Nilotinib is highly effective and produces rapid and durable responses in CML-CP patients who failed prior therapy including imatinib due to resistance or intolerance and is an important treatment option for this patient population. Nilotinib is well tolerated with minimal occurrence of grade 3/4 adverse events; safety profile has not changed with longer follow-up.

### 3234 Efficacy and Tolerability of Nilotinib in Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) Who Failed Prior Imatinib and Dasatinib Therapy: Updated Results of a Phase 2 Study

Monday, December 8, 2008  
Hall A (Moscone Center)  
Poster Board III  

**Francis Giles, MD**¹, Philipp D. le Coutre, MD², Kapil N. Bhalla, MD³, Gert J Ossenkoppele, MD, PhD⁴, Giuliana Alimena, MD⁵, Ariful Haque, M.S.⁶, Neil J. Gallagher, MD, PhD⁷ and Hagop M Kantarjian⁸

¹The Institute for Drug Development, CTRC, University of Texas Health Science Center, San Antonio, TX  
²Department of Hematology and Oncology, Charité - Humboldt-Universitat, Campus Virchow, Berlin, Germany  
³H. Lee Moffit Cancer Center, University of South Florida, Tampa, FL  
⁴Department of Hematology, VU University Medical Center, Amsterdam, Netherlands  
⁵Division of Hematology-Dept. of Cellular Biotechnologies and Hematology, University La Sapienza, Rome, Italy  
⁶Novartis Pharmaceuticals, Florham Park, NJ  
⁷Oncology, Novartis Pharma AG, Basel, Switzerland  
⁸The University of Texas M. D. Anderson Cancer Center, Houston, TX

**Background:** Treatment options are limited for patients with Philadelphia chromosome-positive (Ph+) CML who are resistant or intolerant to both imatinib and dasatinib. Nilotinib is a potent and highly selective BCR-ABL kinase inhibitor approved for the treatment of Ph+ CML patients in chronic (CML-CP) or accelerated phase (CML-AP) who are resistant or intolerant to prior therapy including imatinib. Here we report the updated results evaluating the safety and efficacy of nilotinib in patients with CML-CP who were either resistant or intolerant to both imatinib and dasatinib therapy. **Methods:** Nilotinib was dosed at 400 mg twice daily with an option to dose escalate to 600 mg twice daily in patients with inadequate hematologic and/or cytogenetic responses or disease progression. **Results:** A total of 37 patients (median age 62 years) with CML-CP were included in the analysis. The median time since first diagnosis of CML was 96 months. The median duration of prior imatinib therapy was 40.6 months with 84% being imatinib-resistant and 16% imatinib-intolerant. The median duration of prior dasatinib therapy was 6.6 months, with the majority of patients (65%) being intolerant to dasatinib therapy and 32% of patients were dasatinib resistant. Approximately half (51%) of the patients discontinued dasatinib due to grade 3/4 laboratory abnormalities or adverse events (AEs) and 32% discontinued due to disease progression. The median duration of nilotinib exposure was 218 days (7.3 months; range 43–723 days) and 65% of patients remained on nilotinib at the time of data cut-off. In total, only 4 (11%) patients discontinued nilotinib due to AEs and 9 (24%) discontinued due to disease progression. For CML-CP patients without complete hematologic response (CHR) at baseline, 81% achieved CHR with nilotinib treatment. The median time to first CHR for patients with confirmed HR was 1 month. Major cytogenetic response (MCyR) was achieved in 38% of patients with median time to first MCyR being 1 month and median duration of MCyR being 9.7 months. Complete cytogenetic response (CCyR) was achieved in 18% of patients. Estimated 1-year overall survival was 97%. The most frequent drug-related non-hematologic AEs on nilotinib were rash (22%), nausea (16%), and pruritus (14%). Newly occurring or worsening grade 3/4 hematologic laboratory abnormalities included neutropenia (38%), thrombocytopenia (24%), and anemia (5%). Other common grade 3/4 biochemical laboratory abnormalities included elevated lipase (24%), hyperglycemia (11%), elevated alanine aminotransferase (8%), and hypophosphatemia (8%). Brief dose interruptions were sufficient to manage most adverse events. **Conclusions:** Nilotinib is highly active in heavily pretreated CML-CP patients who failed both prior imatinib and dasatinib therapy. Importantly, most patients in this study were previously intolerant to dasatinib, and discontinuation of nilotinib in this study was uncommon. These results support nilotinib’s significant efficacy and favorable tolerability profile demonstrated in...
earlier trials with nilotinib as second-line therapy for the treatment of CML-CP. The frequency of adverse events among these heavily pretreated patients is low and similar to patients who failed imatinib only.

3233 Nilotinib in Elderly Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) with Imatinib Resistance or Intolerance: Efficacy and Safety Analysis

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-315

Jeffrey H. Lipton, MD, PhD¹, Philipp D. le Coutre, MD², Jim Wang, PhD³*, Mindy Yang, PharmD⁴, Tomasz Szczudlo, MD⁵ and Francis Giles, MD⁶

¹Med. Onc. & Hem., Princess Margaret Hospital, Toronto, ON, Canada
²Department of Hematology and Oncology, Charité - Humboldt-Universitat, Campus Virchow, Berlin, Germany
³Novartis Pharmaceuticals, East Hanover, NJ
⁴Building 105 Room 1E550B, Novartis Pharmaceuticals, Florham Park, NJ
⁵Novartis Pharmaceuticals, Florham Park, NJ
⁶The Institute for Drug Development, CTRC, University of Texas Health Science Center, San Antonio, TX

Background: Nilotinib is a potent and highly selective BCR-ABL kinase inhibitor approved for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) patients in chronic (CML-CP) or accelerated phase (CML-AP) who have failed prior therapy including imatinib. Methods: This subanalysis of the open-label, single-arm, phase 2 study evaluated the efficacy and safety of nilotinib in elderly (≥65 years) CML-CP patients who were resistant or intolerant to imatinib. Nilotinib was dosed at 400 mg twice daily. Results: A total of 321 CML-CP patients (71% imatinib-resistant; 29% imatinib-intolerant) were enrolled. Thirty percent (98/321) of patients were ≥80 years. The baseline characteristics among patients ≥65 and <65 years were similar. Discontinuation of nilotinib due to adverse events was uncommon, and did not differ among the two age groups (18% in both groups). Efficacy was maintained in elderly patients, with 48% of patients achieving MCyR and 38% achieving CCyR, compared with 63% and 44% of patients <65 years achieving MCyR and CCyR, respectively. Duration of cytogenetic response was also consistent among age groups with 84% and 85% of responding elderly patients maintaining MCyR and CCyR at 18 months, compared with 85% and 89% of patients <65 years maintaining MCyR and CCyR at 18 months, respectively. Estimated overall survival (OS) rates at 12 months were 97% and 91%, for patients <65 years and ≥65 years, respectively. Overall, the safety profile of nilotinib was similar among the two age groups. Biochemical laboratory abnormalities were transient, clinically asymptomatic, and consistent in both age groups; elevated lipase occurred in 14% and 23%, and elevated total bilirubin occurred in 9% and 3% of patients <65 years and ≥65 years, respectively. The most common grade 3/4 hematological laboratory abnormalities were also comparable; neutropenia was reported in 31% and 30%, thrombocytopenia in 26% and 36%, and anemia in 8% and 15%, of patients <65 years or ≥65 years, respectively. The incidence of grade 3/4 pleural/pericardial effusions were <1% and 1% and grade 3/4 bleeding events were <1% and 1% in patients <65 or ≥65 years, respectively. The incidence of myocardial infarction (<1% vs 4%), congestive heart failure (2% vs 1%), and QTcF prolongation >500 msec (<1% vs 2%) were also similar among patients <65 years or ≥65 years. Conclusions: Nilotinib is highly active and induced durable clinical responses in CML-CP patients regardless of age. Importantly, the safety profile of nilotinib is maintained in elderly patients and there was no increase in the incidence of cardiac events making it an excellent therapeutic option for patients with Ph+ CML, regardless of age.

183 Randomized Comparison of Imatinib Versus Imatinib Combination Therapies in Newly Diagnosed Chronic Myeloid Leukaemia (CML) Patients in Chronic Phase (CP): First Results of the Phase III (SPIRIT) Trial from the French CML Group (FI LMC)
Imatinib (IM) at 400 mg daily is the first line therapy for newly diagnosed CML patients (pts); however, less than 50% of major molecular responses (MMR) are obtained at 12 months. To improve these results, we designed a phase III, multicenter, open-label, prospective randomized trial. The reference arm was IM 400 mg daily (n=159). The 3 experimental arms were IM 600 mg daily (n=160), IM 400mg daily in combination with Ara-C, (20 mg/m²/day, days 15-28 of 28-day cycles) (n=158) and IM 400mg in combination with Peg-IFN alfa-2a (Peg-IFN2a, 90 µg weekly) (n=159). Treatment was delivered at least 12 months or until treatment failure (disease progression) or major toxicity. The primary endpoint is the overall survival. Other endpoints are: rate and duration of hematologic and cytogenetic responses, major (MCyR) and complete (CCyR), molecular response (major molecular response ie MMR) and the tolerability. Using treatment allocation ratio 1.1.1.1, randomization was stratified according to Sokal risk groups. The current interim analysis of the first 636 patients (Į at 1 year from randomization was planned in order to select the best experimental arm for further comparison with IM 400. The increased dose of IM or a combination regimen would be considered as promising if it increased the 4 log reduction response rate by at least 20 percentage points, e.g. from 15% to 35%, with an acceptable tolerability. Evaluation of molecular response up to 12 months was centralized, blinded and calculated according to International score (IS). Pts were recruited between 9/2003 and 10/2007,[median age 51 yrs (18-82), 62% of pts were male; Sokal distribution was low risk 33%, intermediate risk 41% and 27% high risk]. Median follow-up is 36 months (range 8-57) at the time of analysis. Overall, at 3 months 86% of pts achieved complete hematologic response. The MCyR, CCyR and MMR rates at 6 and 12 months are:

<table>
<thead>
<tr>
<th></th>
<th>IM-400</th>
<th>IM-600</th>
<th>IM-Ara-c</th>
<th>IM-PegIFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months (636 pts, ITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCyR</td>
<td>74%</td>
<td>79%</td>
<td>68%</td>
<td>74%</td>
</tr>
<tr>
<td>CCyR*</td>
<td>48%</td>
<td>67%</td>
<td>55%</td>
<td>56%</td>
</tr>
</tbody>
</table>
At 12 months (562 evaluable pts)

<table>
<thead>
<tr>
<th></th>
<th>MCyR</th>
<th>CCyR</th>
<th>MMR at 6 months**</th>
<th>MMR at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64%</td>
<td>77%</td>
<td>21%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>76%</td>
<td>66%</td>
<td>33%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>77%</td>
<td>66%</td>
<td>27%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>74%</td>
<td>71%</td>
<td>39%</td>
<td>61%</td>
</tr>
</tbody>
</table>

*p< 10^{-2} (overall); ** p<10^{-2} (overall)

Interestingly the rate of MMR at 6 months was significantly higher for IM-PegIFN as compared with IM-400 (p<10^{-3}). The 4-log reduction rate in the BCR-ABL/ABL transcript were 18%, 21%, 22%, 34%, for the IM-400, IM-600, IM-Ara-c and IM-PegIFN arms respectively. The corresponding numbers of undetectable (complete molecular response) pts were 2%, 2%, 3% and 9% at 12 months respectively. Grade 3/4 neutropenia and/or thrombocytopenia occurred in 8% of IM-400 pts, in 14% of IM-600 pts, in 41% of IM-Ara-c pts and in 40% of IM-PegIFN pts respectively. Grade 3/4 non hematological events were reported in 19% of IM-400 pts, in 30% of IM-600 pts, in 27% of IM Ara-c pts and in 31% of IM-PegIFN pts. Among them a relationship between treatment and event was suspected for 21 pts (13%) with IM-400 (7 liver toxicity; 7 oedema+muscle cramps), for 31 pts (19%) with IM-600 (7 liver toxicity, 11 oedema+ muscle cramps) for 36 pts (23%) with IM-Ara-c (2 liver toxicity; 10 gut side effect) and for 47 pts (29%) with IM-PegIFN (6 liver toxicity, 13 skin rash). Discontinuation of experimental treatment occurred within the first 6 and 12 months in 26% and 18% of IM-Ara-c pts and in 35% and 11% pts of IM-PegIFN pts respectively. Within the first 12 months 36% of 600-IM pts reduced their dosage. Although a substantial number of pts stopped PegIFN, this first analysis indicates the usefulness of a combination of IM-PegIFN for the initial treatment of pts with CML CP with a significant molecular response rate improvement. Complete analysis of the 636 pts with a follow-up of 12 months will be presented.
The introduction of imatinib has significantly changed prognosis of CML patients. Despite favourable hematologic and cytogenetic response (CyR) data, patients (pts) on first line imatinib therapy may relapse. Thus, studies have been conducted to improve initial therapy by dose escalation or combination with other drugs. CML Study IV was designed to compare imatinib in standard dose (400 mg/d) vs high dose (800 mg/d) vs combinations with low dose cytarabine or interferon alpha. We sought to evaluate the predictive impact of early molecular response for long term event free survival (EFS). 539 pts (59% m, median age 54 years, range 16-84) randomized to imatinib based therapies by December 2005 were investigated, the median follow up was 39 mo (range, 0-69). At baseline, multiplex PCR was applied to determine the dominating BCR-ABL transcript: b2a2 (n=204), b3a2 (n=247), b2a2 and b3a2 (n=80), e1a2 (n=2), e19a2 (n=4), b3a3 (n=1) and e8a2 (n=1). Quantitative PCR from 5,419 peripheral blood samples was performed using the LightCycler technology in two central labs. PCR data were aligned to the international scale (IS) by introduction of conversion factors (Hughes et al., BLOOD 2006). Cumulative molecular response of 539 pts at 3, 6, 12, 18, and 24 mo after randomization is summarized in the Table:

<table>
<thead>
<tr>
<th>Month</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL IS achieved by % of pts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10%</td>
<td>41</td>
<td>66</td>
<td>81</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>≤1%</td>
<td>16</td>
<td>41</td>
<td>65</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td>≤0.1% (MMR)</td>
<td>3</td>
<td>16</td>
<td>37</td>
<td>51</td>
<td>59</td>
</tr>
<tr>
<td>≤0.01%</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>21</td>
<td>28</td>
</tr>
</tbody>
</table>

For analysis of prognostic impact, events were defined as (i) loss of complete hematologic response, (ii) loss of major CyR following loss of complete CyR, (iii) accelerated phase, (iv) blast crisis, and (v) death for any reason. Pts were censored at the time of allogeneic stem cell transplantation or switch to 2nd generation tyrosine kinase inhibitors because of imatinib intolerance or resistance. The minimum molecular response levels predictive for EFS were BCR-ABL IS of 10% after 6 mo (p=0.0029), 1% after 12 mo (p<0.0001), and 0.1% (major molecular response, MMR; p=0.0016) after 18 mo of imatinib based therapies. In order to investigate the reasons for unsatisfying responses BCR-ABL kinase domain mutations were assessed in 175 pts. 30 pts (17%) harbored 35 mutations affecting 18 different amino acids. In conclusion, prospective molecular surveillance of CML shows that early response predicts stable remissions on first line imatinib therapy. After 6 mo of treatment, PCR data start to be predictive for EFS. In pts with unsatisfactory response or molecular, cytogenetic and hematologic relapse, BCR-ABL mutations have been detected in only 17% of pts. Calculation of molecular response rates dependent on the various imatinib based therapies will be performed after stop of randomization which is expected by the end of 2009.

### 3217 Clinical Significance of Dose Reductions of Second-Generation Tyrosine Kinase Inhibitors (TKI) in Patients (Pts) with Chronic Myeloid Leukemia (CML)

**Monday, December 8, 2008**  
Hall A (Moscone Center)  
Poster Board III-299  

**Fabio P.S. Santos, MD, Hagop Kantarjian, MD, Carmen Fava, MD, Susan O'Brien, MD, Guillermo Garcia-Manero, MD, Steven Kornblau, MD, Farhad Ravandi, MD, William Wierda, MD, PhD and Jorge Cortes, MD**  
Leukemia Department, University of Texas - M.D. Anderson Cancer Center, Houston, TX

**Background:** Second-generation TKI (dasatinib, nilotinib) are effective in patients with all phases of CML. However, dose reductions and treatment interruptions of those drugs are frequently required due to toxicity. The impact such dose reductions may have on outcome is not well known. **Aims:** To determine the impact of dose reduction of 2nd-generation TKI in response, overall survival and event...
free-survival. **Methods:** The records of 236 pts with CML who received therapy with the 2nd-generation TKI dasatinib and nilotinib were analyzed. We considered dose reductions only those below what is considered standard dose today (standard daily dose for dasatinib was defined as 140 mg for blast-phase/accelerated-phase and 100 mg for chronic phase; standard daily dose for nilotinib was 800 mg). Overall survival was defined from the time treatment was started to death from any cause or last follow-up. Event-free survival was defined as the time from start of treatment to the occurrence of an event or last follow-up. An event was defined as death, transformation to accelerated or blast phase, loss of major cytogenetic response, loss of complete cytogenetic response, increase in white blood cell count (>2x10^9/L), loss of complete hematological response, treatment discontinuation because of failure and treatment discontinuation because of toxicity. **Results:** A total of 236 patients were included, with median age 52 yrs (range, 18 to 81). They were divided into: blast-phase or Philadelphia-chromosome positive acute lymphoblastic leukemia (BP; N=34), accelerated phase (AP; N=34), late chronic phase after imatinib failure (LCP; N=70), and early chronic phase (ECP; N=98). Ninety-six pts (41%) received nilotinib and 140 (59%) received dasatinib. For the purposes of this analysis they were all considered together. Overall, 96 (46%) patients had one or more dose reductions. Dose reductions occurred in 10 pts with BP (30%), 20 with AP (59%), 32 with LCP (46%) and 34 with ECP (34%). The most common cause for dose reduction was myelosuppression (41%) The results for major cytogenetic responses, event-free survival and median overall survival according to whether pts had a dose reduction or not are presented in table 1

<table>
<thead>
<tr>
<th>ECP</th>
<th>No.</th>
<th>% MCyR</th>
<th>EFS % at 2 yr (median mo)</th>
<th>OS % at 2 yr (median mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>34</td>
<td>94</td>
<td>88% (NR)</td>
<td>100% (NR)</td>
</tr>
<tr>
<td>No DR</td>
<td>64</td>
<td>88</td>
<td>78% (NR)</td>
<td>100% (NR)</td>
</tr>
<tr>
<td>p value</td>
<td>0.25</td>
<td>0.35</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LCP</td>
<td>DR</td>
<td>32</td>
<td>59</td>
<td>57% (28)</td>
</tr>
<tr>
<td>No DR</td>
<td>38</td>
<td>55</td>
<td>48% (22)</td>
<td>80% (NR)</td>
</tr>
<tr>
<td>p value</td>
<td>0.91</td>
<td>0.58</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>AP</td>
<td>DR</td>
<td>20</td>
<td>50</td>
<td>23% (10)</td>
</tr>
<tr>
<td>No DR</td>
<td>14</td>
<td>21</td>
<td>21% (2)</td>
<td>47% (24)</td>
</tr>
<tr>
<td>p value</td>
<td>0.09</td>
<td>0.34</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>DR</td>
<td>10</td>
<td>60</td>
<td>30% (17)</td>
</tr>
<tr>
<td>No DR</td>
<td>24</td>
<td>29</td>
<td>0% (3)</td>
<td>18% (7)</td>
</tr>
<tr>
<td>p value</td>
<td>0.06</td>
<td>0.0005</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

ECP=Early chronic phase; LCP=Late chronic phase; AP=Accelerated phase; BP=BP (includes Ph+ ALL); DR=Dose reduced; No DR=Not dose reduced; MCyR=Major cytogenetic response; EFS=Event free survival; OS=Overall survival.

**Conclusion:** Dose reductions of 2nd-generation TKI in patients with CML do not have a negative impact in the response rate and survival of patients treated with these agents. Thus, pts who need dose reductions due to toxicity should be managed accordingly. Further studies are required to determine whether there might be a minimum adequate dose of these agents.
Dasatinib has been shown in non-clinical studies to cause fetal toxicities in animals, but the effect of exposure during conception and pregnancy in humans is not known. Despite the requirement for contraception while on therapy with dasatinib, occasional pregnancies have been reported. The current study and post-marketing data report the outcomes of pregnancies occurring among 16 patients (8 females and 8 males) who received dasatinib therapy. Among the 8 female patients found to be pregnant while on dasatinib therapy, induced abortion was reported in 3 cases: 2 due to patient decision and 1 for unknown reasons. Two cases of spontaneous abortion were reported. The first was at 8 weeks gestation in a 38-year-old patient (G1P1) with a history of tobacco use. Birth defects of the fetus were not reported; though it is unknown if an autopsy was performed. The other spontaneous abortion was reported at 9 weeks gestation in a 33-year-old patient (G3P3) taking dasatinib for over 2 years. The medical history of this patient includes tobacco and alcohol use. Of the 3 deliveries, one patient had a normal healthy infant. The second patient (age: 29 years, G2P2) delivered a healthy infant by Caesarean section at 7 months gestation (reason for Caesarean section unknown). This patient received dasatinib 140mg/day for approximately 4 months, but was ‘lost to follow up’ for 2 months and study drug compliance was unknown. Upon her return, the patient had a positive pregnancy test with an estimated gestation of 4 weeks. The infant was reported as ‘small for date’ but without obvious birth defects. Apgar scores were also unknown for this infant. In the final case, a patient on dasatinib 100mg/day for approximately 5 months was identified as pregnant (G0P0) at 21 weeks of gestation. The estimated delivery date has not yet occurred at the time of writing, but the pregnancy course has been normal. Among 8 male patients treated with dasatinib with partners becoming pregnant while on treatment, normal newborns were reported for 7 cases, with the outcome of the other case unknown. All male patients remained on treatment during and after the pregnancies. In 1 case, the mother experienced pre-eclampsia but delivered a healthy newborn at 37 weeks, without birth defects or neonatal complications. In summary, although the limited data reported in this study did not show evidence that dasatinib treatment has a negative impact on pregnancy (for the mother or fetus), patients receiving dasatinib should be advised to practice adequate contraception.

### Table 1. Outcome of Female Patients Electing to Carry Pregnancy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of Fetal Exposure to Dasatinib</th>
<th>Fetal Outcome</th>
<th>Maternal Outcome</th>
<th>Dasatinib Dose*</th>
<th>Duration of Dasatinib Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt D</td>
<td>5 weeks</td>
<td>8wk spontaneous abortion</td>
<td>no adverse reaction reported</td>
<td>180 mg/day</td>
<td>approximately 9.5 months</td>
</tr>
<tr>
<td>Pt E</td>
<td>9 weeks</td>
<td>9wk spontaneous abortion</td>
<td>no adverse reaction reported</td>
<td>100 mg BID</td>
<td>30 months</td>
</tr>
<tr>
<td>Pt F</td>
<td>7 weeks</td>
<td>normal healthy</td>
<td>no adverse reaction reported</td>
<td>140 mg / day</td>
<td>approximately 15 months</td>
</tr>
</tbody>
</table>
Pt G unknown “small for date” – healthy newborn C-section at 7 months 140mg / day approximately 4 months
Pt H 21 days to be determined 100mg / day 5 months
*at time of onset

3228 Patients with Chronic Myeloid Leukemia with Variant Philadelphia Chromosome (Ph) Translocations Have a Similar Outcome as Those with Classic Ph When Treated with Imatinib or 2nd Generation TKI

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-310

Nicolas Batty*, Hagop Kantarjian*, Gautam Borthakur*, Farhad Ravandi*, Susan O'Brien*, Zeev Estrov*, Jianqin Shan, Srdan Verstovsek* and Jorge Cortes*

Leukemia, MD Anderson Cancer Center, Houston, TX

Background: Variant Philadelphia chromosome (Ph) translocations frequently involving 1-2 additional chromosomes besides 9 and 22 and represent 5-10% of patients (pts) with chronic myeloid leukemia (CML). The European LeukemiaNet recommendations provide a warning for patients with variant translocations, although there is limited information about their outcome after therapy with tyrosine kinase inhibitors (TKI). Our prior analysis mostly among pts who had failed prior interferon suggested that these pts had similar outcome to those with classic Ph translocations when treated with imatinib (El-Zimaity et al; Br. J Haematol 2004). Aims: To explore the characteristics and outcome of patients with variant translocations treated with frontline imatinib or 2nd generation TKI (dasatinib or nilotinib) after imatinib failure. Methods: We reviewed the outcome of all pts with CML treated at our institution in 3 groups: 1) early chronic phase (CP) receiving imatinib as initial therapy, and 2) CP treated with 2nd generation TKI after Imatinib failure, 3) accelerated phase (AP) treated with 2nd TKI after imatinib failure. Results of pts with variant Ph were compared to those with classic Ph. Results: Among 554 pts (278 CP frontline imatinib, 190 CP post imatinib failure, 86 AP post Imatinib failure) 33 (6%) had variant Ph (21[8%], 6[3%], 6[7%], in each of the 3 groups, respectively). Median follow up is 55 months (mo) (2 – 90), 24 (1 – 53) mo and 29 (5 - 46) mo, respectively, for the 3 groups. Results are summarized in the following tables:

### Frontline Imatinib Therapy

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Variant Ph</th>
<th>Classic Ph</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=21</td>
<td>N=255</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCyR</td>
<td>95</td>
<td>95</td>
<td>1</td>
</tr>
<tr>
<td>CCyR</td>
<td>86</td>
<td>89</td>
<td>0.49</td>
</tr>
<tr>
<td>2-yr EFS</td>
<td>83</td>
<td>93</td>
<td>0.93</td>
</tr>
<tr>
<td>2-yr TFS</td>
<td>94</td>
<td>96</td>
<td>0.7</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>100</td>
<td>99</td>
<td>0.48</td>
</tr>
</tbody>
</table>

### Second generation TKI

<table>
<thead>
<tr>
<th>Variant Ph Chromosome</th>
<th>Percentage</th>
<th>Variant Ph</th>
<th>Classic Ph</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Phase</td>
<td>N = 6</td>
<td>N = 78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCyR</td>
<td>100</td>
<td>75</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>CCyR</td>
<td>100</td>
<td>72</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>2-yr EFS</td>
<td>100</td>
<td>80</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>2-yr OS</td>
<td>100</td>
<td>98</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Accelerated Phase</td>
<td>N=6</td>
<td>N=80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCyR</td>
<td>33</td>
<td>38</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CCyR</td>
<td>33</td>
<td>32</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion: Pts with variant Ph have a similar prognosis to those with classic Ph translocations when treated with imatinib as initial therapy or with 2nd generation TKI after imatinib failure. The warning category for these patients may no longer be needed in the era of TKI.

3224 Dasatinib 140 Mg Once Daily (QD) Demonstrates Equivalent Efficacy and Improved Safety Compared with 70 Mg Twice Daily (BID) in Patients with Accelerated Phase Chronic Myeloid Leukemia (CML-AP): 2-Year Follow-up Data from CA180-035

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-306

Hagop M. Kantarjian, MD1, Dong-Wook Kim, MD, PhD2*, Pedro Dorthiac-Llacer3*, Ricardo Pasquini4*, Nina Khoroshko5*, John F. DiPersio, MD, PhD6, Martin C Müller, MD7*, M. Brigid Bradley-Garelik8*, Chao Zhu8* and Martin S. Tallman, MD9

1M.D. Anderson Cancer Center, Houston, TX
2Division of Hematology, St. Mary's Hospital, Seoul, South Korea
3Hematology, Hospital das Clínicas da Universidade de São Paulo, São Paulo, Brazil
4Universidade Federal do Paraná, Curitiba, Brazil
5National Research Hematology Center, Moscow, Russia
6Department of Medicine, Siteman Cancer Center, Washington University School of Medicine, St Louis, MO
7Medizinische Fakultät Mannheim, University of Heidelberg, Mannheim, Germany
8Bristol-Myers Squibb, Wallingford, CT
9Division of Hem./Onc., Northwestern University, Chicago, IL

Dasatinib (SPRYCEL®) is the most potent BCR-ABL inhibitor and is 325-fold more potent than imatinib and 16-fold more potent than nilotinib in vitro against unmutated BCR-ABL. Previous studies have demonstrated the efficacy and safety of dasatinib 70 mg BID for patients with CML-AP who are intolerant or resistant to imatinib. In the phase III CA180-035 study, patients with CML-AP, blast phase CML, or Ph+ ALL were randomized to dasatinib 140 mg QD or 70 mg BID. The primary trial objective was to compare major hematologic response (MaHR) rates between the two schedules. Secondary objectives included a comparison of major cytogenetic response (MCyR) rates, time to and duration of responses, progression-free survival (PFS), overall survival (OS), and safety profiles between the two schedules. Previous analyses from this study have demonstrated that QD treatment is associated with equivalent efficacy and less frequent key adverse events (AEs) compared with BID treatment. Here, 2-year results from the subgroup with CML-AP (n=317) recruited from 97 international sites are reported.

Among patients randomized to QD (n=158) or BID (n=159) treatment with dasatinib, rates of MaHR and MCyR were similar (MaHR: 66% vs 68%; MCyR: 39% vs 43%, respectively; Table). Excluding patients that were BCR-ABL positive, Ph negative (n=3), rates of MCyR were nearly identical. Most MaHRs were achieved within 4 months of therapy and most MCyRs were achieved within 6 months. Based on Kaplan-Meier analyses, an estimated 65% vs 60% of patients had maintained a durable MaHR in QD and BID groups, respectively, at 24 months. Estimated PFS rates were 51% vs 55% and OS rates were 63% vs 72%, respectively. Although dasatinib was generally well tolerated with both dose schedules, QD treatment was associated with an improved safety profile compared with BID treatment. Only small increases in AE rates were observed compared with 1-year data. Cytopenias were the most common AEs and for QD vs BID treatment, rates of grade 3/4 events were 59% vs 69% for neutropenia and 64% vs 67% for thrombocytopenia. Fewer drug-related fluid retention events (including pleural effusion, superficial edema, and peripheral edema) were reported in the QD (34%) vs BID (48%) group. In particular, significantly fewer patients experienced a pleural effusion with QD vs BID treatment (p<0.001, all grades). No grade 4 pleural effusions occurred. Pleural effusions were manageable and led to treatment discontinuation in only 5% (QD) and 9% (BID) of patients. Grade 3/4 nonhematologic AEs were reported in less than 7% of all QD and BID patients and included dyspnea (3% vs 7%) and diarrhea (3% in both groups). Median durations of dasatinib therapy were 15 months.
Patient Education Material

(QD) and 12 months (BID), and median values of mean daily doses were 138 mg and 110 mg, respectively. Fewer dose reductions (38% vs 50%) and interruptions (64% vs 74%) occurred in the QD group. At the time of analysis, 34% of the QD group and 35% of the BID group remained on study, with a median duration of therapy of 23 months in both groups. Overall, extended follow-up from the CA180-035 study confirms earlier findings and demonstrates that in patients with CML-AP with imatinib resistance or intolerance, dasatinib 140 mg QD has equivalent efficacy to dasatinib 70 mg BID but with an improved safety profile. Similar durable responses were observed with both schedules.

Table

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QD (n=158)</td>
</tr>
<tr>
<td>MaHR</td>
<td>66</td>
</tr>
<tr>
<td>MCyR</td>
<td>39</td>
</tr>
<tr>
<td>MCyR (excluding BCR-ABL+ Ph–, n=3)</td>
<td>38</td>
</tr>
<tr>
<td>24-month PFS</td>
<td>51</td>
</tr>
<tr>
<td>24-month OS</td>
<td>63</td>
</tr>
<tr>
<td>Neutropenia, grade 3/4</td>
<td>59</td>
</tr>
<tr>
<td>Thrombocytopenia, grade 3/4</td>
<td>64</td>
</tr>
<tr>
<td>Pleural effusion (drug-related)</td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>20</td>
</tr>
<tr>
<td>Grade 3</td>
<td>7</td>
</tr>
<tr>
<td>Interruption</td>
<td>38</td>
</tr>
<tr>
<td>Reduction</td>
<td>64</td>
</tr>
</tbody>
</table>

187 Is It Possible to Stop Imatinib in Patients with Chronic Myeloid Leukemia? An Update from a French Pilot Study and First Results from the Multicentre « Stop Imatinib » (STIM) Study

Monday, December 8, 2008: 8:30 AM
Halls B and C (Moscone Center)

Francois-Xavier Mahon1*, Franoise Huguet, MD2*, Francois Guilhot, MD3, Laurence Legros, MD, PhD4, Franck E Nicolini, MD, PhD5, Aude Charbonnier6, Agnes Guerci, MD7, Delphine Rea, MD, PhD8, Bruno R. Varet, MD9, Martine Gardembas, MD10, Joelie Guilhot11*, Gabriel Etienne12*, Noel-Jean Milpied, MD, PhD13, Emilie Alton14*, Josy Reiffers11* and Philippe Rousselot15

1Hématopoïèse leucémique, Université Victor Segalen CHU de Bordeaux, Bordeaux, France
2Service d’Hématologie, Hôpital Purpan, Toulouse, France
3Cic-P 802 Inserm, CHU de Poitiers, Poitiers, France
4Service d’Hématologie, Hôpital de l’Archet, Nice, France
5Hematology Department, Hospital E. Herriot, Lyon, France
6Institut Paoli Calmette, Marseille, France

The CML Advocates Network – www.cmiadvocates.net
Imatinib (IM) has greatly improved survival rates in chronic myeloid leukemia (CML). However, all patients (pts) must continue treatment for an unknown period of time. A pilot study of the first pts who discontinued IM therapy was previously reported (Rousselot et al. Blood 2007;109:58–60). The new, multicentre «Stop Imatinib» (STIM) study was started in July 2007. The aim of this study is to evaluate in a larger cohort the persistence of complete molecular remission (CMR) after stopping IM, and to determine the factors that could influence the persistence of CMR. The criteria for inclusion were IM treatment for at least 3 years and sustained CMR. Sustained CMR was defined as BCR-ABL/ABL levels below a detection threshold corresponding to a 5-log reduction (undetectable signal using RQ-PCR) for at least 2 years. Molecular relapse, defined as RQ-PCR positivity, was taken into account if confirmed in two successive assessments. In cases of molecular relapse, pts were retreated with IM at 400 mg daily. In the pilot study, 7 out of 15 pts relapsed within 6 months, but CMR was re-attained in all cases after IM was re-started. The other 8 pts (4 male, 4 female) are still in CMR, with a median follow up of 37 months (range 26–49 months) after IM discontinuation. All pts were pretreated with interferon-alpha (IFN) and most responded to IFN before IM treatment.

The STIM study included 50 pts from 18 centres (20 male, 30 female), with a median age of 62 years (range 32–81 years). Of these, 25 pts had received no pre-treatment with IFN. By July 2008, 34 pts had a follow up ≥ 6 months. Eighteen pts relapsed within the first 6 months: 3 pts in month 2 (M2), 8 pts in M3, 4 pts in M4, and 3 pts in M5. One patient relapsed after more than 6 months (M8). Among the 19 pts who relapsed, 11 were not IFN pre-treated and 8 were IFN pre-treated (relapse rate 44% vs 32%). Ten IFN pre-treated pts with follow up ≥ 6 months have not relapsed (M12 in 2 pts, M10 in 5 pts, M8 in 1 pt, M7 in 2 pts), and 5 pts with follow up ≥ 6 months who were not IFN pre-treated have not relapsed (M12 in 1 pt, M10 in 1 pt, M8 in 1 pt, M6 in 2 pts).

These studies confirm that CMR can be sustained after discontinuation of IM, particularly in pts pre-treated with IFN with a long follow-up (pilot study). Among pts in the STIM study who were not pre-treated with IFN, more than half have not relapsed, and 20% have reached a follow-up ≥ 6 months and not relapsed. Updated data will be presented but we conclude that it is possible to stop treatment in pts with sustained CMR, even in those treated with IM as a single agent.

3239 Safety and Efficacy of Subcutaneous (SC) Omacetaxine Mepesuccinate in Imatinib(IM)-Resistant Chronic Myeloid Leukemia (CML) Patients (pts) with the T315I Mutation – Results of An Ongoing Multicenter Phase II Study

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-321

Jorge Cortes, MD1, H. Jean Khoury, MD2, Sélim Corm, MD3, Françck E Nicolini, MD, PhD4, Jeffrey H. Lipton, MD, PhD5, Dan Jones, MD, PhD5, Andreas Hochhaus, MD7, Adam R Craig, MD, PhD8, Annie-Claude Benichou, MD7, Eric Humphris8, and Hagop Kantarjian9

1M.D. Anderson Cancer Center, Houston, TX
2Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA
3Hematology department, Hôpital Huriez, Lille, France
4Hematology Department, Hospital E. Herriot, Lyon, France
5Med. Onc. & Hem., Princess Margaret Hospital, Toronto, ON, Canada
6UT M.D. Anderson Cancer Ctr., Houston, TX
7Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim, Germany
Background: Omacetaxine (homoharringtonine, HHT) shows clinical activity against Ph+ CML, with a mechanism of action independent of tyrosine kinase inhibition. Currently available tyrosine kinase inhibitors (TKIs) have not demonstrated activity in CML pts harboring the T315I BCR-ABL mutation.

Study Goals: To evaluate the safety and efficacy of omacetaxine in pts with IM-resistant T315I+ Ph+ CML.

Methods: Eligible pts include adult CML with confirmed T315I BCR-ABL mutation following imatinib failure after informed consent. Presence of T315I mutation is confirmed at one of 2 central reference labs. Induction schedule consists of 1.25 mg/m² omacetaxine SC twice daily for 14 days every 28 days until complete hematologic response (CHR) or hematologic improvement (HI). Maintenance schedule may start after at least one induction cycle and after initial hematologic response. Maintenance treatment consists of 1.25 mg/m² OMA SC twice daily for 7 days every 28 days, for up to 24 months. Study Results: To date, 50 pts have been enrolled, all having failed prior imatinib therapy, and 82% having failed 2 or more prior TKIs. Enrollment includes 26 pts in chronic phase (CP), 13 in accelerated phase (AP) and 11 in myeloid blast phase (BP). Median age: 58 yrs (19-84), 70% male. Mean baseline WBC values (/µl) were 11.51 (range 1.9-23.76) in CP, 18.88 (range 3.6-78.2) in AP and 16.58 (range 2.4-51.5) in BP patients. Median disease duration is 58 months (range 5-285). Efficacy: Data are available for 30 pts: 15 CP, 10 AP and 6 BP pts. In CP pts, CHR has been achieved in 80% (12/15) with a median duration of response of 8 months (range 2.7 to 13.5+). Of these 12 pts achieving CHR, 11 pts continue on study with the remaining patient achieving complete cytogenetic response (CCyR) and being removed from treatment to receive allograft transplantation. The median time to hematologic response was 1.2 months (range 0.6 to 2.5). Overall cytogenetic response in CP pts is 20% (3/15) with 13% (2/15) achieving CCyR and 1 pt achieving a minimal cytogenetic response. Median duration of cytogenetic response is 9.1 months (range 7.1 to 9.2+) with one pt continuing in CCyR and the second patient receiving allograft as described above. In AP pts, overall hematologic response is 60% (6/10) with 5 of these patients remaining active in treatment. Two pts have achieved CHR, 3 returned to chronic phase and 1 showed HI. Median duration of response was 2.2 months (range 1 to 4.4+). Overall cytogenetic response rate in AP patients is 21% (3/14), with 2 pts achieving major cytogenetic response and 1 pt achieving minimal response. In BP patients, overall hematologic response rate is 33% (2/6) with 1 pt achieving CHR and 1 HI. Duration of response was 3.7 and 3.9 months respectively. The T315I mutated clone has been decreased below the limit of detection in 60% of evaluable patients. Safety: Data are available for 32 pts enrolled in all disease phases. The primary toxicity being myelosuppression which is reversible and managed by adjusting the number of dosing days received per cycle. Incidence of treatment emergent grade 3/4 events includes: thrombocytopenia 44%, neutropenia 34%, anemia 28%, febrile neutropenia 16%, and pancytopenia 9.4%. Injection site reactions have been mild with no grade 3-4 events reported. Four pts have died (3 BP, 1 AP) during the study period, all due to disease progression. Conclusions: Omacetaxine therapy in T315I mutated BCR-ABL+ IM-resistant CML is well tolerated and is producing durable CHRs and cytogenetic responses in these patients.
BACKGROUND. Imatinib therapy for chronic myeloid leukemia (CML) is a long-term treatment potentially compromised by patient nonadherence. OBJECTIVE. To examine whether patients (pts) at different levels of treatment response differ in adherence to imatinib treatment. DESIGN & PATIENTS. The ADAGIO study is a prospective, 90-day (90d) observational, open-label, multicenter study of pts with chronic myeloid leukemia (CML) and treated with imatinib. 169 evaluable pts who had been on imatinib for a minimum 30 days at enrollment were studied. A sub-analysis included pts with optimal vs. suboptimal response (all patients) and complete vs. incomplete cytogenetic response (CgR; all patients and those treated with imatinib ≥12 months). MEASUREMENTS. Adherence: imatinib pill count over 90d expressed as % of prescribed imatinib taken. Suboptimal response (SR): incomplete hematologic response at 3 months, and/or less than partial CgR at 6 months, and/or less than major molecular response and, in case of loss of major molecular response, other limitations or chromosomal abnormalities at 18 months (all else: optimal response [OR]). CgR: complete (0% Ph+ metaphases) or incomplete (≥1 Ph+ metaphases). RESULTS. Pill count percentages ranged from 29%-202% of prescribed dose (M=90.9±20.1). Pts with SR (n=14) had significantly higher %s of imatinib not taken (23.2±23.8) than did those with OR (n=124; 7.3±19.3, P=0.005). Among pts treated with imatinib ≥12 months, those with complete CgR (n=98) had significantly lower mean percentages of imatinib not taken (23.2±23.8) than those with incomplete CgR (n=9; 26.0±24.4, P=0.012). Among all pts regardless of length of treatment, those with complete CgR (n=109) also had significantly lower mean percentages of drug not taken (9.1±18.1) than those with incomplete CgR (n=19; 23.9±19.2, P=0.004). CONCLUSIONS. Proportions of CML patients with poor treatment response are low (10.1%, 8.4%, and 14.8% resp. for parameters above), underscoring the high efficacy of imatinib in CML. Pts with poor response tended to have higher % of imatinib not taken over 90d, an index of overall adherence behavior. Clinicians should be aware of the association between adherence and imatinib response and should query patients about their adherence behavior. Nonadherence should be ruled out prior to classifying a patient as imatinib-resistant. Enhanced adherence is likely to optimize the effectiveness of imatinib treatment in CML.

Patient Education Material

575 Clonal Hematopoiesis in Philadelphia Chromosome-Negative Bone Marrow Cells of Chronic Myeloid Leukemia Patients Receiving Tyrosine Kinase Inhibitors

Monday, December 8, 2008: 5:00 PM
2001-2003-2014-2016 - West (Moscone Center)

Ron Paquette, MD¹, John Nicoll¹, Meenal Chalukya¹, Lukasz P Gondek, MD, PhD², Monika Jasek³, Charles Sawyers, MD⁴, Neil Shah, MD, PhD⁵ and Jaroslaw Maciejewski⁶

¹University of California, Los Angeles, Los Angeles, CA
²Hematologic Oncology and Blood Disorders/Experimental Hematology and Hematopoiesis Section, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH
³Experimental Hematology and Hematopoiesis Section, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH
⁴Human Oncology and Pathogenesis Program, MSKCC, Howard Hughes Medical Institute, New York
⁵University of California, San Francisco, San Francisco, CA

Patients with chronic myeloid leukemia (CML) are experiencing prolonged survival due to successful therapy with tyrosine kinase inhibitors. However, some CML patients who have achieved longstanding remissions with these agents harbor clonal cytogenetic abnormalities in their Philadelphia chromosome negative (Ph-) bone marrow cells. Because CML patients in remission often have peripheral blood count abnormalities, including cytopenias, we investigated whether these patients may have developed myelodysplastic syndrome (MDS) within the Ph- cell population. Bone marrow samples from 26 CML patients who had achieved a major cytogenetic remission (MCyR) with tyrosine kinase inhibitor therapy between 2 and 15 years after diagnosis were evaluated; 6 patients had advanced disease prior to their last therapy, 20 were in chronic phase. At the time of evaluation, 2 of the patients were receiving imatinib, 23 dasatinib, and 1 PHA739358. At least one peripheral blood lineage was abnormal in 21 patients, of whom 7 had pancytopenia. Routine metaphase cytogenetics (MC) revealed a persistent clonal chromosomal abnormality in ≥10% of the Ph- metaphases in 5 patients (+8 in 2, -7 in 2, and 20q- in 1). We hypothesized that clonal hematopoiesis might exist in additional patients and applied single nucleotide array (SNP-A) based karyotyping and X-linked human androgen receptor (HUMARA) clonality assay to further delineate the nature of the hematopoietic defect in these patients. HUMARA was performed on bone marrow samples and germ-line DNA from peripheral blood T lymphocytes of the female patients. Clonality, as assessed by skewing of X-
Patient Education Material

chromosome inactivation in bone marrow cells compared to germline control cells, could not be demonstrated in the 12 female patients. SNP-A karyotyping using 250K Affymetrix SNP array confirmed the known cytogenetic abnormalities. Several microdeletions were found, but comparison with purified T lymphocytes demonstrated that these “lesions” represented germ line-encoded copy number variants. However, SNP-A karyotyping revealed the presence of uniparental disomy (UPD) involving chromosome 17(p12-pter) in bone marrow, but not germ line cells, from one male patient with normal karyotype by routine MC. In the context of secondary AML, del17p or UPD17 have been observed always in the presence of del7q and 5q and were associated with poor prognosis. However, in our patient UPD17 occurred as a sole defect. Because in our studies in AML, UPD of chromosome 17p was found in association with p53 mutations, genomic sequencing of this gene was performed. A 5 bp deletion destroying the splice acceptor region of exon 6 was identified in bone marrow cells from this patient. Alternative splicing leading to loss of exon 6 was predicted to result in a frame shift and premature introduction of a stop codon. These methods revealed clonal hematopoiesis in the Ph- bone marrow cells of 6/26 patients with longstanding CML in remission from tyrosine kinase inhibitors and persistent peripheral blood abnormalities. The approaches used here probably underestimate the frequency of this condition, as oligoclonal populations may be present in numbers below the limit of assay sensitivity. The Ph- clonal bone marrow populations have cytogenetic and molecular features in common with MDS. After a median follow up of two years, one patient with monosomy 7 developed acute myeloid leukemia, but longer follow up will be required to determine the natural history of the Ph- clonal disorders.

2120 Stem Cell Transplant (SCT) for Patients (pts) with Chronic Myeloid Leukemia (CML) Resistant to Tyrosine Kinase Inhibitors (TKI) with BCR-ABL Kinase Domain (KD) Mutation T315I

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-214

Nikolai Velev1, Jorge Cortes1, Richard Champlin2, Hagop M. Kantarjian1, Gabriela Rondon2, Sergio Giralt2, Gautam Borthakur1 and Marcos De Lima2

1Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
2Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Resistance to TKI therapy is associated with development of KD mutations in approximately 50-60% of pts. Although many imatinib-resistant mutations respond well to second generation TKI, T315I is insensitive to all currently available TKI (imatinib, dasatinib, nilotinib) in vitro and in the clinic. SCT is frequently recommended for these pts but there is no available data about the efficacy of SCT in such pts. Aims: To investigate the efficacy and safety of SCT for patients with TKI-resistant CML with a T315I mutation. Methods: We reviewed the outcome of all pts with T315I that have received a SCT at MD Anderson Cancer Center. Results: Seven pts received 8 transplants. Their median age was 44 years (yrs) (range, 26 to 64 yrs). The median time from diagnosis to SCT was 42 months (mo) (range, 9-160 mo). All pts had become resistant to with imatinib; 5 received dasatinib and 1 nilotinib after imatinib failure, and 6 pts received other additional therapy prior to SCT. At the time of SCT 2 pts were in chronic phase (CP), both in partial cytogenetic response; 2 in accelerated (AP) with active disease; and 3 in second or greater CP from lymphoid blast phase (BP). Six transplants were from matched unrelated donors and 2 from cord blood. Best response after SCT was CCyR in 3 (2 AP, 1 BP), CMR in 4 (2 CP, 2 BP), and 1 unknown (died early). After a median follow-up of 11 months from SCT, 4 pts are alive; the 2 transplanted in CP are alive after 11 and 42 months after SCT and in CMR; 1 pt transplanted in AP has a sustained CCyR 20 mo after SCT with persistent T315I representing 94% of transcripts by pyrosequencing; and 1 in BP has a CMR sustained 6 mo after a second SCT (relapsed 5 months after first SCT) 3 pts have died: 1 AP and 2 BP, all with relapse. Conclusion: SCT appears to be an effective strategy for pts with CML with T315I, although longer follow up is needed. Results are significantly better when pts are transplanted.
in CP. Thus, SCT should be considered in pts with resistance to TKI once T315I is identified, ideally in CP.

447 Imatinib (IM) Pharmacokinetic (PK) Exposure and Its Correlation with Clinical Outcome in Patients with Chronic-Phase Chronic Myeloid Leukemia (CML-CP) for 400 Mg and 800 Mg Daily Doses (Tyrosine Kinase Dose Optimization Study [TOPS])

Monday, December 8, 2008: 2:00 PM
2009-2011-2022-2024 - West (Moscone Center)

François Guilhot, MD1, Timothy P Hughes, MD2*, Jorge Cortes, MD3, Yanfeng Wang, PhD4*, Michael Hayes, PhD4*, Anthony Gichangi, PhD5*, Brian J. Druker, MD6 and Michele Baccarani, MD7*

1Clinical Investigational Centre INSERM 802, CHU de Poitiers, Poitiers, France
2Haematology, Institute of Medical and Veterinary Science, Adelaide, Australia
3M.D. Anderson Cancer Center, Houston, TX
4Novartis Pharmaceuticals, East Hanover, NJ
5Novartis Pharmaceuticals, Basel, Switzerland
6Oregon Health & Science University Cancer Institute, Portland, OR
7Dept. Hematology and Medical Oncology, University of Bologna, Bologna, Italy

Background: Correlation between IM plasma level and clinical response has been previously reported [Larson et al., Picard et al.]. TOPS is an open-label, randomized, multicenter Phase III study investigating whether 800 mg of IM (400 mg twice daily) results in an improved efficacy compared with 400 mg daily IM in newly diagnosed, previously untreated CML-CP. This analysis reports IM trough plasma levels (Cmin) at both doses and their correlation with clinical response and safety parameters.

Methods: IM PK trough samples were collected at time 0 (predose), and following 1, 6, 9, and 12 month treatment for both 400 mg/day (mg/d) and 800 mg/d arms. Plasma concentrations of IM and CGP74588 (major metabolite) were determined by a validated LC/MS/MS (liquid chromatography and tandem mass spectrometry) method. Correlation of IM exposure with clinical response (major molecular response [MMR] rates and time to first MMR) was assessed by grouping patients into quartiles based on their measured IM Cmin levels in month 1. For correlation with frequency of adverse events [AEs], an average Cmin (aCmin) over 12 months corrected for dose intensity was used for the analysis. Correlations were assessed for the entire evaluable population and for each dose group separately.

Results: IM PK exposure was proportional to dose and stable over time. For the 400 mg/d dose (n=78-87), the median IM Cmin values at month 1, 6, 9, and 12 were 1190, 1060, 1210, and 1295 ng/mL, respectively; and for the 800 mg/d dose (n=148-167) the corresponding Cmin values for each month were 2720, 2340, 2170, and 2150 ng/mL, respectively. The intra-patient variability (CV%) was low and similar between the 400 mg/d and 800 mg/d doses, 25% and 27%, respectively. The inter-patient variability (CV%) was 38% for 400 mg/d and 58% for 800 mg/d. Despite this inter-patient variability there was a strong correlation between IM Cmin at month 1 (Table 1) and time to MMR or MMR at 3, 6, 9 and 12 months.

Table 1: MMR rates over 12 months based on month 1 IM Cmin quartiles for evaluable patients with PK data

<table>
<thead>
<tr>
<th>Month of treatment (No. of evaluable patients)</th>
<th>MMR Rate (%)</th>
<th>Relative benefit (Fishers Exact Test p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mmin &lt;1165 ng/mL</td>
<td>Q4 vs Q1</td>
<td>Q2-Q3 vs Q1</td>
</tr>
<tr>
<td>IM Cmin Q1</td>
<td>15/108 (14%)</td>
<td>10/56 (18%)</td>
</tr>
<tr>
<td>IM Cmin Q2-3</td>
<td>29/52 (56%)</td>
<td>22/54 (41%)</td>
</tr>
<tr>
<td>IM Cmin Q4</td>
<td>30/51 (59%)</td>
<td>62/107 (58%)</td>
</tr>
</tbody>
</table>

*No. of patients achieving MMR/total number of patients evaluable at each visit

Based on the evaluable population at month 12, patients with higher Cmin, at month 1 (>1165 ng/mL, Q2-Q4) achieved MMR faster than patients with lower Cmin (<1165 ng/mL, Q1) (P=0.0149). The MMR
rate at 12 months was 58% for Q2-Q4 group and 38% for Q1 group (P=0.0263). In the 400 mg/d
group, the MMR rate at month 12 was 24% for patients with C\textsubscript{min} below 851 ng/mL (Q1 for 400 mg/d),
compared to 56% for patients with C\textsubscript{min} above 851 ng/mL (Q2-Q4; P=0.0207). In the 800 mg/d arm,
the overall MMR at 12 month was 50%, and no significant differences were observed between
different C\textsubscript{min} quartiles, although it should be noted that the majority of patients (88%) at this high dose
level achieved a C\textsubscript{min} above 1165 ng/mL as compared with 52% for the 400 mg/d group. Using aC\textsubscript{min}
over 12 months as a rough estimate of exposure including dose changes, a slightly higher incidence of
all grade AEs for the most frequently reported AEs such as rash, diarrhea, fatigue, and all cause
edema, was observed in patients in the highest quartile but no significant differences in the frequency
of grade 3/4 AEs were observed.

**Conclusion:** In TOPS, IM plasma trough level was proportional to dose and stable over time despite a
high inter-patient variability which may have been attributable to dose changes. Patients with a IM C\textsubscript{min}
in the lowest quartile showed a lower MMR rate at 12 months, whereas patients in the highest aC\textsubscript{min}
quartile showed a higher frequency of all grades of some AEs. The TOPS trial confirms previous
observations that IM C\textsubscript{min} of approximately <1000 ng/mL are associated with poorer outcomes.
Monitoring IM levels can provide an added benefit to CML patients on IM to achieve the best clinical
outcomes.

---

**3200 Differential Effects of the BCR-ABL-Inhibitors Imatinib, Nilotinib and Dasatinib on NK Cell Reactivity against Chronic Myeloid Leukemia (CML)**

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-282

**Matthias Krusch, MD\textsuperscript{*}, Julia Salih\textsuperscript{*}, Lothar Kanz, MD and Helmut R Salih, MD**

Hematology and Oncology, Eberhard Karls University, Tuebingen, Germany

CML is characterized by the BCR-ABL fusion protein, which mediates the oncogenic signaling. This
led to the development of BCR-ABL inhibitors revolutionizing therapy of CML. However, as recently
reported for Dasatinib (Schade et al., Blood 111:1366 (2008); Blake et al., Blood 111:4415 (2008)),
these agents may impair the activity of immune effector cells like NK cells and T cells. After initiating
oncogenic events, development and progression of clinically apparent malignancy is dependent on the
evasion of the tumor cells from immunosurveillance. In light of the important role of NK cell reactivity
against leukemia we compared the influence of Imatinib, Nilotinib and Dasatinib on the reactivity of
both resting and IL-2 activated NK cells against CML cells to identify the compound with the least
immuno-compromising side effects. First, the effects of the compounds on NK cell reactivity in
concentrations corresponding to plasma peak levels were studied. Dasatinib (200nM) completely
abolished NK cell granule mobilization, cytotoxicity and IFN-\gamma production, while no substantial inhibition
was observed with Imatinib (5\textmu M) and Nilotinib (3.6\textmu M) mediated a minor but significant inhibition
(p<0.05, Student's T-test). Presence of the compounds in concentrations corresponding to IC\textsubscript{50}
levels (Imatinib 600nM, Nilotinib 30nM, Dasatinib 10nM) revealed no influence of Imatinib and Nilotinib, while
Dasatinib still significantly reduced NK cell cytotoxicity and IFN-\gamma production up to 60%. Since
Dasatinib, in addition to BCR-ABL, potently inhibits SRC kinases, which are involved in the activation
of MAPK pathways and thus crucial for NK cell cytotoxicity, we determined the influence of the
compounds on ERK phosphorylation. While no inhibitory effect was observed using Imatinib and
Nilotinib, Dasatinib markedly reduced ERK phosphorylation in NK cells. Our data demonstrate that NK
cell anti-tumor reactivity is not inhibited by clinically relevant concentrations of Imatinib. While Nilotinib
may mediate a minor effect, Dasatinib substantially impairs NK cell reactivity by inhibition of signaling
pathways crucial for NK cell effector functions. For a given patient, the choice and dosing of the most
suitable BCR-ABL inhibitor may thus require careful consideration of its influence on the immune
system, especially in view of the important role of NK cells in the immunesurveillance of residual
leukemia.
The BCR-ABL T315I mutation is one of the major mechanisms of resistance to tyrosine kinase inhibitors (TKIs). Limited data have suggested that patients harboring a T315I mutation have poor outcomes. The objectives of this study were to estimate overall (OS) and progression-free survival (PFS) for CML in chronic (CP), accelerated (AP), or blastic (BP) phase, and Ph+ ALL patients who developed a T315I mutation; and describe the treatment pattern after T315I detection. 

Methods: This was a retrospective, multi-center observational study. Eligible patients included CML and Ph+ ALL patients who developed T315I mutation between 1999 and 2008. The medical records of 222 patients from 9 countries (France, Italy, Korea, USA, Germany, Singapore, Denmark, UK and Japan) were abstracted, and Kaplan-Meier plots and Cox proportional hazard models were used for survival analysis.

Results: Median age at T315I detection was 54 (range, 18-84) years; 57% were male; 75% were Caucasian and 22% were Asian. Before T315I detection, 97% patients received imatinib (25% as a 1st line) and 50% received second generation TKIs. 16% of patients had other mutations detected before T315I detection. The median time between TKI treatment start and T315I detection was 29 months for CP, 15 for AP, 6 for BP, and 9 for Ph+ ALL. After T315I detection, 56% patients received second generation TKIs (30% started after T315I detection), 39% received hydroxyurea (33% started after T315I detection), 35% received imatinib (13% started after T315I detection), 26% received cytarabine, 21% received investigational drugs including 11% MK-0457, 17% underwent stem cell transplantation, and 6% received interferon alpha (5% started after T315I detection). At the time of T315I detection, T315I formed the predominant clone in 87% of patients; 23% had additional mutations detected (11% of these P-loop mutations). OS and PFS from T315I mutation detection are summarized in Table 1. In a preliminary analysis, the following covariates were associated with worse OS in Cox proportional hazard model (adjusted hazard ratio, 95% confidence interval): older age (by median, 2.30, 1.04-5.09) in Ph+ ALL patients, female gender in BP (1.73, 0.96-3.10); worse performance status in Ph+ ALL (1+ vs. 0; 2.18, 1.02-4.68); and detection of T315I by direct sequencing (vs. other methods) in AP (3.03, 0.89-10.29) and Ph+ ALL (2.33, 1.06-5.12). The effect of different treatments on OS will be available at the time of presentation. Conclusion: These results confirm that survival of patients harboring a T315I mutation is dependent on the disease phase at T315I detection. No clear treatment pattern after T315I detection was observed. Age, gender, performance status, and techniques used for T315I detection might be important prognosis factors affecting OS across different phases of CML and Ph+ ALL.
Table 1. OS and PFS of CML and Ph+ ALL patients from T315I detection

<table>
<thead>
<tr>
<th></th>
<th>CML CP (N=82)</th>
<th>CML AP (N=38)</th>
<th>CML BP (N=56)</th>
<th>Ph+ ALL (N=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up time</td>
<td>12.4</td>
<td>15.2</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>22.4 (18.2, 48.5)</td>
<td>28.4 (15.9, 49.8)</td>
<td>4.0 (2.0, 5.0)</td>
<td>4.9 (3.4, 7.3)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year OS Rate</td>
<td>71% (58-80%)</td>
<td>69% (50-81%)</td>
<td>23% (13-36%)</td>
<td>12% (3-27%)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>11.5 (9.2, 15.7)</td>
<td>22.2 (9.0, N/A)</td>
<td>1.8 (1.2, 4.0)</td>
<td>2.5 (1.8, 3.6)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year PFS Rate</td>
<td>46% (34-57%)</td>
<td>56% (38-70%)</td>
<td>16% (7-27%)</td>
<td>7% (1-19%)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Median survival and survival rates were calculated using Kaplan-Meier method.

3244 Molecular Responses to Dasatinib and Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP)

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-326

Alfonso Quintás-Cardama1*, Hagop Kantarjian2*, Franziska Michor3*, Adam Olshen4*, Mithat Gonen4*, Dan Jones5, Mary Beth Rios2, Susan O’Brien5* and Jorge Cortes, MD1

1Leukemia, M.D. Anderson Cancer Center, Houston, TX
2M.D. Anderson Cancer Center, Houston, TX
3Computational Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY
4Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New City, NY
5Hematopathology, UT M.D. Anderson Cancer Center, Houston, TX
6Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Nilotinib (NIL) and dasatinib (DAS) have a 1- and 2-log higher inhibitory potency than imatinib against ABL1 kinase respectively, and are active against all BCR-ABL1 kinase mutants, except T315I. We investigated the molecular responses to nilotinib and dasatinib in patients (pts) with CML-CP receiving these agents either in the frontline (FL) or the post-imatinib failure (PIF) settings.

Methods: 205 pts with CML-CP received either NIL (n=87; 48 FL, 39 PIF) or DAS (n=118; 48 FL, 70 PIF) at various doses in phase II studies. Quantitative reverse transcription PCR in peripheral blood samples was performed prior to NIL or DAS start, after 1 mo of therapy, and every 3 mo thereafter.

Results: Table 1 illustrates the BCR-ABL1/ABL1 ratios at different time-points during therapy. No significant differences were observed regarding the median baseline BCR-ABL1/ABL1 ratio across groups (p=0.88) or the median at 12 mos between the NIL and the DAS cohorts (p=0.14). We developed an exponential model with one population-based shape parameter and a subject-specific slope and intercept. We estimate the shape parameter, after merging all data from a treatment group, using non-linear least squares. With the shape parameter fixed, we estimate the subject-specific parameters using traditional least squares. A statistically significant difference between the shape parameters of the NIL-FL and the DAS-FL treatments was observed (p=0.005), with NIL inducing a sharper early decline in BCR-ABL1 transcripts. Our exponential model does not fit as well for NIL-PIF vs DAS-PIF, particularly for the latter, possibly due to differences in the number and types of mutations at the start of therapy. Indeed, DAS-resistant mutations (L248V/R, Q252H, E255K, V299L, T315I/A, L319S, etc.)
and F317L/C/I/S/V) were detected in 7 (32%) of 22 patients carrying mutations (all PIF), while NIL-resistant mutations (Q252H, Y253H/F, E255K/V, T315I/A, F359V, V379I) were only found in 1/16 (6%) carrying mutations (all PIF).

**BCR-ABL1/ABL1** ratio reductions occurred in 73 (87%) of 84 pts who had at least 2 PCR analyses during NIL therapy: <1-log in 7 (8%) pts, >1-log in 16 (19%) pts, >2-logs in 18 (21%) pts, and >3-logs in 32 (38%) pts. **BCR-ABL1/ABL1** ratio reductions occurred in 102 (92%) of 111 pts who had at least 2 PCR analyses during DAS therapy: <1-log in 20 (18%) pts, >1-log in 17 (15%) pts, >2-logs in 24 (22%) pts, and >3-logs in 41 (37%) pts. Major molecular response (MMR) and complete molecular response (CMR; undetectable **BCR-ABL1** transcripts) rates were 39%/12% and 38%/7% for the NIL and DAS cohorts, respectively (50%/17% and 58%/7% for pts receiving NIL and DAS as frontline therapy). The MMR and CMR response rates for NIL and DAS among pts with mutations at the start of therapy were 19%/6% and 20%/0%, respectively.

**Conclusion:** NIL and DAS induce molecular responses in a significant number of pts, particularly when used in the frontline setting. Although molecular responses occur across a broad variety of **BCR-ABL1** kinase mutations, CMR in this setting is a rare occurrence. NIL appears to induce faster molecular responses than DAS, at least in the FL setting. Longer follow-up is necessary to establish the clinical consequences of this phenomenon.

**Table 1. BCR-ABL1 transcript dynamics by treatment and cohort**

<table>
<thead>
<tr>
<th>DRUG/COHORT</th>
<th>DAS</th>
<th>DAS-FL</th>
<th>DAS-PIF</th>
<th>NIL</th>
<th>NIL-FL</th>
<th>NIL-PIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>118</td>
<td>48</td>
<td>70</td>
<td>87</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Baseline median</td>
<td>70.65</td>
<td>36.27</td>
<td>75.04</td>
<td>67.71</td>
<td>71.26</td>
<td>53.15</td>
</tr>
<tr>
<td><strong>BCR-ABL1/ABL1 (%)</strong></td>
<td>(0.009-100)</td>
<td>(0.01-100)</td>
<td>(0.009-100)</td>
<td>(0.01-100)</td>
<td>(0.01-100)</td>
<td>(0.15-100)</td>
</tr>
<tr>
<td>Time nadir PCR (mos)</td>
<td>27</td>
<td>24</td>
<td>27</td>
<td>27</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Median <strong>BCR-ABL1/ABL1 (%) nadir</strong></td>
<td>0.05</td>
<td>0.01</td>
<td>0.08</td>
<td>0.07</td>
<td>0.01</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>(0-100)</td>
<td>(0.001-0.65)</td>
<td>(0-100)</td>
<td>(0-30.52)</td>
<td>(0-0.6)</td>
<td>(0-30-54)</td>
</tr>
<tr>
<td>No. Evaluable at nadir PCR</td>
<td>13</td>
<td>21</td>
<td>18</td>
<td>17</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Median <strong>BCR-ABL1/ABL1 (%) at 12 months</strong></td>
<td>0.33</td>
<td>0.155</td>
<td>1.49</td>
<td>0.09</td>
<td>0.025</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>(0-100)</td>
<td>(0-100)</td>
<td>(0-100)</td>
<td>(0-92.29)</td>
<td>(0-0.16)</td>
<td>(0-92.29)</td>
</tr>
</tbody>
</table>
2114 Mutational Analysis of Chronic Phase Chronic Myeloid Leukemia (CML-CP) Clones Reveals Heightened BCR-ABL1 Genetic Instability in Patients Failing Sequential Imatinib and Dasatinib Therapy

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-208

Alfonso Quintas-Cardama, MD\textsuperscript{1}, Don L. Gibbons, M.D., Ph.D.\textsuperscript{11}, Hagop M. Kantarjian, MD\textsuperscript{2}, Moshe Talpaz\textsuperscript{3}, Nicholas Donato, PhD\textsuperscript{4} and Jorge Cortes, MD\textsuperscript{5}

\textsuperscript{1}Medical Oncology, UT MD Anderson Cancer Center, Houston, TX
\textsuperscript{2}Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX
\textsuperscript{3}Comprehensive Cancer Ctr., Univ. of Michigan, Ann Arbor, MI
\textsuperscript{4}Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI
\textsuperscript{5}Leukemia, U.T.M.D. Anderson Cancer Center, Houston, TX

ABL1 kinase domain (AKD) mutations are the most important mechanism of resistance to tyrosine kinase inhibitors (TKIs) in CML. Direct sequencing (DS) techniques detect AKD mutations in 20\%-40\% of imatinib-resistant pts. Therefore, most pts fail TKI therapy for unknown reasons. We evaluated the incidence and clinical consequences of AKD mutations among 70 pts in CML-CP after imatinib failure (13 intolerant) enrolled in a phase I study of dasatinib. Mutations were studied by DS of nested PCR-amplified BCR-ABL1 products and by DNA expansion of specific clones (DESC) followed by DNA sequencing of ≥10 clones. Patients had received imatinib at 400 mg/d (n=60), 600 mg/d (n=8), or 800 mg/d (n=2). Prior to dasatinib, AKD mutations were detected in 61/70 (87\%) pts by DESC, including 38 (54\%) with mutations in ≥20\% of sequenced clones. Mutations were only detected in 18/38 (47\%) by DS. Overall, 125 mutations at 113 amino acid positions were detected by DESC (78 previously unreported). Mutations conferring resistance to >1µM imatinib (M244V, G250E, Q252H, Y253H, E255K/V, F359V, H396R, and T315I) were detected in 30 (43\%) pts by DESC, but only in 5 (7\%) by DS. Two or more mutations within the same clone (polymutants) were detected in 29/70 (41\%) pts by DESC, with clones expressing 2 (n=38), 3 (n=11), 4 (n=1), or even 5 (n=2) distinct mutations. By contrast, only 1 pt was found to carry 2 different mutations (M244V and M351T) by DS. Pts received dasatinib for a median of 19 months (range, 2-52), of whom 68 (97\%) are evaluable for response. DESC available in 32 pts during dasatinib therapy revealed 20 additional mutations not present at dasatinib start (19 amino acid positions), including 5 previously not reported (all in polymutant clones). Dasatinib-resistant mutations (L248V/R, Q252H, E255K, V299L, T315I/A, and F317L/C/I/S/V) were detected in 10/32 (31\%) cases (5 with T315I) by DS (but only in 3/16 [19\%] by DS). Of these 16 pts 13 died (all in BP) and 3 are alive in CP carrying E255K, T315I, and F317L respectively.

The percentage of clones with unmutated BCR-ABL1 before dasatinib decreased significantly compared to those present after a median of 16 wks (range, 4-84) during dasatinib (p=0.001), particularly in pts carrying highly dasatinib-resistant mutants. No differences were seen in the proportion of unmutated BCR-ABL1–expressing clones between pts with no cytogenetic (CG) response and those who achieved a partial (PCyR) or a complete CG (CCyR) response prior to dasatinib therapy. Conversely, DESC during dasatinib therapy showed the proportion of unmutated clones was lower among pts who failed to achieve a CG response compared to those who had a PCyR or CCyR (p=0.0001).

<table>
<thead>
<tr>
<th>DASATINIB RESPONSE</th>
<th>No. Evaluable Pts</th>
<th>No. clones sequenced</th>
<th>No. unmutated Clones (%)</th>
<th>No. Evaluable Pts</th>
<th>No. clones sequenced</th>
<th>No. unmutated Clones (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CG Response</td>
<td>68</td>
<td>680</td>
<td>311 (46)</td>
<td>32</td>
<td>305</td>
<td>94 (30)</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>309</td>
<td>149 (48)</td>
<td>13</td>
<td>120</td>
<td>17 (14)</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Medical Oncology, UT MD Anderson Cancer Center, Houston, TX
\textsuperscript{2}Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX
\textsuperscript{3}Comprehensive Cancer Ctr., Univ. of Michigan, Ann Arbor, MI
\textsuperscript{4}Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI
\textsuperscript{5}Leukemia, U.T.M.D. Anderson Cancer Center, Houston, TX

ABL1 kinase domain (AKD) mutations are the most important mechanism of resistance to tyrosine kinase inhibitors (TKIs) in CML. Direct sequencing (DS) techniques detect AKD mutations in 20\%-40\% of imatinib-resistant pts. Therefore, most pts fail TKI therapy for unknown reasons. We evaluated the incidence and clinical consequences of AKD mutations among 70 pts in CML-CP after imatinib failure (13 intolerant) enrolled in a phase I study of dasatinib. Mutations were studied by DS of nested PCR-amplified BCR-ABL1 products and by DNA expansion of specific clones (DESC) followed by DNA sequencing of ≥10 clones. Patients had received imatinib at 400 mg/d (n=60), 600 mg/d (n=8), or 800 mg/d (n=2). Prior to dasatinib, AKD mutations were detected in 61/70 (87\%) pts by DESC, including 38 (54\%) with mutations in ≥20\% of sequenced clones. Mutations were only detected in 18/38 (47\%) by DS. Overall, 125 mutations at 113 amino acid positions were detected by DESC (78 previously unreported). Mutations conferring resistance to >1µM imatinib (M244V, G250E, Q252H, Y253H, E255K/V, F359V, H396R, and T315I) were detected in 30 (43\%) pts by DESC, but only in 5 (7\%) by DS. Two or more mutations within the same clone (polymutants) were detected in 29/70 (41\%) pts by DESC, with clones expressing 2 (n=38), 3 (n=11), 4 (n=1), or even 5 (n=2) distinct mutations. By contrast, only 1 pt was found to carry 2 different mutations (M244V and M351T) by DS. Pts received dasatinib for a median of 19 months (range, 2-52), of whom 68 (97\%) are evaluable for response. DESC available in 32 pts during dasatinib therapy revealed 20 additional mutations not present at dasatinib start (19 amino acid positions), including 5 previously not reported (all in polymutant clones). Dasatinib-resistant mutations (L248V/R, Q252H, E255K, V299L, T315I/A, and F317L/C/I/S/V) were detected in 10/32 (31\%) cases (5 with T315I) by DS (but only in 3/16 [19\%] by DS). Of these 16 pts 13 died (all in BP) and 3 are alive in CP carrying E255K, T315I, and F317L respectively.

The percentage of clones with unmutated BCR-ABL1 before dasatinib decreased significantly compared to those present after a median of 16 wks (range, 4-84) during dasatinib (p=0.001), particularly in pts carrying highly dasatinib-resistant mutants. No differences were seen in the proportion of unmutated BCR-ABL1–expressing clones between pts with no cytogenetic (CG) response and those who achieved a partial (PCyR) or a complete CG (CCyR) response prior to dasatinib therapy. Conversely, DESC during dasatinib therapy showed the proportion of unmutated clones was lower among pts who failed to achieve a CG response compared to those who had a PCyR or CCyR (p=0.0001).
In conclusion, DESC demonstrates a high prevalence of AKD mutations among pts who fail imatinib, revealing heightened BCR-ABL1 genomic instability in this setting. This high incidence of mutations might partly explain TKI resistance in pts found to carry unmutated BCR-ABL1 by DS. The latter might be mediated by generation of resistant polymutant clones that perpetuate a “mutator phenotype” and by exhaustion of clones carrying unmutated BCR-ABL1 alleles.

3215 Minimal Cross-Intolerance Between Nilotinib and Imatinib in Patients with Imatinib-Intolerant Chronic Myeloid Leukemia in Chronic Phase (CML-CP) or Accelerated Phase (CML-AP)

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-297

Elias Jabbour, MD1*, Hagop M Kantarjian2, Michele Baccarani, MD3*, Philipp D. le Coutre, MD4*, Ariful Haque2*, Neil J. Gallagher, MD, PhD5, Jorge Cortes, MD1 and Francis Giles, MD7

1M.D. Anderson Cancer Center, Houston, TX
2The University of Texas M. D. Anderson Cancer Center, Houston, TX
3Institute of Hematology and Medical OncologySeragnoli, Bologna, Italy
4Department of Hematology and Oncology, Charité - Humboldt-Universitat, Campus Virchow, Berlin, Germany
5Novartis Pharmaceuticals, Florham Park, NJ
6Oncology, Novartis Pharma AG, Basel, Switzerland
7The Institute for Drug Development, CTRC, University of Texas Health Science Center, San Antonio, TX

Background: Nilotinib is a rationally designed, potent and highly selective BCR-ABL kinase inhibitor with significant clinical efficacy in the treatment of patients with Philadelphia chromosome-positive chronic myeloid leukemia patients in chronic (CML-CP) or accelerated phase (CML-AP) who are resistant or intolerant to prior therapy including imatinib. This subanalysis of the phase 2 registration study of nilotinib was designed to examine the occurrence of cross-intolerance to nilotinib in patients with prior intolerance to imatinib. Methods: Imatinib intolerance was defined as discontinuation due to grade 3/4 adverse events (AEs) or persistent (>1 month) or recurrent (recurred >3 times) grade 2 AEs despite optimal supportive care. Additionally, patients with major cytogenetic response (MCyR) at baseline were excluded from the trial. Cross-intolerance between nilotinib and imatinib was defined as treatment with nilotinib and occurrence (regardless of causality) of grade 3/4, or persistence or recurrent grade 2, of the same AE(s) that previously led to discontinuation of imatinib therapy. Nilotinib was dosed at 400mg twice daily with the option to escalate to 600 mg twice daily for lack of response. Results: Ninety-five of 321 (30%) CML-CP patients and 27 of 138 (20%) CML-AP patients were included in this subanalysis of cross-intolerance following imatinib intolerance. Patients experiencing multiple reasons for imatinib intolerance were counted for each AE category and these included patients (8 CML-CP, 3 CML-AP) with unusual symptoms during imatinib therapy, none of these patients discontinued nilotinib due to the same AE. Median dose intensity for nilotinib (CML-CP 688mg/day, range 151-800; CML-AP 769mg/day range 184-1149) closely approximated the planned dose of 800mg/day. Among these patients, 64% of CML-CP and 52% of CML-AP patients experienced dose interruptions, however, the median cumulative duration of dose interruptions were short (CML-CP 24 days, range 1-301; CML-AP 17 days, range 4-234). Of the 72 patients (57 CML-CP, 15 CML-AP) who discontinued imatinib due to non-hematologic AEs, 3/72 (4%) experienced same persistent grade 2 AEs, only 1 patient (1%) experienced a recurrence of same grade 3/4 AE during
These results confirm that there is remarkable activity in CML, IM fails to eliminate all malignant stem and progenitor cells in CML disease relapse of Bcr-Abl+ progenitors persist in IM-treated CML patients following achievement of CCR. These observations suggest that despite its remarkable activity in CML, IM fails to eliminate all malignant stem and progenitor cells in CML patients. However our previous studies were conducted on patients within the first year or two of IM treatment, whereas recent studies have indicated that Bcr-Abl levels continue to decline on Q-PCR analysis with continued IM treatment. This together with the decreasing rate of disease relapse observed after 3 years of IM treatment raises the possibility that prolonged IM treatment may cause depletion of residual CML stem cells. In this study we investigated whether prolonged IM treatment may cause disease relapse in Bcr-Abl+ stem and progenitor cells. We evaluated 14 CML patients followed at our center who were in CCR, had been treated with IM for at least 4 years, and from whom multiple cryopreserved bone marrow samples were available for study. Bone marrow mononuclear cells (MNC) were thawed, CD34+ cells were selected by immunomagnetic columns, and CD34+CD38- (38-) committed progenitors and CD34+CD38+ (38+) stem/primitive progenitor cells were isolated by flow cytometry sorting. Q-PCR analysis of Bcr-Abl and Bcr transcript levels was performed on RNA isolated from MNC, 38+ and 38- cells and Bcr-Abl levels were reported as the ratio of Bcr-Abl to Bcr. Bcr-Abl levels in MNC were 0.010±0.005, 0.011± 0.005and 0.013±0.005 at 3, 4 and 5 years. We observed that Bcr-Abl levels were higher in both 38+ and 38- cells in comparison with levels in MNC. A gradual decline in Bcr-Abl levels in 38+ cells was seen (0.285±0.185 at 3 years, 0.121±0.056 at 4 years, and 0.071±0.028 at 5 years). In contrast high Bcr-Abl levels were maintained in the 38- fraction despite continued IM treatment (0.162±0.086 at 3 years, 0.116±0.041 at 4 years, and 0.361±0.107 at 5 years). In contrast to IM-treated patients, Bcr-Abl transcripts were not detected.
in MNC and CD34+ cells from BM of CML patients who had received allogeneic hematopoietic cell transplants (n=5). To further investigate whether malignant stem cells persisted after prolonged IM treatment, MNC from 5 of the patients described above were transplanted by tail vein injection into sublethally irradiated NOD/SCID-IL2Rγ-chain knockout (NSG) mice. High levels of human cell engraftment were observed 4-5 weeks after injection, and Q-PCR analysis revealed high levels of Bcr-Abl expression in engrafted cells from 4 of 5 patients, confirming the presence of Bcr-Abl+ cells with NOD/SCID mouse repopulating capacity. In conclusion, our results clearly demonstrate the persistence of Bcr-Abl+ stem cells in the BM of CML patients in prolonged remission after 5 years of IM treatment. The observed persistence of leukemia stem cells raises the concern that patients remain at risk for relapse on drug discontinuation or through acquisition of IM resistance. The assays described here may have considerable utility for evaluating and monitoring the effects of experimental treatment strategies directed against residual CML stem cells.

1103 Homo-Harringtonine (Omacetaxine mepesuccinate) Induces a Dramatic and Sustained Reduction of BCR-ABL T315I mutated Transcripts in Chronic Phase Chronic Myelogenous Leukemia Patients Resistant to Tyrosine Kinase Inhibitors

Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-208

Franck Nicollini, MD, PhD1, Laurence Legros, MD, PhD2, Lydia Roy, MD, PhD3, Jean-Claude Chomel, MD4, Kadjour Chabane, BSc5, Sophie Ducastelle, MD1, Selim Corm, MD6, Mauricette Michallet, MD, PhD7, Francois Guilhot, MD3, Ali Turhan, MD, PhD4* and Sandrine Hayette, PhD5*

1Hematology Department, Hospital E. Herriot, Lyon, France
2Hematology department, Hôpital de l’Arche, Nice, France
3CHU de Poitiers, CIC 802 INSERM, Poitiers, France
4Laboratory for Hematology and molecular biology, CHU de Poitiers, Poitiers, France
5Laboratory for molecular biology and cytogenetics, Centre Hospitalier Lyon Sud, Pierre Benite, France
6Hematology department, Hôpital Huriez, Lille, France
7Hematology, Hopital Edouard Herriot, Lyon, France

The treatment of chronic myelogenous leukemia (CML) has been revolutionized by the introduction of tyrosine kinase inhibitors in the therapeutic arsenal. Disease response and survival have been dramatically improved with these agents, however a significant cohort of patients may resist to such inhibitors. In tyrosine kinase inhibitors (TKIs)-resistant CML patients, the identification of the BCR-ABL T315I mutation is a rare event, but usually translates into poor survival rates and therapeutic options remain few in the absence of a suitable allogeneic donor. In this study, within the CGX trial or not, we investigated the impact of cycles of sub-cutaneous Homo-harringtonine (HHT) [Omacetaxine mepesuccinate] as monotherapy on wild-type and mutated transcripts in 7 chronic phase CML patients resistant to TKIs, harbouring a BCR-ABL T315I mutation. Patients were monthly monitored in a centralized manner for total disease burden (RQ-PCR) and BCR-ABL T315I transcripts (PCR-RFLP, sensitivity threshold 1%) for up to 14 cycles. There were 4 M and 3 F, median age: 51 (38-79) at HHT start. All patients were in chronic phase (CP) at diagnosis, Sokal score was high for 5, intermediate for 1 and unknown for 1 patient. One patient had a Ph1 duplication at diagnosis. Two patients had short term IFN before imatinib. Median time of imatinib treatment was 27 (15-54) months with, as best responses: CHR for 2, a minor CyR for 1, PCyR for 2, CCyR without MMR for 2. Three patients had a second generation TKI for a median of 1 (1-22) month for unsatisfactory response to imatinib. At T315I identification, all patients were in CP CML, 4 in hematological relapse, 3 in CHR (1 molecular progression in CCyR, 1 in cytogenetic progression, 1 with no cytogenetic response). The proportion of T315I transcripts among total BCR-ABL transcripts was 95 (20-100) % and the BCR-ABL/ABL ratio (IS) was 67 (26-112) % at T315I discovery. Three patients had clonal evolution (Ph1 duplication, -7, -Y+v)ariant Ph1. The median interval imatinib start-T315I was 27 (10-65) months. After T315I discovery, imatinib was withdrawn and, if necessary, patients went on hydroxyurea. The median time between T315I detection and HHT start was 2 (1-4.3) months. All patients demonstrated hematologic or cytogenetic improvements to HHT (7 patients in CHR, 1 in CCyR, after a median follow-up of 11 months). A rapid decline and a sustained disappearance of T315I mutated transcripts...
was observed in 6 out of 7 patients, median proportion of T315I transcripts was 65 % at Cycle 2, 19 % at cycle 3, 1 % at cycle 4, < 1 % at cycle 5 and beyond. The total tumour burden reduction was moderate with one patient converted to a CCyR after 3 cycles, but with no other cytogenetic improvement. A moderate decline was observed in BCR-ABL/ABL ratios from a median of 67 before HHT to 39 % at cycle 10, suggesting a differential activity of HHT on wild-type versus BCR-ABL T315I cells. Patients received a median of 8 (4-17) cycles of HHT at last follow-up and none of the patients have progressed. Transient grade 3-4 hematological toxicities after the first cycle and grade 0-2 after maintenance cycles were observed in all patients. Non-hematological toxicities were grade1-2 (site pain after injections, nausea, diarrhea). Since high levels of BCR-ABL T315I transcripts in CML are thought to be associated with disease progression, HHT (i.e. a non-targeted therapy) in these cases seems to exert a somewhat preferential activity on T315I mutated CML cells through an unknown mechanism yet. Therefore, by reducing the T315I tumor burden, this treatment is expected to decrease progression rates, and improve survival.

3183 Persistent Telomeric Loss and Functional Impairment of Ph-Negative Hematopoiesis after Successful Treatment of Chronic Myelogenous Leukemia

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-265

Chiara Lobetti Bodoni, MD1, Dario Ferrero, MD1, Elisa Genuardi, PhD1, Daniela Sia, MD2, Mariella Genuardi, MD2, Valentina Giai, MD2, Alberto Roccì, MD2, Luigia Montillo, PhD3, Daniela Drandi, PhD1, Alessandra Risso, PhD1, Simone Ferrero, MD1, Barbara Mantoan, PhD1, Rossana Critelli, PhD1, Serena Bussano, PhD1, Monia Lunghi, MD2, Roberto Passera, Pharm, D3, Corrado Tarella, MD3, Gianluca Gaidano, MD3, Mario Boccadoro, MD3, Carmelo Carlo-Stella, MD2 and Marco Ladetto, MD1

1Cattedra di Ematologia, Università di Torino, Torino, Italy
2Istituto Tumori, Cattedra Di Ematologia, Milano
3Divisione di Ematologia dell’Università di Torino, A.O.U. San Giovanni Battista, Torino, Italy
4Dept. of Med. Sciences & IRCAD, Amedeo Avogadro Univ., Novara, Italy
5Statistical Consultant, Ospedale San Giovanni Battista, Torino

Background. Most chronic myelogenous leukemia (CML) patients (pts) restore non-neoplastic hematopoiesis following treatment with tyrosine kinase (TK) inhibitors. However little is presently known on the functional and genetic integrity of Ph-negative hematopoietic cells (HC) repopulating the bone marrow after successful treatment. Indeed, the frequent detection of cytogenetic abnormalities (CA) reminiscent of those seen in myelodysplastic syndromes suggests the potential presence of functional and genetic defects. These issues have been addressed using short and long term HC cultures and telomere restriction fragment length (TRF-L) analysis, which is considered a reliable marker of proliferative and oxidative damage. Patients and methods. We investigated 71 CML pts in stable complete cytogenetic remission (CR) (CR had to be documented at least one year before the analysis). 62 pts were treated with Imatinib and 10 with α-interferon associated or not to ara-C. Median age was 64 (23-88), M/F ratio was 1.5, median time from diagnosis and from complete CR were 58 (7-915), and 40 months (12-150). 31 pts had low Sokal score, 27 intermediate, and 13 high. Complete and partial molecular responders were 35 and 21, respectively. 6 pts showed evidence of acquired CA in Ph-negative HC. TRF-L analysis was performed by Southern Blotting as previously described (Ladetto M et al, Blood 2004), both on polymorphonucleates (PMN) and on monocyte-depleted PBMC (MD-PBMC) (as described by Rocci et al Exp Hematol 2007) to monitor both the myeloid and lymphoid compartment. Colony-forming unit granulocyte-macrophage (CFU-GM), burst-forming unit erythroid (BFU-E) and colony forming unit-mix (CFU-Mix) along with long-term culture-initiating cells (LTC-ICs) have been so far performed on 30 patients, using bone marrow mononuclear cells as previously described (Sutherland HJ et al Blood 1994). For both TRF-L and cell culture studies a control database of 86 healthy subjects has been used for comparison. Results. PMN from CML patients showed a striking erosion of their telomeric DNA (figure 1A). Also MD-PBMC showed a degree of telomere shortening although the finding was much less pronounced (mean telomeric loss in PMN 1683 pb p<0.001; in MD-PBMC: 323 pb, p=0.04) We found no correlation between TRF-L and previously mentioned clinical parameters. Telomeric erosion is more severe in younger CML pts,
resulting in loss of the association between TRF-L and age, typically seen in healthy subjects (figure 1B). Telomere shortening was observed regardless of the use of TK inhibitors. When a multivariate analysis on pts and healthy controls was performed, the presence of CML resulted in a stronger predictor of telomeric damage compared to age. We found no correlation between TRF-L and previously mentioned clinical and demographic parameters. Telomeric erosion show no evidence of recovery on 40 follow-up samples taken after a median time of 10 months (range 6-13). Moreover, Ph-negative HC of CML pts were functionally impaired compared to controls with reduced numbers of CFU-Mix (median 2.62 vs 4, p=0.01), CFU-GM (median 99.5 vs 181, p<0.0001) and particularly of LTC-IC (median 88 vs 198, p<0.0001) (figure 1C). Discussion. Ph-negative HC repopulating the bone marrow after successful CML treatment display severe telomeric DNA erosion, roughly comparable to 34 years of physiological aging. Moreover they display major defects in their functional performances. These findings, underline the need of additional investigation and careful clinical monitoring of the Ph-negative haemopoietic compartment in these subjects.

1089 Genome-Wide Analysis of Genetic Alterations in Chronic Myelogenous Leukemia
Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-194

Charles G Mullighan, MBBS(Hons), MSc, MD
1, Ina Radtke, PhD1*, Jinghui Zhang, Ph.D.2*, Letha A. Phillips, BS1*, Xiaoping Su, PhD1, Jing Ma, PhD3*, Zhongling Cal1*, Timothy P. Hughes, MBBS, PhD4, Deborah L White, PhD4*, Andrew W. Roberts, MBBS, PhD5, Lynda J. Campbell, MBBS, FRCPA6*, Sheila A. Shurtleff7* and James R. Downing, MD1*

1Pathology, St. Jude Children’s Research Hospital, Memphis, TN
2National Cancer Institute, Rockville, MD
3Hartwell Center, St. Jude Children’s Research Hospital, Memphis, TN
4Haematology, Institute of Medical and Veterinary Science, Adelaide, Australia
Expression of **BCR-ABL1** is the hallmark of chronic myelogenous leukemia (CML) and a subset of **de novo** acute lymphoblastic leukemia (ALL), but the factors determining disease lineage, and progression of CML to myeloid or lymphoid blast crisis, are incompletely understood. We recently reported deletion of **IKZF1** (encoding the lymphoid transcription factor Ikaros) in 85% of **de novo** pediatric and adult **BCR-ABL1** ALL, and in lymphoid blast crisis in a small cohort of CML cases (Nature 2008;453:110), suggesting that **IKZF1** deletion is important in the pathogenesis of **BCR-ABL1** lymphoid leukemia.

To identify genetic determinants of disease stage and blast crisis lineage in CML, we have now performed high-resolution, genome wide analysis of DNA copy number abnormalities (CNA) and loss-of-heterozygosity (LOH) and candidate gene resequencing in a cohort of 90 CML patients that included 64 samples obtained at chronic phase (CP), 15 samples at accelerated phase (AP), 9 lymphoid blast crisis (LBC) and 22 myeloid blast crisis (MBC) samples. Importantly, 25 patients had sequential samples (CP and/or AP, as well as blast crisis samples) enabling analysis of lesions acquired at progression to blast crisis. All blast crisis samples were flow sorted to at least 90% purity prior to DNA extraction. Germline samples for 28 cases obtained at remission or by flow sorting of blast crisis samples were also examined. Affymetrix SNP 6.0 arrays, interrogating over 1.87 million genomic loci, were used for 85 samples, and 500K arrays for the remainder. Identification of tumor-specific (somatic) copy number analysis was performed by directly comparing CML samples to matched germline samples were available, or by filtering results against databases of inherited copy number variants for samples lacking germline material. Genomic resequencing of **IKZF1**, **PAX5** and **TP53** was performed for all AP, LBC and MBC samples. There were few CNAs in CP-CML (mean 0.27 deletions and 0.07 gains per case), with no recurring lesions identified apart from deletions or gains at the chromosomal breakpoints of **BCR** and **ABL1** (3 cases each). Notably, the size of these translocation associated deletions was highly variable, ranging from 6kb (one **ABL1** deletion) and 15 kb (one **BCR** deletion) to deletions extending to the telomeres of chromosomes 9 and 22. No significant increase in lesion frequency was identified in AP cases (0.14 deletions and 0.9 gains per case), however the number and cumulative extent of genomic aberrations was significantly higher in both lymphoid and myeloid blast crisis samples. LBC cases had a mean of 8.1 deletions/case (P<0.0001 v CP) and 2.8 gains/case (P=0.0024), whereas MBC had fewer alterations with only an average of 2.8 deletions/case (P=0.028 v CP) and 2.2 gains/case (P=0.0018). Similarly, the cumulative extent of DNA altered by CNAs was higher in both LBC (200 Mb/case) and MBC (257 Mb/case) than CP-CML (4.1 Mb/case).

There were striking differences in the type of CNAs in MBC and LBC samples. Seven of 9 LBC cases had focal CNAs targeting genes regulating normal B-lymphoid development, including **IKZF1** (6 cases, 2 homozygous), **PAX5** (4 cases), and **EBF1** (1 case with focal homozygous deletion restricted to the **EBF1** locus). Thus, of these 7 cases, two had a single CNA in this pathway, three had two lesions, and two cases had three lesions. In contrast, only 4 of 22 MBC cases had lesions in this pathway, most commonly from whole or sub chromosomal deletions involving chromosomes 7 and 9. Deletion of the **CDKN2A** locus (encoding the tumor suppressors and cell cycle regulators **INK4A**, **ARF** and **INK4B**) was seen in 6 (67%) LBC samples, but only 2 (9%) MBC cases, and never in CP or AP CML. Other lesions commonly seen in **de novo** **BCR-ABL1** ALL were also observed in LBC samples, including deletions of **MEF2C**, **C20orf94**, and the **HBS1L** gene immediately upstream of the oncogene **MYB**. Apart from acquisition of new or more complex abnormalities involving **BCR** and **ABL1**, the only recurring mutation observed in MBC was deletion (4 cases) or splice-site point mutations (2 cases) of **TP53**.

These data demonstrate a lack of genomic instability with few genetic alterations in CP or AP CML. Lymphoid blast crisis samples have similar genetic alterations to those seen in **de novo** **BCR-ABL1** ALL, whereas myeloid blast crisis displays completely distinct patterns of mutation, most commonly targeting **P53**. These results indicate that genomic abnormalities are important determinants of lineage and disease progression in **BCR-ABL1** leukemia.

---

**Patient Education Material**

5\textsuperscript{5}Div. of Cancer and Haem., The Walter & Eliza Hall Inst. of Med. Rsch., Parkville, VIC, Australia

5\textsuperscript{6}Cytogenetics, St Vincent's Hospital, Melbourne, Australia

Expression of **BCR-ABL1** is the hallmark of chronic myelogenous leukemia (CML) and a subset of **de novo** acute lymphoblastic leukemia (ALL), but the factors determining disease lineage, and progression of CML to myeloid or lymphoid blast crisis, are incompletely understood. We recently reported deletion of **IKZF1** (encoding the lymphoid transcription factor Ikaros) in 85% of **de novo** pediatric and adult **BCR-ABL1** ALL, and in lymphoid blast crisis in a small cohort of CML cases (Nature 2008;453:110), suggesting that **IKZF1** deletion is important in the pathogenesis of **BCR-ABL1** lymphoid leukemia.

To identify genetic determinants of disease stage and blast crisis lineage in CML, we have now performed high-resolution, genome wide analysis of DNA copy number abnormalities (CNA) and loss-of-heterozygosity (LOH) and candidate gene resequencing in a cohort of 90 CML patients that included 64 samples obtained at chronic phase (CP), 15 samples at accelerated phase (AP), 9 lymphoid blast crisis (LBC) and 22 myeloid blast crisis (MBC) samples. Importantly, 25 patients had sequential samples (CP and/or AP, as well as blast crisis samples) enabling analysis of lesions acquired at progression to blast crisis. All blast crisis samples were flow sorted to at least 90% purity prior to DNA extraction. Germline samples for 28 cases obtained at remission or by flow sorting of blast crisis samples were also examined. Affymetrix SNP 6.0 arrays, interrogating over 1.87 million genomic loci, were used for 85 samples, and 500K arrays for the remainder. Identification of tumor-specific (somatic) copy number analysis was performed by directly comparing CML samples to matched germline samples were available, or by filtering results against databases of inherited copy number variants for samples lacking germline material. Genomic resequencing of **IKZF1**, **PAX5** and **TP53** was performed for all AP, LBC and MBC samples. There were few CNAs in CP-CML (mean 0.27 deletions and 0.07 gains per case), with no recurring lesions identified apart from deletions or gains at the chromosomal breakpoints of **BCR** and **ABL1** (3 cases each). Notably, the size of these translocation associated deletions was highly variable, ranging from 6kb (one **ABL1** deletion) and 15 kb (one **BCR** deletion) to deletions extending to the telomeres of chromosomes 9 and 22. No significant increase in lesion frequency was identified in AP cases (0.14 deletions and 0.9 gains per case), however the number and cumulative extent of genomic aberrations was significantly higher in both lymphoid and myeloid blast crisis samples. LBC cases had a mean of 8.1 deletions/case (P<0.0001 v CP) and 2.8 gains/case (P=0.0024), whereas MBC had fewer alterations with only an average of 2.8 deletions/case (P=0.028 v CP) and 2.2 gains/case (P=0.0018). Similarly, the cumulative extent of DNA altered by CNAs was higher in both LBC (200 Mb/case) and MBC (257 Mb/case) than CP-CML (4.1 Mb/case).

There were striking differences in the type of CNAs in MBC and LBC samples. Seven of 9 LBC cases had focal CNAs targeting genes regulating normal B-lymphoid development, including **IKZF1** (6 cases, 2 homozygous), **PAX5** (4 cases), and **EBF1** (1 case with focal homozygous deletion restricted to the **EBF1** locus). Thus, of these 7 cases, two had a single CNA in this pathway, three had two lesions, and two cases had three lesions. In contrast, only 4 of 22 MBC cases had lesions in this pathway, most commonly from whole or sub chromosomal deletions involving chromosomes 7 and 9. Deletion of the **CDKN2A** locus (encoding the tumor suppressors and cell cycle regulators **INK4A**, **ARF** and **INK4B**) was seen in 6 (67%) LBC samples, but only 2 (9%) MBC cases, and never in CP or AP CML. Other lesions commonly seen in **de novo** **BCR-ABL1** ALL were also observed in LBC samples, including deletions of **MEF2C**, **C20orf94**, and the **HBS1L** gene immediately upstream of the oncogene **MYB**. Apart from acquisition of new or more complex abnormalities involving **BCR** and **ABL1**, the only recurring mutation observed in MBC was deletion (4 cases) or splice-site point mutations (2 cases) of **TP53**.

These data demonstrate a lack of genomic instability with few genetic alterations in CP or AP CML. Lymphoid blast crisis samples have similar genetic alterations to those seen in **de novo** **BCR-ABL1** ALL, whereas myeloid blast crisis displays completely distinct patterns of mutation, most commonly targeting **P53**. These results indicate that genomic abnormalities are important determinants of lineage and disease progression in **BCR-ABL1** leukemia.

---

1102 The Majority of Chronic Myeloid Leukaemia Patients Who Cease Imatinib after Achieving a Sustained Complete Molecular Response (CMR) Remain in CMR, and Any Relapses Occur Early

The CML Advocates Network – www.cmladvocates.net
After 5 years of imatinib treatment 40-50% of chronic myeloid leukaemia (CML) patients will have stable undetectable BCR-ABL by real-time quantitative RT-PCR (RQ-PCR) using strict sensitivity criteria (‘complete molecular response’, CMR). Many patients who stop imatinib in CMR will relapse, but small numbers have been reported with sustained CMR after imatinib withdrawal. We designed a non-randomised prospective Phase 2 study of imatinib withdrawal in adult chronic phase CML patients in CMR for ≥2 years (ACTRN01260600118505). Patients were treated in multiple centres around Australia, and RQ-PCR for BCR-ABL was performed centrally: monthly for the first year after imatinib withdrawal, and 2-monthly in the second year. Molecular relapse was defined as a single PCR result above the level of major molecular response (MMR) or any two consecutive positive results. Molecular relapse was treated with imatinib and patients were monitored monthly for 12 months to assess response to re-treatment. Patients were enrolled in two cohorts: imatinib de novo (IM only, n=5) and imatinib after prior interferon therapy (IFN-IM, n=13). The median duration of prior IFN was 39 months. Both cohorts continue to accrue. For all 18 patients the median age at study entry was 58 years; 44% were male. The median duration of imatinib treatment was 60 months (R40-89). The Kaplan-Meier estimate of the rate of sustained CMR after 12 months off treatment was 67% (95% confidence interval 40-85%, see Figure). Ten of 13 IFN-IM patients (77%) remain in CMR, and 7 of these have been in CMR for at least 12 months without treatment (maximum 23 months). The median follow-up in the IM only patients is currently only 7 months (R1-15), and 3/5 remain in CMR. All molecular relapses in both groups have occurred within 5 months of stopping imatinib. The median duration of prior imatinib treatment was not different in the 5 patients with loss of CMR (76 months) versus those in stable CMR (60 months; p=0.59). Among the 5 patients with loss of CMR the median time to molecular relapse was 3 months (range 2-5 months). Two relapsing patients lost MMR, and 3 had detectable BCR-ABL mRNA below this level. No patient has experienced haematological relapse or developed a kinase domain mutation. At last follow-up all 5 relapsing patients had regained CMR after a median of 5 months of re-treatment with imatinib. Patient-specific DNA Q-PCR assays were developed to test whether minimal residual disease (MRD) was detectable in genomic DNA in patients in CMR defined by RQ-PCR for BCR-ABL mRNA. Results are available for 6 patients, 3 of whom have relapsed. One relapsing patient had BCR-ABL DNA detected prior to imatinib withdrawal. In the remaining 2 relapsing patients BCR-ABL DNA was detected after imatinib withdrawal, but 2-3 months prior to the detection of BCR-ABL mRNA by RQ-PCR. BCR-ABL DNA increased by at least 1-log between the time of the first positive result and the detection of molecular relapse by RQ-PCR. The 3 patients in stable CMR had no detectable BCR-ABL DNA. In conclusion, with close molecular monitoring imatinib withdrawal in stable CMR appears to be safe: currently all patients are either in stable CMR off treatment or back in CMR after re-treatment. Withdrawal of effective treatment outside the setting of a clinical trial is not recommended. Monitoring of MRD by genomic DNA Q-PCR was able to detect molecular relapse prior to mRNA RQ-PCR, and shows promise for the prospective identification of patients at high risk of relapse. There is an apparent dichotomy of response between early molecular relapse and durable CMR, at least in patients treated with imatinib after IFN. It is too early to identify clinical or laboratory factors (such as prior IFN treatment) that may influence the probability of sustained CMR without treatment.
3222 Management of Chronic Myelogenous Leukemia Using Therapeutic Drug Monitoring of Imatinib: The French Experience of a Centralized Laboratory

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-304

Mathieu Molimard1*, Stephane Bouchet2*, Gabriel Etienne2*, Laurence Legros3*, Delphine Rea4*, Francoise Huguet5*, Karine Titier6*, Nicholas Moore1*, Josy Reiffers6*, Coralie Belanger7* and Francois-Xavier Mahon2*

1Department of Clinical Pharmacology and Toxicology, Université Victor Segalen CHU de Bordeaux, Bordeaux, France
2Hématopoïèse leucémique, Université Victor Segalen, Bordeaux, France
3CHU de Nice, Nice, France
4CML Advocates Network – www.cmladvocates.net
Pharmacokinetic monitoring is widely used in different medical specialities, but it has been rarely applied in clinical oncology practice. The current gold standard treatment of chronic myelogenous leukemia (CML) is imatinib, a tyrosine kinase inhibitor. We have previously shown the necessity to obtain a trough plasma threshold of 1000 ng/mL for efficient treatment with imatinib. We routinely perform centralized quantification for patients in France and this has allowed the assessment of imatinib therapeutic monitoring and its use in a real-life setting.

After 16 months of data collection, we had gathered 1607 samples for 1044 CML patients (mean age 55 years, F/M sex ratio 0.67) treated with imatinib 400 mg (median) range (100-800mg). We received only one sample for 739 patients and more than one sample for 305 patients.

The mean trough plasma concentration of imatinib (Cmin) was 1043 ng/mL (median: 876 ng/mL) and 596 of the 1044 CML patients (57%) had a Cmin <1000ng/mL at first determination. Plasma concentration increased with dose, but there was a large inter-individual variability (64%) and intra-individual variability was twice as small. For plasma concentrations < 1000 ng/mL, mean dose was 420 mg and for those ≥ 1000 ng/mL, this was 510 mg.

For the 189 patients having had at least 2 correct Cmin determination, 70% had initial Cmin< 1000 ng/mL (mean concentration of 1st determination: 583 ng/mL). Among the 62 patients who initially had a Cmin below 1000 ng/mL that subsequently rose above this threshold, 63% had their imatinib dose increased; the rest did not have a dose modification. For the latter, it is probable in view of low intra-individual variability that this was due to enhanced compliance. For the 32 patients with a first Cmin <1000 and no CCyR, none of those with Cmin remaining below 1000 ng/mL achieved CCyR, whereas 5 (28%) achieved CCyR when Cmin rose above 1000 ng/mL. In cases where there was suspicion of a drug–drug interaction, the most frequently combined drugs were proton pump inhibitors (such as omeprazole), diuretics, allopurinol and NSAIDs. The most recurrent adverse effects were digestive, hematological and muscular.

Although the studied population had characteristics generally described for this pathology (age, sex ratio), there was probably selection bias at the beginning of study: we received first and foremost the patients having an insufficient response, and therefore low plasma concentration. Therapeutic drug monitoring of imatinib appears to be helpful for the management of CML patients and the resulting database allows a better understanding and use of this treatment.

970 Allogeneic Myeloablative Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia in the Imatinib Era

Chronic Myelogenous Leukemia in the Imatinib Era

Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-75

Jiri Pavlu1*, Matthias Klammert1, Ian Gabriel1, Richard Szydlo1, Eduardo Olavarria1, Dragana Milojkovic1, Andrea Kew2, Katy Rezvani1, Francesco Dazzi1, David Marin1, John Goldman1 and Jane Apperley1

1Department of Hematology, Imperial College London, Hammersmith Hospital, London, United Kingdom
2Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is no longer the first treatment option for patients with chronic myelogenous leukemia (CML) but there is a considerable debate about its use as a second line therapy. When used in this indication the second-generation tyrosine kinase inhibitors (2G-TKI) induce complete cytogenetic responses (CCyR) in 40-50% of patients in chronic phase but
those without CCyR are unlikely to benefit in long term. It is therefore important to identify groups of patients with a good outcome after transplantation so that this may be offered as second line therapy where appropriate. The outcome of allo-SCT has improved over time so we restricted our analysis to the most recent 8 years to coincide with the introduction of imatinib into clinical practice. 131 patients received myeloablative transplants from January 2000 till December 2007. 67 patients were transplanted in chronic phase (14 in second and 2 in third chronic phase), 46 in accelerated phase and 2 in blastic phase. Forty-nine patients received imatinib at some point prior to transplantation and 30 of these experienced failure of imatinib therapy (as defined by European LeukemiaNet criteria).

Conditioning consisted of cyclophosphamide and total body irradiation for 51 recipients of sibling stem cells. In addition in vivo T cell depletion with anti CD52 antibody (Campath 1H) was used for 80 unrelated donor transplants. The median age of the patients was 33.4 (15 to 56) years and the median disease duration at transplant was 13 (2 to 105) months.

The probability of overall survival (OS) at 3 and 5 years was 64.8% and 62.6% respectively. We confirmed the prognostic value of the EBMT risk assessment score (Gratwohl) and pre-transplant level of the C-reactive protein (CRP) and developed a combined additive pre-transplant scoring system based on these predictive factors (EBMT risk assessment score plus 0 for CRP <2 mg/L, 1 for CRP from 2 to 10 mg/L, and 2 for CRP >10 mg/L). This identified 5 prognostic groups (Figure 1) with 3yr probabilities of survival of 92.6% (N= 27, score 0-1), 86.2% (N=29, score 2), 58.2% (N=29, score 3), 47.5% (N=20, score 4) and 30.8% (N=26, score 5 or more). The patients who failed imatinib (N=30) had significantly higher prognostic scores on the above described pre-transplant scoring system compared to the rest of patients transplanted (p=0.001). However, in a multivariate analysis adjusted for prognostic scores, their OS was significantly better (p=0.032).

The OS in the best prognostic group is comparable with that of unselected patients treated with imatinib and it is possible that their long-term survival might be better. Allogeneic transplantation is unlikely to be preferred as the first line therapy even in selected patients due to its higher early mortality but our data support its use as second line therapy in patients in chronic phase who failed imatinib and have poor pre-2G-TKI predictive factors for CCyR as determined previously at our institution (namely Sokal risk score at diagnosis, the best cytogenetic response obtained on imatinib, G-CSF requirement during imatinib therapy and time from detection of imatinib failure to onset of 2G-TKI therapy) but achieved good score on the pre-transplant scoring system. It should also be used for those whose disease is more advanced where the 2G-TKI do not offer durable remissions.

Figure 1
445 Significance of Rising Levels of Minimal Residual Disease in Patients with Philadelphia Chromosome-Positive Chronic Myelogenous Leukemia (Ph+ CML) in Complete Cytogenetic Response (CGCR)

Monday, December 8, 2008: 1:30 PM
2009-2011-2022-2024 - West (Moscone Center)

Hagop M Kantarjian¹, Jianqin Shan²*, Dan Jones², Susan O’Brien²*, Mary Beth Rios², Elias Jabbour²* and Jorge Cortes²

¹The University of Texas M. D. Anderson Cancer Center, Houston, TX
²M.D. Anderson Cancer Center, Houston, TX

Background. Patients with Ph+ CML receiving tyrosine kinase inhibitors (TKIs) are frequently monitored for response by quantitative polymerase chain reaction (QPCR) studies for minimal molecular disease. The clinical significance of rising levels of QPCR in CGCR is uncertain. Study Aims. To evaluate the relevance of increases of QPCR levels in patients with CML in CGCR on therapy. Study Group and Methods. Of 258 patients on imatinib therapy for newly diagnosed CML, 116 patients in durable CGCR on imatinib therapy for at least 18 months had significant QPCR increases (documented at least twice) as defined by literature reports. These were analyzed by the achievement of major molecular response (MMR; QPCR < 0.05%), and by the degree of QPCR increase. Results. The outcome of patients by disease status (still in MMR vs. loss of MMR vs. never in MMR) and by the QPCR level increase are shown in the Table. Only 13 of 116 patients (11%) with significant QPCR increases had CML progression; 11 of them were among 44 patients (25%) who either lost a MMR or never had a MMR, and had > 1 log increase of QPCR. The 5-year survival of all 116 patients was 92%, suggesting the minimal relevance of QPCR increases in patients in CGCR. Conclusion. Most patients with significant QPCR increases remain in CGCR. Patients who lose a MMR or never achieve a MMR, and have > 1 log increase of QPCR, should be monitored more closely, and may be evaluated for mutations of BCR-ABL kinase domain and considered for investigational therapeutic interventions. Allogeneic stem cell transplant should not be considered in view of the excellent survival.

Outcome of Patients in CGCR by QPCR Increases

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>QPCR Log increase</th>
<th>No. Patients</th>
<th>CML Progression</th>
<th>Median follow-up from QPCR increase in months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent MMR</td>
<td>Any</td>
<td>28</td>
<td>0</td>
<td>36 (3-62)</td>
</tr>
<tr>
<td>Loss of MMR</td>
<td>&gt;0.5-1</td>
<td>12</td>
<td>0</td>
<td>34 (14-59)</td>
</tr>
<tr>
<td></td>
<td>&gt;1-2</td>
<td>25</td>
<td>3</td>
<td>31 (6-52)</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>11</td>
<td>4</td>
<td>45 (20-57)</td>
</tr>
<tr>
<td>Not in MMR</td>
<td>&lt;1</td>
<td>32</td>
<td>2</td>
<td>35 (10-70)</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>8</td>
<td>4</td>
<td>25 (12-56)</td>
</tr>
</tbody>
</table>

2122 The M351T BCR-ABL Kinase Mutation Is Uncommon in Asian Patients with Imatinib-Resistant Chronic Myeloid Leukemia: Possible Relationship with Imatinib Plasma Levels

Sunday, December 7, 2008
To date, more than 50 BCR-ABL kinase domain mutations have been described in patients with imatinib-resistant (IM-R) chronic myeloid leukemia (CML) and 66% of these reported cases have mutations occurring at seven amino acid substitutions (G250, Y253, E255, T315, M351, F359 and H396) (Apperley JF. Lancet Oncol. 2007;8:1018-29). These data have been derived from a predominantly Caucasian population and the pattern of mutations among Asian patients has not been well characterized. In this study, direct sequencing of the BCR-ABL kinase domain was performed in 94 IM-R CML patients of different Asian ethnicities (52% Chinese, 19% Malay, 18% Indian and 11% of other Asian ethnic origins). The median age at diagnosis of CML was 43 years with 90% diagnosed in the chronic phase (CP), 3% in the accelerated phase (AP) and 7% in blast crisis (BC). At diagnosis, 16% had a low Sokal score, 29% an intermediate score and 54% a high score. At the time of mutation analysis, the median duration of disease was 35 months (1-192) and 56% were in CP, 16% in AP and 28% in BC. The median dose of imatinib (IM) was 600 mg OD and the median duration of treatment was 24 months (1-80). Primary IM resistance occurred in 16% and 36% had acquired resistance. The incidence of mutations detected is listed in the table below. A total of 46 BCR-ABL kinase domain mutations were detected in 42 patients. Three patients had more than 1 mutation. Compared to the reported incidence of mutations in the Caucasian population, the distribution of mutations in our study cohort was fairly similar with 55% of the mutations occurring at six amino acid substitutions (G250, Y253, E255, T315, F359 and H396). A significant difference is the absence of M351T mutation which accounts for approximately 10% of mutations detected in the Western population (p=0.017, Fisher’s exact test). This mutation has a low level IM-insensitivity (cellular proliferation IC_{50} = 880 nM) and is thought to be associated with a loss of function and may be selected on drug exposure (Griswold IJ. Mol Cell Biol. 2006;26:6082-93). A possible hypothesis for the absence of the M351T mutation in our population is that, at the same doses of IM, plasma IM levels in Asian patients are higher than that of Caucasian patients, thus resulting in the suppression of this low level IM-insensitive mutation but not of the high level IM-insensitive mutations. Pharmacokinetic analysis in a separate cohort of 27 patients treated with IM 400 mg OD in our institution revealed a mean steady-state plasma trough level of 2782 ng/ml. This level is higher than the level of 979 ng/ml reported in patients from the IRIS trial which enrolled a predominantly Caucasian population (Larson RA. Blood 2008;111:4022-28). Our study suggests that the incidence of certain BCR-ABL kinase domain mutations may vary in different ethnic origins and that this variation may be related to different pharmacokinetic profiles. This observation may have important implications for planning and monitoring the ideal therapeutic IM dose for CML patients from different ethnicities.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>n</th>
<th>%</th>
<th>Approx reported incidence (%) (Apperley, 2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T240A</td>
<td>1</td>
<td>2</td>
<td>Not reported</td>
</tr>
<tr>
<td>M244V</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>L248V</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>G250E</td>
<td>3</td>
<td>7</td>
<td>10 (incl G250A)</td>
</tr>
<tr>
<td>Q252H</td>
<td>2</td>
<td>4</td>
<td>2 (incl Q252R)</td>
</tr>
</tbody>
</table>
973 Results of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Advanced Chronic Myeloid Leukemia (CML) Patients (pts) Who Failed Tyrosine Kinase Inhibitors (TKIs) after Developing BCR-ABL Kinase Domain (KD) Mutations

Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-78

Elias Jabbour1, Jorge Cortes1, Leandro de Padua Silva2, Marcos De Lima2, Dan Jones3, Susan O’Brien1, Gabriela Rondon2, Uday Popat2, Sergio Giralt2, Hagop Kantarjian1 and Richard Champlin2

1Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
2Department of Stem Cell Transplantation & Cell Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX
3Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** HSCT is curative for many pts with CML, and may be effective after imatinib failure. Resistance to TKI therapy is often associated with point mutations in the BCR-ABL KD. **Aims:** We assessed the efficacy of HSCT in pts with CML post TKI therapy failure, and who had BCR-ABL KD sequencing. **Patients and methods:** Forty-seven pts with CML (chronic phase [CP]=34, accelerated phase [AP]=9, blast phase [BP] =4) had KD sequencing. Patient and treatment-related characteristics are described in the table. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and...
mini-methotrexate. **Results:** Nineteen pts (40%) harbored 20 different KD mutations; one pt harbored 2 different mutations. P-loop mutations were detected in 9 (45%) pts; the most common mutations were E255K and T315I detected in 4 pts, each. Table 1 describes pts characteristics. Forty-five pts (96%) engrafted within 12 days (range, 5-20). Both patients with primary graft failure received cord blood transplantation. There was no significant early regimen-related toxicity. Acute (GVHD) was observed in 28 (62%) pts (Grade I in 13, Grade II/III in 12, Grade IV in 3). Chronic GVHD was observed in 21 (47%) pts (extensive in 9). Chimerism studies at day 30 post HSCT were 100% of donor type in 27 (60%) and mixed in 18 (40%). Forty-one pts (91%) responded: 31 achieved a major molecular remission (complete in 30) and 11 (24%) achieved a complete cytogenetic response only. Three pts harboring E255K did not respond. After a median follow-up of 22 months (range, 5-53) from HSCT, 31 (66%) pts were alive; 16 patients died, 10 of disease progression, 3 of GVHD, two of uncontrollable infection, and one of unknown cause. Sixteen pts relapsed (8 of them with mutations) after a median of 8 months (range, 1-44) from HSCT. The estimated 2-year survival was 63%. Table 2 summarizes outcome by phase at HSCT and mutation status. **Conclusion:** HSCT is an important salvage option for pts with or without BCR-ABL KD mutations who develop resistance to TKI therapy. Outcomes were primarily determined by disease stage, and pts with mutations were more likely to have advanced CML at transplant, suggesting that they should be allografted once the mutation is identified after TKI failure. **Table 1. Patients characteristics**

<table>
<thead>
<tr>
<th>Total N=47</th>
<th>Mutant BCR-ABL N=19</th>
<th>Non Mutant BCR-ABL N=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ; range))</td>
<td>43 (19-64)</td>
<td>43 (19-63)</td>
</tr>
<tr>
<td>Median time from diagnosis to HSCT (mos, range)</td>
<td>54 (6-170)</td>
<td>75 (6-117)</td>
</tr>
<tr>
<td><strong>Best Response to imatinib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHR (%)</td>
<td>20 (43)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>MCyR (%)</td>
<td>17 (36)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>CCyR (%)</td>
<td>15 (32)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Failure to 2nd TKI (%)</td>
<td>29 (62)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>Ablative regimen (%)</td>
<td>9 (19)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Match related ASCT (%)</td>
<td>23 (49)</td>
<td>11 (58)</td>
</tr>
<tr>
<td><strong>Stage at ASCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP (%)</td>
<td>16 (34)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>AP (%)</td>
<td>12 (26)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>BP (%)</td>
<td>9 (19)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>2nd CP (%)</td>
<td>10 (21)</td>
<td>5 (26)</td>
</tr>
</tbody>
</table>

**Table 2. Outcomes**

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Mutant BCR-ABL (N=19)</th>
<th>Non Mutant BCR-ABL (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage @ ASCT</strong></td>
<td>CP</td>
<td>Advanced phases*</td>
</tr>
<tr>
<td></td>
<td>4 (21)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Best Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>4 (100)</td>
<td>7 (46)</td>
</tr>
<tr>
<td>CCyR</td>
<td>5 (33)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 (25)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Median (mos)</td>
<td>4</td>
<td>15 (3-45)</td>
</tr>
<tr>
<td>Alive in CR</td>
<td>2 (50)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Median (mos, range)</td>
<td>27+ (13+-40+)</td>
<td>19+ (9+-25+)</td>
</tr>
<tr>
<td>Death in CR</td>
<td>1 (25)</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

*Accelerated, blastic, and second chronic phases.
ASCT=allogeneic stem cell transplantation; MMR=major molecular response; CCyR=complete cytogenetic response; CR=complete response.
2110 Prognostic Impact of Deletions of Derivative Chromosome 9 on Patients (PTS) with Chronic Myelogenous Leukemia (CML) in Chronic Phase Treated with Nilotinib or Dasatinib

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-204

Alfonso Quintas-Cardama, MD1, Hagop M. Kantarjian, MD2*, Susan O’Brien, M.D.3*, Gautam Borthakur4, Srdan Verstovsek5, William Wierda6, Jenny Shan6* and Jorge Cortes, MD5

1Medical Oncology, UT MD Anderson Cancer Center, Houston, TX
2Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX
3Leukemia, UT MD Anderson Cancer Center, Houston, TX
4The University of Texas M.D. Anderson Cancer Center, Houston, TX
5M.D. Anderson Cancer Center, Houston, TX
6Department of Leukemia, U.T.M.D. Anderson Cancer Center, Houston, TX

Background: Submicroscopic deletions of the derivative chromosome 9 [Del der(9)] mapping to regions adjacent to the translocation breakpoints occur in 9% to 15% of patients with CML. Del der(9) is a powerful prognostic indicator associated with unfavorable prognosis in patients treated with interferon-alpha (IFN-α)–based therapies. Imatinib is currently the standard treatment for patients with CML and it appears to overcome the adverse prognostic impact imparted by Del der(9).

Methods: We investigated the prognostic impact of Del der(9) in 353 patients with CML treated at our institution with the 2nd generation tyrosine kinase inhibitors (TKIs) nilotinib (n=161) or dasatinib (n=192). The presence of Del der(9) prior to 2nd generation TKIs was investigated by FISH analysis using the LSI-BCR/ABL-(ES) probe (Vysis, Downers Grove, IL) in 245 patients. The median age was 53 years (range, 15-83) and the median follow-up was 24 months (range, 1-53). The primary endpoints evaluated were complete hematologic response (CHR), cytogenetic response, and survival.

Results: Twenty-eight (11%) patients carried Del der(9) and 217 an intact der(9). Among patients with deletions, 22 were in chronic phase (CP), 4 in accelerated phase (AP), and 2 in blast phase (BP) at the start of nilotinib or dasatinib therapy. In the group of patients without deletions, 122 were in CP, 55 in AP and 40 in BP. Overall, 229 (93%) patients were assessable for response after a median of 25 months (range, 1-53) of therapy. The outcome by CML phase is shown in Table 1.

<table>
<thead>
<tr>
<th>CML phase</th>
<th>Deletion der(9)</th>
<th>No.</th>
<th>CCyR (%)</th>
<th>p</th>
<th>EFS (12 mo)</th>
<th>p</th>
<th>OS (12 mo)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>No</td>
<td>122</td>
<td>79</td>
<td>0.77</td>
<td>86</td>
<td>0.05</td>
<td>97</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>22</td>
<td>75</td>
<td></td>
<td>60</td>
<td></td>
<td>78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP</td>
<td>No</td>
<td>55</td>
<td>36</td>
<td>1.0</td>
<td>37</td>
<td>0.47</td>
<td>60</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4</td>
<td>25</td>
<td></td>
<td>67</td>
<td></td>
<td>75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>No</td>
<td>40</td>
<td>19</td>
<td>1.0</td>
<td>0</td>
<td>0.85</td>
<td>35</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There was no difference in response rates among patients in CP, but those without Del der(9) had an improved EFS and OS at 24 months compared with those carrying Del der(9) (EFS: 86% vs 60%, p=0.05; OS: 97% vs 78%; p=0.04). Notably, whereas a trend towards worse EFS (p=0.05) and OS (p=0.12) was observed in patients in CP with Del der(9) treated with nilotinib, these outcomes were not significantly affected by Del der(9) in patients receiving dasatinib (EFS: p=0.47; OS: p=0.76).

**Conclusion:** Our results suggest that, in contrast to what has been reported with imatinib therapy, patients with CML-CP carrying Del der(9) who failed imatinib may have a worse survival than their counterparts without deletions after treatment with 2nd generation TKI. This deleterious effect is more apparent among patients treated with nilotinib than among those receiving dasatinib.

### 2125 Malignancies Occurring during Therapy with Tyrosine Kinase Inhibitors (TKI) for Chronic Myeloid Leukemia (CML) and Other Hematologic Malignancies

**Sunday, December 7, 2008**  
Hall A (Moscone Center)  
Poster Board II-219

**Dushyant Verma, MD, FACP, Hagop M. Kantarjian, MD, Mary Beth Rios, Susan O'Brien, MD, Pat Ault**, Elizabeth M. Burton*, Zeev Estrov, MD, Gautam Borthakur, MD, Srdan Verstovsek, MD, PhD, Guillermo Garcia-Manero, MD, Farhad Ravandi, MBBS and Jorge Cortes, MD

**M.D. Anderson Cancer Center, Houston, TX**

**Background:** Success of tyrosine kinase inhibitors (TKIs) (imatinib, dasatinib, nilotinib, bosutinib) in chronic myeloid leukemia (CML) has given patients (pts) hope for a long disease free survival, and with increased survival, may be some late effects of TKI treatment in the form of development of another malignancy. One prior report suggested an unexpected increased incidence of cancers among pts treated with imatinib after failure to interferon (Roy et al, Leukemia 2005). **Aims:** To investigate the frequency and characteristics of 2nd malignancies (other than AML, ALL or MDS) among pts with CML or other hematologic malignancies treated with TKI. **Methods:** We analyzed the records of 1647 pts treated with TKIs at our institution: 384 in chronic phase treated with imatinib after interferon failure, 338 treated with imatinib in advanced phases, 312 treated with imatinib as initial therapy, 422 treated with 2nd generation TKI after imatinib failure, and 109 treated with 2nd generation TKI as frontline therapy. 422 treated with 2nd generation TKI after imatinib failure, and 109 treated with 2nd generation TKI as frontline therapy. **Results:** A total of 67 (4.07%) pts (47 male, 20 female) developed a 2nd cancer. Their median age was 67 (range 31-85) years; the median follow-up after CML diagnosis was 94 (range 13-480) months (mo), and median time from start of TKI to development of another cancer was 38 (range 2-95) mo. These included 31/67(46%) pts who received imatinib as 1st line therapy for median 39.5 (range 16-88) mo, 5 pts who received 2nd generation TKI after imatinib failure (4 dasatinib, 1 bosutinib) for a median 10 (range 3-22) mo, and 1 pt received nilotinib as frontline therapy  for 3 mo before diagnosis of 2nd cancer. The accompanying table summarizes the findings. The most common cancer was non-melanoma skin cancer representing 31% of all cancers. Excluding these, the 2nd cancers were seen in 2.8% of all pts treated. The skin cancers and melanomas were scattered and not localized to any particular anatomical site. Prostate cancer patients had median age 69 (range 43-83) years and imatinib treatment of median 18-74 mo, for a cumulative incidence of 1.18% among male pts. Two patients with CLL were diagnosed on flow cytometry after loosing their hematologic response while still maintaining complete cytogenetic response (CCyR) on imatinib. After median follow up of 22 (range 1-95) mo from diagnosis of 2nd cancer, 12 (18%) pts have died (none from 2nd cancer). 49 pts continue on therapy with TKI after the diagnosis of 2nd cancer with 15 in complete molecular response (CMR), 25 with complete cytogenetic response (CCyR), 4 with partial cytogenetic response (PCyR), 5 having only complete hematologic response (CHR). All the frontline imatinib patients who are alive with a second cancer are in CCyR except one who is having CHR only.

<table>
<thead>
<tr>
<th>Type of second cancer</th>
<th>No. of patients (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Cancer (BCC+SCC)</td>
<td>21 (11+10)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7</td>
</tr>
</tbody>
</table>
Prostate cancer 11
GU cancer (Ovarian+Uterine) 2 (1+1)
GU cancer (Urinary bladder+Kidney) 4 (1+3)
GI cancer (Colon+Gastric+Esophageal) 6 (3+2+1)
GI cancer (Hepatobiliary) 1
Lung cancer 1
Thyroid cancer (Papillary+Follicular) 2 (1+1)
Thymoma 1
Lymphoma (large B-cell) 1
CLL 2
MPD 1
Breast cancer (relapse+new) 4 (2+2)
Head & neck cancer 2
Cancer of Unknown Primary 1


**Conclusion:** Second cancers occur in a small percentage of pts receiving therapy with TKI for hematologic malignancies, mostly CML. These results need to be analyzed in the context of the underlying lifetime risk of developing cancer in the general population and in cancer survivors. There is no evidence at the moment to suggest that exposure to TKI is carcinogenic.

---

**2111 Outcome of Patients with Chronic Myeloid Leukemia (CML) with Multiple ABL1 Kinase Domain Mutations during Tyrosine Kinase Inhibitor Therapy**

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-205

**Alfonso Quintas-Cardama, MD**, Hagop M. Kantarjian, Gautam Borthakur, MD, Stefan Faderl, MD, Guillermo Garcia-Manero, MD, William G. Wierda, Elizabeth M Burton and Jorge Cortes

**1**Medical Oncology, UT MD Anderson Cancer Center, Houston, TX
**2**M.D. Anderson Cancer Center, Houston, TX
**3**Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX
**4**Leukemia, U.T. M.D. Anderson Cancer Center, Houston, TX
**5**Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
**6**Dept. of Leukemia, MD Anderson Cancer Ctr., Houston, TX

**BACKGROUND:** BCR-ABL1 kinase domain mutations are the main mechanism of resistance to tyrosine kinase inhibitors (TKIs) by destabilizing the inactive conformation of the enzyme or by causing steric hindrance. Although mutations usually affect one amino acid residue within the ABL1 kinase domain, some patients have been shown to carry multiple ABL1 mutations (MAMs). The outcome of these patients is not well defined.

**OBJECTIVES:** To define the clinical characteristics and outcome of patients harboring MAMs detected by direct sequencing during TKI therapy.

**RESULTS:** MAMs were detected in 24 patients (5%) among a series of 502 patients assayed during TKI therapy: 22 with CML and 2 with BCR-ABL1-positive acute lymphoblastic leukemia (Ph+ALL). Median age was 57 years (range, 27-92). Median time from diagnosis to ABL1 mutation detection was 54 months (range, 8-254) and to detection of MAMs 77 months (range, 8-261). Overall, 21 different mutations affecting 15 amino acid residues were detected. The most frequent mutations were M351T (n=7), T315I (n=6), Y253H (n=6), G250E (n=6), and F317L (n=5). P-loop mutations (residues 244-255) were found in 16 (67%) patients. At the time of detection of MAMs, 13 patients were in CP, 4 in AP, and 7 in BP. Patients had received a median of 5 prior therapies (range, 2-9), including 2 TKIs (range, 1-4). Best response to TKI therapy prior to detection of MAMs (24 imatinib, 10 nilotinib, 15 dasatinib, 6 SKI-606, 1 INNO-406, 1 MK-0457) was complete hematologic response (CHR) in 16 (67%) patients and cytogenetic response in 7 (29%); complete [CCyR] in 4, partial [PCyR] in 1, minor [mCyR] in
Patient Education Material

1. One patient had achieved a complete molecular response (CMR).

The median follow-up from the detection of MAMs was 10 months (range, 1–51). Twenty-two patients received a 2nd generation TKI after imatinib failure. Among 13 with MAMs prior to start of 2nd generation TKI, 7 (54%) responded (5 CHR, 1 return to CP, and 1 CCyR) for a median of 6.5 months (range, 2–31). By contrast, all 9 (100%) patients without MAMs prior to 2nd generation TKI responded (4 CHR, 3 CCyR, 1 PCyR, 1 CMR) for a median of 43 months (range, 7–48) (p=0.005).

Although most patients with MAMs prior to 2nd generation TKIs start had short-lived responses to those agents, those were sustained for significant periods of time in 3 patients: one in BP harboring simultaneously M244V and M351T achieved a CHR and a mCyR with dasatinib 35mg twice daily, sustained for 8 months. A second patient acquired M351T and F359V while receiving imatinib 800mg/d in CP. Therapy with bosutinib 300mg/d rendered a mCyR that has been sustained for more than 9 months. A third patient in AP receiving imatinib 800mg/d acquired G250E and F317L mutations. Therapy with nilotinib 800mg/d resulted in CCyR for 33 months; although F317L became undetectable, CCyR was lost and later regained and has been ongoing for the last 11 months on bosutinib 500mg/d.

Four patients underwent allogeneic stem cell transplant (allo-SCT) and 2 are alive: 1 in CHR 2+ months after allo-SCT and 1 who relapsed 3 months post transplant and is currently in CCyR (BCR-ABL1/ABL1 ratio 0.55%) after 19+ months on dasatinib. Ten (42%) of the 24 patients died. The 2-year survival for patients in CP, AP, or BP at the time of detection of MAMs was 86%, 50%, and 0%, respectively. CONCLUSION: Patients expressing more than 1 ABL1 kinase domain mutation respond poorly to TKI therapy. Responses to 2nd generation TKIs, when they occur, are mostly hematologic and typically last <12 months. The long-term survival of patients with MAMs is highly influenced by CML phase.

1098 Efficacy and Safety of Bosutinib (SKI-606) in Patients with Chronic Phase (CP) Ph+ Chronic Myelogenous Leukemia (CML) with Resistance or Intolerance to Imatinib

Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-203

Jorge Cortes, MD, Hagop M Kantarjian, Dong-Wook Kim, MD, PhD, H. Jean Khoury, MD, FACP, Anna G. Turkina, MD, Zhi-Xiang Shen, MD, Tim H Brummendorf, MD, Mammen Chandy, MD, Steven Arkin, MD and Carlo Gambacorti-Passerini, MD

1M.D. Anderson Cancer Center, Houston, TX
2The University of Texas M. D. Anderson Cancer Center, Houston, TX
3Hematology, St. Mary's Hospital, Seoul, South Korea
4Emory University, Atlanta, GA
5Hematology Research Center, Russia
6Rui Jin Hospital, China
7Universitäts-Klinikum Hamburg-Eppendorf, Hamburg, Germany
8Christian Medical College Hospital, India
9Wyeth Research, Cambridge, MA
10University Milano Bicocca, Monza, Italy

Bosutinib (SKI-606) is an orally bioavailable dual Src/Abl inhibitor demonstrating inhibitory activity against BCR-Abl phosphorylation, and is 200 times more potent than imatinib but with minimal inhibition of platelet-derived growth factor receptor (PDGFR) or c-kit. The phase I portion of this study identified a treatment dose of 500 mg daily and showed evidence of clinical efficacy. The phase II portion of the study to investigate the efficacy and safety of bosutinib in patients (pts) with CP Ph+CML who have failed imatinib therapy is ongoing. Preliminary data for 283 treated pts, median age 54 yrs (range 18 – 91 yrs) and 52% male are reported. A subset of pts received treatment in addition to imatinib, including interferon (91 pts), dasatinib (71 pts), nilotinib (7 pts) and stem cell transplant (13 pts). Among pts who failed imatinib (and received no other tyrosine kinase inhibitor treatment), 137 were imatinib-resistant (all received imatinib ≥600mg) and 64 pts were imatinib-intolerant; median duration of bosutinib treatment to date is 7.7 mos (range 0.2 – 28.2 mos) and 4.5 mos (range 0.5 – 21.5 mos), respectively. Among 67 imatinib-resistant pts evaluable for hematological response, 53 (79%) had complete hematological response (CHR). Of 84 imatinib-resistant pts evaluable for cytogenetic response, 34 (40%), achieved a major cytogenetic response (MCyR), including 24 (29%)
with a complete cytogenetic response (CCyR). Of 34 pts with MCyR, 31 have maintained their response to date. Of 60 evaluable imatinib-resistant pts, 20 (33%) achieved major molecular response, 10 (17%) of which were complete. Among imatinib-intolerant pts, 22 of 29 evaluable (76%) achieved CHR, and 13 of 22 evaluable (59%) achieved MCyR, including 11 (50%) with CCyR. Of 25 evaluable imatinib-intolerant pts, 7 (28%) achieved major molecular response, 5 (20%) of which were complete. Of 105 pts with baseline samples tested for mutations, 17 different mutations were found in 45 pts (43%). CHR occurred in 5/6 pts (83%) with P-loop mutations and 13/17 (76%) with non-P-loop mutations; MCyR occurred in 3/6 pts (50%) and 11/24 pts (46%), with P-loop and non-P-loop mutations, respectively. Treatment was generally well tolerated. The most common adverse events among treated pts (n=283) were gastrointestinal (nausea, vomiting, diarrhea), these were usually grade 1 – 2, manageable and transient, diminishing in frequency and severity after the first 3 – 4 weeks of treatment. Grade 3 – 4 non-hematologic toxicity occurring in ≥5% of pts were diarrhea (8%), rash (8%) and increased ALT (5%). 27 pts (10%) reported grade 1/2 fluid retention adverse events, including 21 pts with edema, and 6 pts with effusions: 4 pleural, 1 pericardial, and 1 pleural and pericardial. A single patient experienced grade 3 pleural effusion possibly related to bosutinib with concomitant pneumonia and a pre-treatment history of recurrent pleural effusions. Grade 3 – 4 hematologic laboratory abnormalities included thrombocytopenia in 65 pts (23%), neutropenia in 37 pts (13%) and anemia in 17 pts (6%). 124 pts (44%) had at least 1 temporary treatment interruption and 85 pts (30%) had at least 1 dose reduction due to toxicity. 37 pts (13%) have permanently discontinued treatment due to adverse event. Bosutinib is effective in pts with CP CML with resistance or intolerance to imatinib across a range of mutations. Unlike other tyrosine kinase inhibitors, bosutinib does not significantly inhibit PDGFR or c-kit, and this may be responsible for the relatively favorable toxicity profile with few pts experiencing hematologic toxicity or fluid retention.
various E:T ratio (5:1, 10:1, 20:1, 35:1) and incubated 4 hours at 37°C. After co-incubation, Propidium Iodide (PI) red fluorescent was applied and the samples were run on flow cytometer for the determination of DIOC+/PI+ dead cells. Spontaneous cell death was determined by incubation at 37°C of target cells alone and maximum cell death was determined by incubation of target cells with 2% paraformaldeide. Control experiments included different effector cells: 1) freshly isolated CD4+ T cells from the same 3 vaccinated patients not further in vitro expanded (in this experimental condition the percentage of b3a2-25-specific CD4+/CD25+/Fopx3+ is about 10% of total CD4+ cells while b3a2-specific CD4+/perforin+ is about 2%); 2) CD4+ T cells in vitro stimulated with IL-2 (without b3a2-25 peptide) from healthy subjects or from not previously vaccinated CML patients. Our results showed a specific killing of JURL-MK2 cells only in the presence of expanded peptide-specific CD4+ T cells from all 3 vaccinated patients with a linear increase of DIOC+/PI+ target cells from 5.3% (E:T 5:1) to 33% (E:T 35:1). No cytotoxicity was observed when CD4+ cells were expanded from healthy donors of from not vaccinated patients ruling out the possibility of killing mediated by a “non specific” activation of CD4+ cells due to IL-2 exposure. On the contrary, specific cytotoxicity appeared to correlate to the increased percentage of peptide-specific CD4+ cells obtained after in vitro re-stimulation with b3a2-25 peptide, as only background killing was observed when freshly isolated CD4+ T cells from all 3 vaccinated patients were cultured with JURL-MK2 cells. In conclusion, CMLVAX100 induced b3a2-25-peptide specific CD4+ T cells appear to exert direct cytotoxicity toward b3a2-CML JURL-MK2 cells. To our knowledge this is the first time that CML-peptide specific CD4+/cytotoxic T cells are induced in vivo and they could mediate the minimal disease reduction observed after CMLVAX100 vaccinations in CML patients. Experiments focused on determining which subtype, CD4+/CD25+/Fopx3 or CD4+/perforin+, is the main effector of cytotoxicity as well as experiments clarifying if CD4+ cytotoxicity is mediated by HLA-DR molecules presentation of b3a2-p210 derived peptides are ongoing.

332 Prediction of Cytogenetic Response to Second Generation TKI Therapy in CML Chronic Phase Patients Who Have Failed Imatinib Therapy and Early Identification of Factors That Influence Survival

Monday, December 8, 2008: 11:15 AM
2009-2011-2022-2024 - West (Moscone Center)

Dragana Milojkovic, Marco Buà, Jane F Apperley, Kasia Kozlowski, Jamshid Sorori, Letizia Foroni, Alistair Reid, Jiri Pavlu, Katy Rezvani, Francesco Dazzi, Eduardo Olavarria, Matthias Klammer, John M Goldman and David Marin

Department of Hematology, Imperial College London, Hammersmith Hospital, London, United Kingdom

Second generation tyrosine kinase inhibitors (2G-TKI) have displaced allogeneic stem cell transplant as the preferred therapy for patients with CML in chronic phase (CP) who fail imatinib. However a significant proportion of patients still fail to respond to 2G-TKI and may benefit from alternative therapy (including stem cell transplant). We have performed univariate and multivariate analyses in our cohort of 80 patients treated with dasatinib (n=67) or nilotinib (n=13) while still in first CP after imatinib failure in order to identify those patients who will benefit most with these therapies.

The median age was 50 years and 46% were male; 72 patients were resistant to imatinib (2 primary haematological resistance, 40 primary cytogenetic, 32 secondary cytogenetic and 25 developed secondary hematologic resistance) and 8 were intolerant. 20 had developed kinase domain mutations while on imatinib therapy. 31 and 29 patients received maximal doses of imatinib 600 and 800 mg per day respectively. The median follow up was 28.3 months (range 6-42).

The 3-year cumulative incidence of CCyR was 52.6%. The multivariate analysis identified four pre-2G-TKI independent predictive factors for CCyR, namely low Sokal risk score at diagnosis, the best cytogenetic response obtained on imatinib, G-CSF requirement during imatinib therapy and time from detection of imatinib failure (as defined by European LeukemiaNet criteria) to onset of second 2G-TKI therapy. Using these factors we devised a scoring system that could be used to predict the probability of achieving CCyR on 2G-TKI therapy. The score was calculated by allocating one point when any one of the following four features was present: (1) intermediate or high Sokal risk group, (2) need of G-CSF support during imatinib therapy, (3) institution of 2G-TKI more than 18 months after imatinib...
failure, and (4) failure to achieve a cytogenetic response on imatinib (≥95% Ph-pos). The 3-year cumulative incidence of CCyR for patients with 0-1 points was 95.6%, with 2 points 50% and with 3-4 points 18.7% (p<0.0001, Figure 1).

For the 80 patients the probability of 3-year survival was 89.6%. We performed a 3-month landmark analysis to study the relationship between molecular response and subsequent outcome. The 44 patients with a BCR-ABL1/ABL ratio less than 15% at 3 months had a 3-year overall survival of 100% while the 36 patients with a ratio >15% had a survival of 77.4% (p=0.003, Figure 2). We performed a multivariate analysis including all relevant variables defined at the start of 2G-TKI and the 3-month transcript level. The 3-month transcript level was the only independent predictor for survival.

Similarly we performed a 6-month landmark analysis where we explored the relationship between cytogenetic response and outcome. Patients who had achieved a MCyR (n=38) or a CCyR (n=32) had a significantly better survival than those with lower levels of cytogenetic response (100% vs. 79.2% (p=0.006) and 100% vs 82.6 (p=0.02)) respectively. We also performed a multivariate analysis including the variables defined at the initiation of therapy, the 3-month transcript levels and the cytogenetic response at 6 months. Interestingly the 3-month molecular response was the only independent variable predicting for survival. Similar results were found for progression-free survival (data not shown).

We conclude that factors measureable before starting treatment with 2G-TKI may be valuable for predicting response; molecular responses at 3-months and cytogenetic responses at 6 months provide further information about the value of continuing treatment with 2G-TKI.

---

**2121 Imatinib Discontinuation Following a Major Molecular Response: Impact of Interferon Alpha and Leukemia Stem Cell Burden (The STOP Study)**

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-215

**Perttu Koskenvesa, MD1, Satu Mustjoki, MD, PhD1, Anu Räsänen, MD2, Mirja Vapaatalo, MD3, Kari Remes, MD, PhD4, Tuija Lundán, MSc, PhD5, Jukka Vakkila, MD, PhD6, Bengt Simonsson, MD, PhD7 and Kimmo Porkka, MD, PhD1**

1Hematology Research Unit, Department of Medicine, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland
2Department of Hematology, Kymenlaakso Central Hospital, Kotka, Finland
3Department of Hematology, Hyvinkää Hospital, Hyvinkää, Finland
4Department of Medicine, Turku University Central Hospital, Turku, Finland
5Hematology Research Unit, Department of Medicine and Laboratory of Molecular Pathology,
Tyrosine kinase inhibitor (TKI) imatinib mesylate (IM) is the standard of care for patients with chronic myeloid leukemia (CML). Leukemia-initiating CML stem cells are resistant to TKIs and thus it is unlikely that CML patients will be cured with IM monotherapy. Recent data indicate that in a proportion of CML patients primed with preceding interferon alpha (IFNα) therapy, IM may be discontinued without rapid leukemia re-expansion. In the Nordic CML study group intermediate and low risk study (IR/LR, NordCML002), newly diagnosed CML patients were randomized after 3 months of IM induction therapy to receive 12 months of either standard IM monotherapy or IM-IFNα combination therapy. In the STOP study (NordCML004) we prospectively discontinued IM and IFNα in IR/LR study patients who achieved major molecular response (MMR) during 12 months of randomized therapy (n=10; IM 5, IM-IFN 5). In this study the monotherapy patients continued imatinib 400mg QD for 6 months while the combination therapy patients stopped IM at study entry and continued IFNα for 6 months. Molecular monitoring by blood RQ-PCR was done monthly after any drug discontinuation. In the monotherapy group IM was reinitiated when a confirmed loss of MMR was seen. In the IFNα group a rise up to the -2 log (1%) level was allowed before restart. The patients in the monotherapy group had received IM for a median of 23 months (range 21-25 mos) at the time therapy was discontinued. Four of the 5 patients had complete molecular response (CMR); 1 patient had a 3,2 log reduction. No Philadelphia positive (Ph+) cells were detected in either the CD34 positive or the CD34 positive/CD38 negative cell fractions prior to drug discontinuation when analyzed by FISH (n=3, 1000 cells counted). All 5 patients lost MMR rapidly within 4 months. The median time of IM discontinuation was 114 days (range 64-166 days). All evaluable patients re-responded to IM promptly. In the combination therapy group the median duration of IM therapy was 18 months (range 15-19 mos). The patients had used IFNα (Pegintron®) for a median of 14 months (range 12-16 mos). The target dose of 50 μg s.c. once weekly was used by 3 patients and 2 patients used only 20 μg s.c. once weekly due to toxicity. Four of the 5 patients had CMR when they stopped IM; 1 patient had a 3,2 log reduction. As in the monotherapy group no Ph+ cells were detected in the examined stem cell fractions prior to drug discontinuation (n=2). Two of the 5 patients rapidly relapsed within 4 months while still using IFNα corresponding the monotherapy patients. Three patients discontinued all treatment. One patient was in MMR and 2 had log-reductions between 2-3 log units. The latter 2 patients relapsed after 3 months off all treatment. One patient is still in sustained MMR at 18 months off IM and 12 months off all treatment. The median time of IM discontinuation for the combination therapy group is 277 days (range 151-559+ days). Relapsed patients have started IM monotherapy and all have re-responded. In conclusion, in concord with previous data, discontinuation of IM monotherapy in patients having MMR/CMR resulted in a rapid disease relapse in all patients. However, in 3 out of 5 patients concomitant IFNα enabled IM discontinuation by inducing a state of stable minimal residual disease. One of these patients has been able to discontinue both IM and IFNα and sustain MMR for a considerable time. The occurrence of relapse was not correlated with the number of residual leukemic stem cells as no Ph+ CD34+/CD38- cells were detected prior to drug discontinuation in either group (n=5). Further clinical studies on combinations of TKIs and IFNs are warranted. Elucidating the molecular and immunological mechanisms of priming effects of IFN would enable rational patient selection and putatively result in operational cure of a significant number of CML patients.
2112 Association of Pleural Effusion and Bleeding in Patients with Chronic Myelogenous Leukemia Receiving Dasatinib

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-206

Alfonso Quintas-Cardama, MD1, Hagop M. Kantarjian2*, Susan O’Brien, M.D.3, Farhad Ravandi, MBBS1, Alessandra Ferrajoli5, Guillermo García-Manero, MD6 and Jorge Cortes, MD2

1Medical Oncology, UT MD Anderson Cancer Center, Houston, TX
2M.D. Anderson Cancer Center, Houston, TX
3Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX
4Department of Leukemia, M.D. Anderson Cancer Center, Houston, TX
5Department of Leukemia, U.T.M.D. Anderson Cancer Center, Houston, TX
6Leukemia, U.T.M.D. Anderson Cancer Center, Houston, TX

BACKGROUND: Dasatinib is an oral potent multikinase inhibitor that has demonstrated high efficacy and safety in patients (pts) with chronic myelogenous leukemia (CML). Pleural effusion (PE) and bleeding (BL) occur in some patients receiving dasatinib, frequently resulting in therapy discontinuation. The incidence of the occurrence of both events in the same pt either concomitantly or sequentially is unknown.

METHODS: We evaluated the incidence of PE and BL either simultaneously or sequentially among 138 consecutive pts (69 female) with CML after failure of imatinib treated at our institution in phase I and II studies of dasatinib between November 2003 and January 2006.

RESULTS: The median age for the entire cohort was 57 years (range, 15-81), median time on imatinib 164 wks (range, 21-253). Among 50 pts treated in the phase I study, 23 (46%) were in chronic (CP), 7 (14%) in accelerated (AP), and 20 (40%) in blastic phase (BP) at the time of dasatinib start, whereas 88 pts received dasatinib in phase II studies, 43 (49%) in CP, 25 (28%) in AP, and 20 (23%) in BP. Fifteen (11%) pts started dasatinib at a dose <100 mg, 22 (16%) at 100 mg, 92 (67%) at 140 mg, and 9 (6%) at >140 mg daily. The median time on dasatinib was 42 wks (range, 4-120). PE occurred in 48 (35%) pts, being grade 3–4 in 23 (17%). The median time to its development was 5 wks (range, 1 to 107). PE occurred in 29% of pts in CP, 50% in AP, and 33% in BP. Thirty-seven BL episodes were recorded in 32 (23%) pts. Seven (5%) pts had grade 1, 16 (12%) grade 2, 9 (7%) grade 3, and none grade 4-5 BL. The median time to development of BL was 6 weeks (range, 0.5-38), occurring within the first 3 months of therapy in 22 (69%) pts. BL occurred in 12% of pts in CP, 31% in AP, and 35% in BP. Basic coagulation studies were normal in all pts. Fourteen (37%) BL episodes occurred with platelets >100x10^9/L (2 with normal platelet counts). Seventeen (12%) patients had both PE and BL (2 CP, 5 AP, and 11 BP), representing 36% of those with PE and 53% of those with BL. PE preceded BL

The CML Advocates Network – www.cmladvocates.net
in 8 pts while BL preceded PE in 9. The median time from dasatinib start to PE was 28 days (10-230) and to BL was 34 days (3-218). The median time between PE and BL was 17 days (range, 4-216). Six pts had grade 1, 3 grade 2, and 7 grade 3 PE, whereas 4 had grade 1, 10 grade 2, and 3 grade 3 BL ($\gamma$=0.03). The median hemoglobin drop was 2.1 g/dL (range, 1.1-4.5). PE and BL were more frequent among pts treated at daily doses $\geq 140$ mg compared to those treated at $\leq 100$ mg (100% vs 0%) and among those receiving dasatinib twice daily compared to once daily (88% vs 12%; $p=0.001$). Dasatinib was discontinued for a median of 10 days (median, 0-97) and the dose reduced in 7 pts due to PE. Loop diuretics were given to 10 pts, steroids to 2, and thoracentesis was required in 4 pts with PE, all of the latter demonstrating exudative features (median 91% lymphocytes [range, 73-100]). Dasatinib dose was discontinued for a median of 10 days (range, 0-23) and the dose reduced in 6 pts due to BL. BL types included gastrointestinal in 14 (82%) pts (lower in 11, upper in 3), gingival in 2, and epistaxis in 1. Nine patients had endoscopic examination demonstrating inflammatory changes (n=4), gastric ulcer (n=1), rectal ulcer (n=1), no lesion (n=3). Twelve pts required transfusions of packed red blood cells (PRBCs) and platelets, 3 only platelets, 1 only PRBCs, and 1 none. Dasatinib was terminated due to PE in 1 and due to BL in 2.

**CONCLUSION:** PE and BL can occur in a subset of pts with CML during dasatinib therapy, particularly among pts with AP or BP receiving dasatinib $\geq 140$ mg twice daily. Appropriate clinical monitoring, transient dasatinib interruption and dose reduction are required to adequately manage these complications.

**3218 Characteristics of Chronic-Phase CML Patients Having Durable Cytogenetic Response to Low-Dose Imatinib**

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-300

Tatsuya Kawaguchi, MD, PhD∗, Akinobu Hamada, PhD∗, Reiko Nakashima‡, Kentaro Horikawa, MD, PhD∗, Sonoko Ishihara, MD, PhD†, Hideyuki Saito, PhD‡ and Hiroaki Mitsuya, MD, PhD†

∗Hematology & Infectious Diseases, Kumamoto University, Kumamoto, Japan
‡Pharmacy, Kumamoto University, Kumamoto, Japan

Imatinib mesylate (IM), a BCR-ABL tyrosine kinase inhibitor, has been established as first-line treatment of chronic-phase chronic myeloid leukemia (CML). On the basis of the IRIS study, 400mg/day IM has been recommended as an initial dose for adult CML patients. Although most patients usually tolerate the recommended dose, serious adverse effects such as grade 3 or 4 cytopenia may occur and require dose reduction of IM to 200-300mg/day. In fact, 8% of patients were receiving less than 400mg IM during 5-year follow-up in the IRIS study (Druker et al, New Engl J Med, 2006). In clinical settings, low-dose IM is actually effective for some patients; however, clinical and laboratory features of such patients have not been well investigated. Recently, it was demonstrated that the effective plasma threshold for trough IM levels should be maintained above 1,002 ng/ml to obtain maximal effects in CML patients (Picard et al, Blood, 2007). In this regard, determination of trough IM plasma levels may help to predict efficacy of low-dose IM. To evaluate the association of optimal IM doses with trough IM levels and patients’ basic characteristics such as body surface area (BSA), we assessed trough plasma concentrations of IM using high performance liquid chromatography (Hamada et al, J Pharmacol Exp Ther, 2003) in 31 chronic-phase CML patients, who were treated in Kumamoto University Hospital during 2003 to 2007. An optimal dose of IM was determined by a favorable response to IM achieving complete cytogenetic response and tolerable adverse events. Twenty-seven patients tolerated IM therapy during the observation period: optimal doses of IM were 400mg/day in 13 patients, 300mg/day in 9 patients, and 500 or 600 mg/day in 5 patients. Four patients discontinued IM for some reasons: two for toxicity, one for a concomitant unrelated disease and one for inefficacy due to drug-resistance. The trough plasma concentrations of IM were 1.64±0.68 µg/ml (mean±SD) in patients on the standard dose of 400mg/day IM (standard dose group) and 1.38±0.53 µg/ml in patients on the reduced dose of 300mg/day IM as an optimal dose (reduced dose group). Both mean trough levels of two groups showed no significant difference and exceeded the effective plasma threshold. Interestingly, BSA was significantly smaller in patients of the reduced dose group than those of the standard dose group (1.50± 0.16 vs. 1.75 ± 0.15 m² [mean± SD], p=0.001). An optimal IM dose was found to be significantly associated with age and gender as well as BSA. These results suggest that the reduced dose of 300mg/day IM may be sufficient for the
treatment of CML patients with smaller body sizes. Monitoring of trough IM levels should enable proper management of individual patients in combination with regular monitoring of optimal response to IM.

184 Randomized Comparison of Imatinib 400 Mg Vs. Imatinib + IFN Vs. Imatinib + AraC Vs. Imatinib after IFN Vs. Imatinib 800 Mg: Optimized Treatment and Survival. Designed First Interim Analysis of the German CML Study IV

Monday, December 8, 2008: 7:45 AM
Halls B and C (Moscone Center)

Ruediger Hehlmann, MD, Susanne Saussele, MD, Michael Lauseker, Ulrike Proetel, MD, Elena Kovalevskaya, MD, Armin Leitner, MD, Claudia Haferlach, MD, Brigitte Schlegelberger, MD, Martin C Müller, MD, Benjamin Hanfstein, MD, Markus Pfirrmann, PhD, Gerhard Ehnninger, Thomas Fischer, MD, Joerg Hasford, MD, Andreas Hochhaus, MD, Dieter K. Hossfeld, MD, PhD, Hans-Jochem Kolb, MD, Stefan W Krause, MD, Christoph Nerl, MD, Hans Pralle, MD, Alois Gratwohl, Andreas Tobler, MD, Hermann Heimpel, MD and The German CML Study Group

In spite of favorable response and survival results for the majority of CML patients on imatinib therapy, in a substantial minority imatinib fails or shows suboptimal responses. A treatment optimization study was therefore designed to compare in a randomized fashion standard imatinib vs. imatinib + interferon alpha (IFN) vs. imatinib + low dose araC vs. imatinib after IFN (for low- and intermediate-risk patients) or vs. imatinib 800 mg (for high-risk patients). Inclusion criteria were newly diagnosed BCR/ABL positive CML in chronic phase. In July 2005, randomization to the arms imatinib + araC and imatinib after IFN was discontinued and recruitment for imatinib 800 mg was expanded to low- and intermediate-risk patients. Primary goals are: rates of hematologic, cytogenetic and molecular remissions, duration of chronic phase, overall survival, adverse events and analysis of subsequent allografting. Since its activation in 7/2002, 1203 patients have been randomized. The current evaluation represents the first of three designed, statistically adjusted interim analyses of 710 patients randomized by the end of 2005 with a follow-up of at least 2 years. Analysis was according to intention to treat. 666 patients (545 with primary imatinib, 121 with primary IFN) were evaluable for hematologic, 621 for cytogenetic, and 631 for molecular responses. Median age was 53 years, 60% were male, median values were for Hb 12.5 g/dl, WBC 71.2/nl and platelets 384/nl, 35% had low, 53% intermediate and 12% high risk (Euro score). Median observation time was 3.5 years. Median duration of IFN pretreatment was ~4 months. At 1 year, the cumulative incidence of complete hematologic remission (CHR) was 82.3% and 74.4%, of major cytogenetic remission (MCR) 65.6% and 40.6%, of complete cytogenetic remission (CCR) 52% and 19.7%, and of major molecular remission (MMR) 33.2% and 4.7% for primary imatinib and IFN therapies, respectively. At 3 years, the cumulative incidence of CHR was 96.4% and 93.8%, of MCR 89.5% and 89.1%, of CCR 85.2% and 78.5%, and of MMR 79% and 63% for primary imatinib and IFN therapies, respectively. 5-year-survival probability of all patients currently exceeds 90% (94% for imatinib- , 91% for IFN-based therapy, Figure 1). Event
free survival after two years (no progression, no death, CCR within the first 18 months, no loss of CHR or MCR) was 80.3%. 36 patients died, 51 patients were transplanted in first chronic phase, and 80 patients progressed, 43 of which were switched to alternative treatments (16 to new drugs, 18 to transplantation, 9 received both). Type and severity of adverse events (AE) did not significantly differ from those reported previously. Hematologic AEs (leukopenia, thrombocytopenia) were most frequent in the imatinib 800 mg arm. Nonhematologic AEs (gastrointestinal) were most frequent in the combination arms and with imatinib 800 mg. In no case recruitment had to be changed due to superiority or inferiority of any arm. This applies also to the high dose imatinib arm where earlier response might translate into better survival. In conclusion, this first interim analysis shows favorable survival and long term response rates. Imatinib in combination with, or after, IFN or with low dose araC are feasible and equally safe treatment alternatives. More definite information will be provided by the next interim evaluation after recruitment has been terminated.

SHAPE \* MERGEFORMAT

---

1099 Imatinib Long Term Effects (ILTE) Study: An Independent, International Study in CML Patients

Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-204

Carlo Gambacorti-Passerini\textsuperscript{1}, Dong-Wook Kim\textsuperscript{2}, François-Xavier Mahon\textsuperscript{3}, Giuseppe Saglio\textsuperscript{4*}, Fabrizio Pane\textsuperscript{5}, François Guilhot\textsuperscript{6}, Michael W.N. Deininger\textsuperscript{7}, Arnon Nagler\textsuperscript{8}, Alessandro Rambaldi\textsuperscript{9}, Enrica Morra\textsuperscript{10}, Laura Antolini\textsuperscript{1*}, IL-Young Kweon\textsuperscript{2*}, Josy Reiffers\textsuperscript{3*}, Lucia Tornaghi\textsuperscript{1*} and Maria Grazia Valsecchi\textsuperscript{11*}

\textsuperscript{1}Dept of Clinical and Preventive Medicine, Università Milano Bicocca, Monza, Italy
\textsuperscript{2}Division of Hematology, St. Mary's Hospital, Seoul, South Korea
\textsuperscript{3}Université Victor Segalen Bordeaux - Institut Bergonié, Bordeaux, France
\textsuperscript{4}Internal Medicine and Hematology, Università di Torino - Ospedale San Luigi, Orbassano, Italy
\textsuperscript{5}A.F. di Oncologia Ematologica Diagnostica, Azienda Ospedaliera, Napoli, Italy
\textsuperscript{6}Clinical Investigational Centre INSERM 802, CHU Poitiers, Poitiers, France
\textsuperscript{7}Cell and Developmental Biology, Oregon Health and Science University, Portland, OR
Imatinib is an effective first line therapy for chronic myeloid leukemia (CML) and has substantially changed its biological and clinical behavior. Durable complete cytogenetic responses (CCyR) were reported in the majority of patients, with a rather benign side effect profile, despite the ‘off target’ inhibition of several other kinases, including Kit, PDGFR and Lck. Since available information is largely based on industry-sponsored trials and long-term field studies are lacking, the ILTE study was conceived as an industry-independent, academic, multicenter trial supported by the Italian Drug Safety Agency (AIFA). ILTE is an international study on a retrospective cohort and includes 31 centers in Europe, North/South America, Africa and Asia; therefore it is uniquely positioned to present a global picture of imatinib long-term effects. Consecutive patients with Ph+ CML who started imatinib between 01 September 1999 and 31 December 2004 were eligible if they were in Complete Cytogenetic Response (CCyR) after two years of imatinib treatment. Study endpoints were (a) survival, (b), serious adverse events (SAE, including second cancers), (c) toxicities not qualifying as SAE (NSAE) but judged by the referring physician as substantially impacting quality of life, (d) loss of CCyR, and (e) development of PCR negativity. A total of 957 patients were enrolled, 92% of which met eligibility criteria. The median age of eligible patients was 50 (range 15-92) years; 59% of patients were males and the median follow-up was 3.1 years (excluding the first 2 years of treatment). As of Dec. 31 2007, 2564 person years were available for analysis. Eleven deaths were observed (only 3 of them caused by relapsed CML), with a standardized rate of 0.4/100 person years and an observed/expected ratio of 0.48 (95% CI = 0.24-0.85). One-hundred SAE were recorded (rate 3.9/100 person years, most frequent type “heart failure”), with 21% being considered related to imatinib. Second cancers were documented in 28 patients (rate 1.1/100 person years), with an observed/expected ratio of 1.27 (95% CI = 0.84-1.84). Among the 576 NSAE recorded (0.65/patient) the most frequent types were “edema, cramps, skin fragility, diarrhea”; 71% of them were related to imatinib. A total of 12 patients (1.4 %) discontinued imatinib because of toxicities during the period of observation. Thirty-four patients lost CCyR, corresponding to a rate of 1.4/100 person years (1.0 in patients with imatinib as first-line treatment, 1.5 in patients who were treated with imatinib >6 months after diagnosis), with stable or increasing rates over time. Finally, 214 patients (24.5%) developed durable (> 1 year) PCR negativity.

In conclusion, the first report from ILTE shows that CML patients on imatinib die infrequently of CML related causes, do not appear to have substantially higher second cancer rates than the general population, have mortality rates lower than expected in an age/sex matched population and do not show new types of imatinib-related adverse events. They also experience a low but steady rate of loss of CCyR and develop PCR negativity in approximately ¼ of cases. Follow-up and further analysis are ongoing. (Presented on behalf of the ILTE Investigators group)
Chronic myeloid leukemia (CML) is a stem cell disease characterized by the BCR/ABL oncoprotein. The ABL kinase inhibitor imatinib is effective in most patients and considered standard first line therapy. However, not all patients show a long-lasting response. Treatment failure is usually associated with the occurrence of imatinib-resistant mutants of BCR/ABL. For these patients, novel multi-kinase inhibitors such as dasatinib represent alternative treatment options. Still, however, not all patients respond to these drugs, especially when leukemic cells bear the BCR/ABL mutant T315I that confers resistance against most kinase-blockers. Bosutinib is a novel multi-kinase inhibitor that has been described to act growth-inhibitory in ABL-transformed leukemias. In the current study, we examined the effects of bosutinib alone and in combination with dasatinib on growth and survival of CML cells. Bosutinib was found to inhibit 3H-thymidine uptake and thus proliferation in imatinib-sensitive and imatinib-resistant K562 cells in a dose-dependent manner, with identical IC_{50} values (10-100 nM). Moreover, bosutinib was found to inhibit the growth of primary CML cells and Ba/F3 cells bearing various imatinib-resistant mutants of BCR/ABL, except the T315I mutant (IC_{50}>1 µM). The growth-inhibitory effects of bosutinib were found to be associated with signs of apoptosis. Dasatinib showed similar effects on CML cells, and again did not block the growth of subclones bearing BCR/ABL T315I. Unexpectedly, however, we found that bosutinib and dasatinib synergize with each other in producing growth inhibition in primary CML cells exhibiting BCR/ABL T315I at pharmacologic concentrations (0.01-1 µM). Clear synergistic effects were also observed in imatinib-sensitive and imatinib-resistant K562 cells as well as in Ba/F3 cells bearing BCR/ABL T315I. In parallel, we performed multiplexed kinase assays as well as chemical proteomics analysis and mass spectrometry using K562 cells and primary CML cells and coupleable dasatinib and bosutinib analogues. In these experiments, dasatinib and bosutinib were found to express an overlapping, but non-identical profile of target kinases. As expected, both drugs were found to bind to wt ABL, SRC kinases, and TEC-family kinases including BTK. Specific targets preferentially bound and inhibited by bosutinib were STE20s, the FES/FER family, CAMKIIG, PYK2 and TKB1. We were also able to confirm that the dasatinib-targets KIT and PDGFRA are not recognized by bosutinib. Interestingly, whereas wt ABL (IC_{50}<0.5 nM) and most of the ABL mutants tested (H396P, M351T, Q252H, and Y253F) were all completely inhibited by both drugs at 1 µM in the kinase assay, the ABL T315I mutant was inhibited by bosutinib (IC_{50}=26 nM) almost 70 times more potently than by dasatinib. Together, these data show that bosutinib and dasatinib synergize with each other in producing antileukemic effects on CML cells including BCR/ABL T315I+ subclones. These synergistic effects may be explained by differential target kinase profiles and by the fact that bosutinib retains some activity against the BCR/ABL T315I mutant kinase.

3232 Preliminary Clinical Activity in a Phase I Trial of the BCR-ABL/IGF-1R/Aurora Kinase Inhibitor XL228 in Patients with Ph+ Leukemias with Either Failure to Multiple TKI Therapies or with T315I Mutation

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-314

Jorge Cortes, MD1, Ronald Paquette, MD2, Moshe Talpaz2, Javier Pinilla, MD, PhD4, Ekatherine Asatiani, MD3, Meir Wetzler, MD6, Jeffrey H. Lipton, MD, PhD7, Corynn Kasap, BS8, Lynne A. Bui, MD8, Douglas O. Clary, PhD8 and Neil Shah, MD, PhD8

1M.D. Anderson Cancer Center, Houston, TX
2Ronald Reagan UCLA Medical Center, Los Angeles, CA
3Comprehensive Cancer Ctr., Univ. of Michigan, Ann Arbor, MI
4H. Lee Moffitt Cancer Ctr., Tampa, FL
5Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC
6Roswell Park Cancer Inst., Buffalo, NY
7Med. Onc. & Hema., Princess Margaret Hospital, Toronto, ON, Canada
8University of California, San Francisco, San Francisco, CA
9Exelixis, Inc., South San Francisco, CA

XL228 is a protein kinase inhibitor with potent activity against wild-type and T315I isoforms of BCR-ABL (wild-type ABL kinase, IC_{50} = 5 nM; ABL T315I, 1.4 nM), Aurora A (3.1 nM), IGF-1R (1.6 nM), SRC (6.1 nM), and LYR (2 nM). A Phase 1 dose escalation clinical trial in patients (pts) with CML or
Ph+−ALL who are resistant or intolerant to at least two prior standard therapies (including imatinib, dasatinib, and nilotinib) or have a known BCR-ABL T315I mutation is ongoing. XL228 is administered as a 1-hour IV infusion either once weekly or twice weekly. Twenty-seven pts have been enrolled into six cohorts with the once-weekly dosing schedule (dose range from 0.45 mg/kg to 10.8 mg/kg). All pts have failed prior imatinib therapy, and received nilotinib, dasatinib, and other therapies. The majority of pts harbor mutations in BCR-ABL, with the most common mutations being T315I (n=10), F317L (n=7), and V299L (n=3). The maximum administered dose (MAD) of once-weekly IV dosing of XL228 is 10.8 mg/kg. Dose escalation of pts in the twice-weekly dosing schedule at an initial XL228 dose of 3.6 mg/kg on Days 1 and 4 of each week is ongoing. XL228 has been generally well-tolerated. Dose limiting toxicities observed with once-weekly dosing included Grade 3 syncope and hyperglycemia in two pts dosed at 10.8 mg/kg. Grade 2 adverse events reported to be possibly related to XL228 in the once-weekly dosing schedule were usually transient and manageable, and included hyperglycemia, fatigue, nausea, vomiting, and bradycardia. Pharmacokinetic analysis across five cohorts treated with once-weekly dosing of XL228 demonstrated an approximately dose-proportional exposure, with a mean terminal half life of 15 to 38 hours. In the 7.2 mg/kg cohort, the Cmax of approximately 13 µM exceeds the IC50 for modulation of phospho-CrkL levels determined in mouse K562 xenograft pharmacodynamic studies. Peak exposures of XL228 in the 7.2- and 10.8-mg/kg cohorts were associated with inhibition of peripheral blood leukocyte CrkL phosphorylation in several patients, including three harboring the T315I mutation. Transient increases in mean plasma glucose levels (up to three fold) and mean insulin levels (up to 40 fold) post-infusion are coupled, dose-related, and imply inhibition of the IGF1R and IR pathways by XL228. Preliminary evidence of clinical activity has been observed in pts treated at doses of 3.6 mg/kg and higher, including stable or decreasing white blood cell count and/or platelet count within 2 months (14 pts, 5 with T315I), and/or >1 log reduction in BCR-ABL levels by QPCR within 3 months (3 pts, 2 with T315I). Pts in the 7.2 mg/kg and higher cohorts have been followed a minimum of 1 month to a maximum of 4 months at the time of abstract submission. XL228 shows potential for treating drug-resistant CML and Ph+−ALL, including pts harboring the T315I gatekeeper mutation.

3220 Determination of the Activity Profile of Bosutinib, Dasatinib and Nilotinib against 18 Imatinib Resistant Bcr/Abl Mutants

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-302
Sara Redaelli, MS¹*, Rocco Piazza, MD¹*, Roberta Rostagno¹*, Marianna Sassone, MD¹*, Vera Magistroni, PhD¹*, Pietro Perini, MS¹*, Manuela Marega, MS¹*, Frank Boschelli, PhD²* and Carlo Gambacorti, MD³

1Dept.Clinical Medicine and Prevention, University Milano Bicocca S.Gerardo Hospital, Monza, Italy
2Oncology, Wyeth, Pearl River, NY
3Dept.Clinical Medicine and Prevention, University Milano Bicocca S.Gerardo Hospital, Monza, Italy

The treatment of Chronic Myeloid Leukemia (CML) has been radically modified by the discovery of imatinib (IM), a selective inhibitor of the fusion protein Bcr-Abl, the cause of the disease. A variable portion of CML patients experience resistance to IM therapy. Resistance can arise from different mechanisms but in the vast majority of cases is due to point mutations into the protein sequence that alter directly or indirectly the drug-protein binding. Mutation sites can be schematically clustered in four region: the P loop, the IM binding site, the catalytic domain and the activation loop (A loop). At present more than 70 mutations conferring different levels of resistance have been found in CML patients. Recently, several new inhibitors have been developed in order to obtain an increased potency and a broad range of activity against IM resistant mutants. Nilotinib (NIL) is an IM derivative about 30-fold more potent than IM. Dasatinib (DAS) is a dual-specific Src/Abl inhibitor, structurally unrelated to IM and characterized by an activity 100 to 300-fold higher than IM. Bosutinib (BOS) is a dual Src/Abl inhibitor that shows an activity 10 to 30-fold higher than IM. It is known that resistance to second
Patient Education Material

generation TKIs can also arise and the analysis of mutation profiles reveals substantial differences among different TKIs. Presently the choice of a TKI to treat a patient resistant to IM is mostly based on an empirical basis, e.g. the fact that a certain patient has not been previously exposed to that particular TKI. The possibility to directly compare the different activities of TKIs against a given mutation is of remarkable importance in clinical practice. Such a tool could be used similarly to an antibiogram for bacterial diseases, guiding the choice of the most appropriate inhibitor for each patient.

In our study, we investigated the activity of BOS, DAS, IM and NIL against a panel of 18 mutated forms of BCR/ABL chosen to cover the most common mutations found in patients. Stable Ba/F3 transfectant cell lines were generated and the TKIs antiproliferative activity was determined by tritiated thymidine incorporation assay. The relative IC50 increase over wild type BCR/ABL (Relative Resistance RR) was calculated. We classified the RR values in three categories: sensitive (RR ≤ 2), resistant (between 2.01 and 10) or highly resistant (>10) as presented in the table.

<table>
<thead>
<tr>
<th>IC50-fold increase (WT=1)</th>
<th>Imatinib</th>
<th>Bosutinib</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental</td>
<td>10.78</td>
<td>38.31</td>
<td>&gt;50</td>
<td>38.43</td>
</tr>
<tr>
<td>WT</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>P-LOOP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L248V</td>
<td>3.54</td>
<td>2.97</td>
<td>5.11</td>
<td>2.80</td>
</tr>
<tr>
<td>G250E</td>
<td>6.86</td>
<td>4.31</td>
<td>4.45</td>
<td>4.56</td>
</tr>
<tr>
<td>Q252H</td>
<td>1.39</td>
<td>0.81</td>
<td>3.05</td>
<td>2.64</td>
</tr>
<tr>
<td>Y253F</td>
<td>3.58</td>
<td>0.96</td>
<td>1.58</td>
<td>3.23</td>
</tr>
<tr>
<td>E255K</td>
<td>6.02</td>
<td>9.47</td>
<td>5.61</td>
<td>6.69</td>
</tr>
<tr>
<td>E255V</td>
<td>16.99</td>
<td>5.53</td>
<td>3.44</td>
<td>10.31</td>
</tr>
<tr>
<td>D276G</td>
<td>2.18</td>
<td>0.60</td>
<td>1.44</td>
<td>2.00</td>
</tr>
<tr>
<td>C-Helix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E279K</td>
<td>3.55</td>
<td>0.95</td>
<td>1.64</td>
<td>2.05</td>
</tr>
<tr>
<td>V299L</td>
<td>1.54</td>
<td>26.10</td>
<td>8.65</td>
<td>1.34</td>
</tr>
<tr>
<td>Active site</td>
<td>T315I</td>
<td>17.50</td>
<td>45.42</td>
<td>75.03</td>
</tr>
<tr>
<td>F317L</td>
<td>2.60</td>
<td>2.42</td>
<td>4.46</td>
<td>2.22</td>
</tr>
<tr>
<td>SH2-contact</td>
<td>M351T</td>
<td>1.76</td>
<td>0.70</td>
<td>0.88</td>
</tr>
<tr>
<td>Active site</td>
<td>F359V</td>
<td>2.86</td>
<td>0.93</td>
<td>1.49</td>
</tr>
<tr>
<td>A-LOOP</td>
<td>L384M</td>
<td>1.28</td>
<td>0.47</td>
<td>2.21</td>
</tr>
<tr>
<td>H396P</td>
<td>2.43</td>
<td>0.43</td>
<td>1.07</td>
<td>2.41</td>
</tr>
<tr>
<td>H396R</td>
<td>3.91</td>
<td>0.81</td>
<td>1.63</td>
<td>3.10</td>
</tr>
<tr>
<td>G398R</td>
<td>0.35</td>
<td>1.16</td>
<td>0.69</td>
<td>0.49</td>
</tr>
<tr>
<td>C terminal lobe</td>
<td>F486S</td>
<td>8.10</td>
<td>2.31</td>
<td>3.04</td>
</tr>
</tbody>
</table>

Sensitivity: ≤2
Resistant: 2.01 - 10
Highly resistant: >10

(Updated table available online at http://www.dimep.medicina.unimib.it/en/staff_174.php?docente_id=32)
Our study points out at the differences in the activity spectrum of the 4 TKIs against the 18 Bcr/Abl mutations considered. The activity pattern presented in this work will help to reach a rational and tailored therapy offering to physicians a tool to use the new TKIs in the most efficient way for their patients.

2119 The Use of 2nd generation Tyrosine Kinase Inhibitors (TKI) after Failure to 2 Prior TKI: Long-Term Follow-up

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-213

Ravin Jain Garg, M.D.1, Hagop M Kantarjian2, Susan O’Brien, M.D.3, Alfonso Quintas-Cardama, MD4, Stefan Faderl, MD5, Zeev Estrov, MD5 and Jorge Cortes, MD5

1Hematology and Oncology Fellow, M.D. Anderson Cancer Center, Houston, TX
2The University of Texas M. D. Anderson Cancer Center, Houston, TX
3Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX
4Medical Oncology, UT MD Anderson Cancer Center, Houston, TX
5M.D. Anderson Cancer Center, Houston, TX
6Department of Leukemia, U.T.M.D. Anderson Cancer Center, Houston, TX

The 2nd generation tyrosine kinase inhibitors (TKI), nilotinib and dasatinib, are effective after imatinib failure. These agents are now also being used as 3rd line therapy after failure to 2 prior TKI. Preliminary data suggests responses can be achieved with this strategy, but the long-term benefit is unknown.

To investigate the long-term benefit of using a 2nd generation TKI after having failed imatinib and another TKI.

Patients with CML who were sequentially treated with 3 different TKI’s at M.D. Anderson Cancer Center were reviewed. Response to the 3rd TKI were scored according to standard definitions. Event-free survival (EFS) was considered from the time the 3rd TKI was started to loss of major hematologic response, loss of cytogenetic response, transformation to accelerated (AP) or blast (BP) phase, or death. Failure-free survival (FFS) was considered from start of 3rd TKI to event as defined for EFS, or loss of complete cytogenetic response (CCyR) or discontinuation because of toxicity.

37 patients were treated: 29 with dasatinib after imatinib and nilotinib failure, and 8 with nilotinib after imatinib and dasatinib failure. The median age was 61 years (yrs) (range, 19 to 70). The median time on imatinib was 33 months (mo) and 15 (41%) had transformation before starting 2nd TKI. Median time on 2nd TKI was 7.7 mo. At the start of 3rd TKI, 16 pts (43%) were in chronic phase (CP), 9 (24%) in AP, and 12 (32%) in BP. Best response to 3rd TKI in CP was 1 major molecular response (MMR), 2 CCyR, 1 partial cytogenetic response (PCyR), 5 minor cytogenetic response (mCyR), 2 complete hematologic response (CHR), and 5 no responses (NR); in AP, there was 1 CCyR, 2 PCyR, 1 mCyR, 4 CHR, and 1 NR; in BP, 2 CCyR, 1 PCyR, 1 mCyR, 2 return to CP (RCP), and 6 NR. Four patients discontinued treatment because of toxicity despite an acceptable response. The median CCyR duration was 28 mo; only 2 pts in CP who achieved CCyR (1 had MMR) had a sustained response lasting 20 and 24 mo, respectively. Both received dasatinib after imatinib and nilotinib failure, and had G250E and H396R at start of dasatinib, respectively. The table shows median (in months) OS, EFS and FFS by disease stage.

<table>
<thead>
<tr>
<th></th>
<th>CP</th>
<th>AP</th>
<th>BP</th>
<th>OVERALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>16</td>
<td>9</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>OS</td>
<td>NR</td>
<td>19.6</td>
<td>4.8</td>
<td>18</td>
</tr>
<tr>
<td>EFS</td>
<td>NR</td>
<td>4.7</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>FFS</td>
<td>20</td>
<td>4.7</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

MMR), 1 PCyR (lost CCyR), 2 mCyR, 2 no cytogenetic response (1 lost mCyR).
Mutations Leading to Relapse Are Mainly Detected during the First Year

Use of 2nd generation TKI after failure to 2 TKI may induce responses in some pts but these are usually not durable except in some pts in CP. New treatment options are needed for these pts.

2118 Long-Term Mutation Follow-up of Philadelphia-Chromosome Positive Leukemia Patients Treated with Second-Generation Tyrosine Kinase Inhibitors after Imatinib Failure Shows That Newly Acquired Bcr-Abl Kinase Domain Mutations Leading to Relapse Are Mainly Detected during the First Year

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-212

Simona Soverini, Alessandra Gnani, Sabrina Colarossi, Fausto Castagnetti, Francesca Palandrini, Stefania Paolini, Cristina Papayannis, Antonella Gozzini, Valeria Santini, Daniela Cillonii, Ester Orlandi, Serena Merante, Franca Radaelli, Michela Rondoni, Michele Malagola, Angela Poerio, Marilina Amabile, Ilaria Iacobucci, Gabriele Gugliotta, Gianantonio Rosti, Giovanni Martellini and Michele Baccarani

1Department of Hematology/Oncology “L. and A. Seràgnoli”, University of Bologna, Bologna, Italy
2Department of Hematology and Oncological Sciences “L. e A. Seràgnoli”, University of Bologna, Bologna, Italy
3Hematology, University of Florence, Florence, Italy
4Department of Clinical and Biological Sciences, University of Turin, Turin, Italy
5Hematology, San Matteo, Pavia, Italy
6Hematology Unit, Milano
7Haematology Department, University of Siena, Siena, Italy
8Chair of Hematology, University of Brescia, Brescia, Italy

Resistance to imatinib in Philadelphia-positive (Ph+) leukemia patients is often associated with selection of point mutations in the Bcr-Abl kinase domain (KD). Dasatinib and nilotinib are second-generation tyrosine kinase inhibitors (TKIs) with different binding modes with respect to imatinib, that have been shown to confer in vitro and in vivo activity against many Bcr-Abl mutated forms. However, both dasatinib and nilotinib have been shown to retain some ‘Achilles heels’, and they include both imatinib-resistant mutations (e.g., T315I) and some novel, inhibitor-specific ones. Selection of either type of KD mutations has frequently been observed in patients (pts) who relapse after an initial response to dasatinib or nilotinib and represents one of the major hurdles on the road to successful treatment of imatinib-resistant pts. We have monitored Abl KD mutation status in a total of 121 pts who received dasatinib (n= 78) or nilotinib (n=43) as 2nd TKI after imatinib failure since February 2005. Fifty-eight (48%) pts had chronic phase (CP) chronic myelogenous leukemia (CML), 63 pts (52%) had accelerated phase (AP) or blast crisis (BC) CML or Ph+ acute lymphoblastic leukemia (ALL). Median age was 55 years (range, 18-76); median time from diagnosis was 49 months (range, 4-181); median time on imatinib was 32 months (range, 4-66). Median follow-up of all pts who received a 2nd TKI is 7 months (range, 1-38). Median follow-up of pts who are still on 2nd TKI treatment is 32 months (range, 28-38). Relapses after an initial response have so far been observed in 46/121 pts. Thirty-eight out of these 46 pts had AP/BC CML or Ph+ ALL at the time 2nd TKI was started. Forty-one out of 121 (34%) pts have experienced relapse after an initial response during the first 12 months of 2nd TKI treatment (median time to relapse, 6,5 months; range 4-12 months), while only five of the 45 (11%) pts who were still on 2nd TKI treatment after >12 months have relapsed (at 13, 15, 18, 20 and 33 months, respectively). Interestingly, none of these 5 pts had never achieved more than a minor cytogenetic response (CgR), and 4/5 pts were receiving a reduced TKI dose because of toxicity. In 36/48 (76%) cases, relapse was associated with newly acquired Abl KD mutations. In particular 26/30 (87%) pts who relapsed on dasatinib and 10/16 (63%) pts who relapsed on nilotinib had evidence of a newly acquired KD mutation presumably responsible for treatment failure. Newly acquired mutations in pts who relapsed on dasatinib as 2nd TKI were T315I (n= 12 pts) F317L (n= 8 pts) T315A (n=3 pts); V299L (n=3 pts); F317I (n=2 pts); 2 pts had multiple mutations. Newly acquired mutations in pts who relapsed on nilotinib as 2nd TKI were E255K (n=3); E255V (n=2); Y253H (n=2); T315I (n=1); F359V (n=1); F359C (n=1). Sixteen pts (but none of those harboring the T315I) switched to dasatinib or nilotinib or high-dose imatinib as 3rd TKI and this rescued hematologic or even cytogenetic responses in a
**Patient Education Material**

Proportion of cases. Our observations suggest that: a) newly acquired mutations leading to relapse in Ph+ leukemia pts receiving dasatinib or nilotinib as 2nd TKI usually arise rapidly; the likelihood of mutation selection consistently decreases over time, and seems mainly confined to advanced phase pts and to pts with no or minor CgR; b) almost all (87%) cases who developed resistance to dasatinib had newly acquired KD mutations - suggesting that the higher potency with respect to imatinib can overcome Bcr-Abl gene amplification and that Src kinase inhibition may turn off Bcr-Abl-independent resistance mechanisms; c) a lower incidence (63%) of newly acquired KD mutations was observed in pts who developed resistance to nilotinib; d) with the exception of T315I, there is little if no overlap between dasatinib and nilotinib-resistant mutants, which may allow to regain responses by switching TKIs. Supported by European LeukemiaNet, AIL, AIRC, FIRB and PRIN.

**2113 Long Term Follow up of Patients with CML in Chronic Phase Treated with First-Line Imatinib Suggests That Earlier Achievement of a Major Molecular Response Leads to Greater Stability of Response**

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-207

Susan Branford1, Rebecca Lawrence1, Andrew Grigg2, John Francis Seymour, MBBS2, Anthony Schwarer3, Christopher Arthur2, Zbigniew Rudzki1 and Timothy Hughes4

1Institute of Medical & Veterinary Science, Adelaide, Australia
2Med. Onc./Hem., Royal Melbourne Hospital, Melbourne, Australia
3Peter MacCallum Cancer Institute, Richmond, Australia
4Australasian Leukaemia & Lymphoma Group, Australia

A major molecular response (MMR) by 12 or 18 months (m) of standard dose imatinib for patients (pts) with newly diagnosed chronic phase CML is associated with a low risk of progression to accelerated phase or blast crisis. Phase II/III trials suggest that MMR may be achieved earlier with higher doses of imatinib. We determined whether the timing of MMR affects the long term stability of response with regard to the acquisition of BCR-ABL mutations and/or loss of MMR (collectively defined as an "event") for pts with up to 8 years of follow up since commencing first-line imatinib. All pts treated with 400 to 600mg of first-line imatinib who were monitored regularly at our institution for BCR-ABL levels by real-time quantitative PCR and mutation analysis by direct sequencing were evaluated: 181 pts were followed for a median of 45m (range (r) 3-96m). The event rate was compared for pts dependent on the time to MMR (≤0.1% IS (international scale)) in 6m intervals to 18m of imatinib. The events for pts with undetectable BCR-ABL (complete molecular response, CMR) were also determined. Strict sensitivity criteria were used for CMR: undetectable BCR-ABL where the sensitivity of analysis indicated BCR-ABL was <0.003% IS, (equivalent to at least 4.5 log below the standardized baseline) which was confirmed on a subsequent analysis. Loss of MMR was defined as a confirmed >2 fold rise from nadir to a level >0.1% IS in pts who maintained imatinib dose. 144/181 pts (80%) achieved MMR at a median of 12m (r 3-53m). Consistent with other studies, maintaining a higher dose of imatinib in the first 6m of therapy was associated with a significantly higher frequency of pts achieving MMR by 6m. 118 pts received an average dose of <600mg in the first 6m and 18/118 (15%) achieved MMR by 6m, whereas 63 pts received an average dose of 600mg in the first 6m and 23/63 (37%) achieved MMR by 6m, P=0.002. Mutations were detected in 14/181 pts (8%) at a median of 9m (r 3-42m). An event occurred in 8 pts with MMR at a median of 36m (r12-57m) after commencing imatinib, including one patient who had achieved CMR. Mutations were found in 4 pts and 3/4 lost MMR. The remaining 4 lost MMR without a mutation. The one patient with a mutation who did not lose MMR had a 3-fold rise in BCR-ABL at the time of mutation detection and responded to a higher imatinib dose. The other pts with mutations had therapeutic intervention upon cytogenetic relapse (2) or loss of MMR (1). The 4 pts with loss of MMR and no mutation had accelerated phase (1), cytogenetic relapse (2) and one maintained CCR with 3m of follow up. The median fold rise in BCR-ABL upon loss of MMR was 26 (r 4-220). The probability of an event if MMR was achieved by a) 6m was 0% (n=41 evaluable pts), b) >6 to 12m was 12% (n=40) and c) 12 to 18m was 19% (n=33). The median follow up since MMR was achieved was not significantly different for the groups: 49m (r 3-87m), 38m (r 6-87m), 40m (r 9-78m), respectively, P=0.5. The risk of an event for pts with MMR
achieved by 6m was significantly lower than in pts with MMR achieved by >6 to 18m, *P*=0.04. CMR occurred in 55 pts who were followed for a median of 24m (r 3-55m) after its attainment. Only 1 event occurred in these 55 pts, which was at 6m after CMR was achieved and 57m after commencing imatinib. This patient had maintained MMR for 45m but loss of a major cytogenetic response occurred 6m after loss of MMR. There was a significant difference in the probability of CMR by 60m of imatinib dependent on the time to MMR, *P*<0.0001 (Figure). All pts failed to achieve CMR by 60m if not in MMR at 18m whereas the actuarial rate of CMR at 60m was 93% in those with MMR by 6m. The initial slope of BCR-ABL decline correlated strongly with the decline over the longer term. The mean time to CMR after attainment of MMR was significantly faster for pts with MMR by 6m compared to those with MMR at >6 to 12m and >12 to 18m: 24m vs 37m vs 42m, respectively, *P*=0.001. This suggests the rate of BCR-ABL reduction below the level of MMR was faster in pts with MMR by 6m, which may be clinically beneficial as none of these pts had a subsequent event. Based on these findings we propose that inducing earlier molecular responses with higher dose imatinib or more potent kinase inhibitors may lead to more durable and deeper responses. It remains possible however, that early molecular response reflects a more biologically favourable disease rather than being the direct cause of more durable response. Finally, CMR was associated with an extremely low risk of events, making it an appropriate next target of therapy after MMR is achieved.

![Probability of CMR dependent on the time to MMR](image)

Comparisons
- MMR by 6m vs MMR >6 to 12m: *P*=0.0002
- MMR >6 to 12m vs MMR >12 to 18m: *P*=0.01
- MMR >12 to 18m vs No MMR at 18m: *P*=0.001

331 The Initial Molecular Response of Chronic Phase CML Patients Treated with Second Generation ABL Inhibitor Therapy after Imatinib Failure Can Predict Inadequate Response and Provide Indications for Rational Mutation Screening

Monday, December 8, 2008: 11:00 AM
2009-2011-2022-2024 - West (Moscone Center)

Susan Branford, Rebecca Lawrence*, Linda Fletcher, Chani Field*, Zbigniew Rudzki* and Timothy Hughes

Institute of Medical & Veterinary Science, Adelaide, Australia

Molecular analysis is recommended for monitoring patients (pts) with CML. For imatinib treated pts in chronic phase (CP), molecular analysis provides important prognostic information. A major molecular response (MMR, BCR-ABL ≤0.1% IS (international scale)) is associated with favourable progression free survival and is a primary endpoint of clinical trials. The 3 month (m) BCR-ABL level is predictive of
MMR and almost all de-novo pts with values ≤1.0% IS subsequently achieve MMR. The second generation tyrosine kinase inhibitors nilotinib and dasatinib (2TKI) have demonstrated efficacy for CP pts who fail imatinib therapy due to resistance or intolerance. However, treatment failure associated with the presence of a limited spectrum of resistant mutations is evident. Furthermore, it has recently been suggested that failure to achieve a major cytogenetic response (MCR) by 12m defines inadequate response and these pts should be considered for alternative therapies (Cortes et al, Blood, 2008, 112, 516). Pts in minor cytogenetic response or complete hematologic response at 12m had a projected 1 year progression rate of 17% compared to 3% for those with MCR at 12m. The value of molecular monitoring in the setting of 2TKI has not been defined in terms of the early prediction of response or emergence of resistant mutations. We monitored BCR-ABL levels and mutation status in 155 CP pts treated with nilotinib (n=73; 400mg BD) or dasatinib (n=82; ≥100mg (76/82 70mg BD)) after imatinib failure for a median of 18m (range (r) 3-36). The BCR-ABL level at 3m of 2TKI was highly predictive of subsequent MMR, P=0.0001 (Figure A). Similarly, the 3m BCR-ABL level was highly predictive of MCR, P=0.0001 (Figure B). Among pts with BCR-ABL >10% IS, those who failed to achieve at least 50% at 3m had a significantly lower probability of MCR compared to those between 10-50%; 11% vs 56% by 24m, P=0.003. These analyses were also performed for pts with mutations at baseline (72/155, 46%) and for those without baseline mutations (83/155, 54%). The MMR and MCR rates based on the 3m BCR-ABL were still highly significant irrespective of the baseline mutation status, P<0.0001. We investigated factors associated with emergence of new mutations that have demonstrated a degree of resistance to 2TKI (2TKI resistant): T315I/A, F317L/I/V, V299L for dasatinib and T315I, Y253H, E255K/V, F359V/C (IC50 >150nM) for nilotinib. All pts with new mutations during dasatinib therapy (19/82, 23%) had one of the dasatinib 2TKI resistant mutations: T315I 9, F317L/I 6, V299L 4 pts. Mutations emerged in 15/73 (21%) nilotinib treated pts and were nilotinib 2TKI resistant in 11 pts (15%): T315I 5, F359V 4, Y253H 4, E255V 1 (2 pts had multiple mutations). 2TKI resistant mutations were detected at a median of 6m (r 1-24) and were more frequent in pts who already had a mutation at baseline compared to those without: 24/72 (33%) vs 6/83 (7%), P<0.0001. At the time of last molecular analysis 18 of 30 pts with new 2TKI resistant mutations had progressed, 7 had not progressed and the outcome was unknown for 5. Among pts with baseline mutations, the 3m BCR-ABL did not predict the emergence of 2TKI resistant mutations by 24m. Conversely, for pts without a baseline mutation the 3m BCR-ABL was predictive of emergent 2TKI resistant mutations when pts were divided into 2 groups: 1/53 pts (2%) ≤10% IS vs 5/30 pts (17%) >10% IS, P=0.02. In 16/30 pts (53%) with emergent 2TKI resistant mutations, BCR-ABL never fell below 10% IS. The rise in BCR-ABL associated with emergent mutations was minimal in these pts: median 2.2-fold and 6 pts had no change in BCR-ABL from baseline. This is a reflection of minimal response to 2TKI and hence minimal BCR-ABL reduction in these pts. The outcome is known for 13 of the 16 pts and 11/13 progressed. Regular mutation screening would be warranted in all pts with BCR-ABL >10% IS rather than upon a significant rise. The rise associated with emergent mutations when BCR-ABL was ≤10% IS was significantly higher: median 7.3-fold, P<0.0001. This degree of rise should be readily detected by serial analysis and would trigger mutation screening. In conclusion, BCR-ABL measured at 3m of 2TKI could predict response and for pts without baseline mutations it could predict the emergence of new mutations. All pts with BCR-ABL >10% IS are at risk of acquiring 2TKI resistant mutations and would benefit from regular mutation screening until BCR-ABL falls below 10% IS. Thereafter, a significant rise of >5-fold in BCR-ABL should trigger mutation screening.
Bosutinib (SKI-606) is an orally available, Src/Abl kinase inhibitor with minimal activity against platelet-derived growth factor receptor (PDGFR) and c-kit. An open-label study of patients (pts) with Philadelphia chromosome positive (Ph+) accelerated phase (AP) and blast phase (BP) CML and Ph+ ALL who failed prior imatinib therapy is ongoing. Patients receive 500 mg/day of bosutinib. Preliminary data for 101 subjects, median age 51.5 yrs (range 18 – 84 yrs) and 56% male are reported. 44 pts were in AP, 35 in BP, 21 had Ph+ ALL, and 1 was unclassified. Prior therapy in addition to imatinib included interferon (35 pts), dasatinib (40 pts), nilotinib (15 pts) and stem cell transplant (11 pts). 49 pts failed imatinib (and received no other tyrosine kinase inhibitor [TKI]) and 52 pts failed both imatinib
Patient Education Material

and other TKIs, with median duration of bosutinib treatment to date 4.4 mos (range 0.3 – 21.3 mos) and 2.0 mos (range 0.3 – 18.8), respectively. Among pts with no TKI exposure other than imatinib, complete hematological response (CHR) was obtained in 12/25 evaluable pts (48%), including 7/11 pts (64%) with AP-CML, 4/11 pts (36%) with BP-CML and 1 pt with Ph+ ALL. Major cytogenetic response (MCyR) was achieved in 16/22 evaluable pts (73%) with no TKI exposure other than imatinib, including 9/13 pts (69%) with AP-CML and 6/8 pts (75%) with BP-CML; 1 pt with Ph+ ALL achieved MCyR. Major molecular response (MMR) was achieved in 9/25 evaluable pts (36%) with no TKI exposure other than imatinib, including 1/7 pts (14%) with AP-CML, 4/10 pts (40%) with BP-CML and 4/8 pts (50%) with Ph+ ALL. Among pts with other TKI exposure in addition to imatinib, CHR was obtained in 3/15 evaluable pts (20%), all with AP-CML; MCyR was achieved in 6/20 evaluable pts (30%), including 3/12 pts (25%) with AP-CML and 2/7 pts (29%) with BP-CML; 1 pt with Ph+ ALL achieved MCyR. Of the 20 pts with other TKI exposure in addition to imatinib who were evaluable for MMR, 1 pt with Ph+ ALL (5%) achieved this response. Of 60 pts with baseline samples tested for mutations, 15 different mutations were found in 32 pts (53%), including 8 instances of T315I. CHR occurred in 2/8 evaluable pts (25%) with non-P-loop mutations; the 1 evaluable pt with a P-loop mutation did not achieve CHR. MCyR occurred in 4/11 evaluable pts (36%) with non-P-loop mutations and in 1/2 evaluable pts (50%) with P-loop mutations. Treatment was generally well tolerated. The most common adverse events among treated pts (n=101) were gastrointestinal (diarrhea [66%], nausea [46%] and vomiting [42%]) but these were usually grade 1 – 2, manageable and transient, reducing in frequency and severity after the first 3 – 4 weeks of therapy. Grade 3 – 4 non-hematologic toxicities occurring in ≥ 5% of pts were diarrhea (7%), vomiting (6%), pneumonia (6%) and increased ALT (5%). Fluid retention was reported as grade 1 – 2 in 18 pts and grade 3 – 4 in only 3 pts (including 2 pleural effusions, neither related to bosutinib). Grade 3 – 4 hematologic laboratory abnormalities reported include thrombocytopenia (68%), neutropenia (48%) and anemia (37%). 38 pts had at least 1 temporary treatment interruption and 22 pts had at least 1 dose reduction due to toxicity. 11 pts have permanently discontinued treatment due to adverse event. Bosutinib is effective in imatinib-resistant pts with advanced CML. Responses were observed across a wide range of Bcr/Abl mutations.

1624 Bcr-Abl-Independent Activation of Src Kinases Associated with Development of Dasatinib Resistance in a CML Patient

Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-729

Jitka Veselovska, MSc1*, Renata Solna, PhD1*, Marje Jarosova, PhD2*, Edgar Faber, MD, PhD2*, Helena Urbanova, MSc2, Milena Holzerova, MSc2, Jana Balcarkova, MSc2, Karel Indrak, MD, PhD2* and Vladimir Divoky, PhD1

1Dept. of Biology, Palacky Univ. Faculty of Med., Olomouc, Czech Republic
2Department of Hemato-Oncology, University Hospital Olomouc, Olomouc, Czech Republic

Activation of Src family of kinases (SFK) is associated with chronic myeloid leukemia (CML) disease progression and resistance to imatinib (IM) therapy. Activation of SFK can be either Bcr-Abl-dependent or Bcr-Abl-independent in IM-resistant CML patients and clinical importance of this phenomenon is not completely understood. Second generation of tyrosine kinase inhibitors (TKIs) such as dasatinib, targeting both Bcr-Abl kinase as well as SFK, could represent a logical alternative for treatment of patients with acquired IM resistance due to SFK activation. Recent studies raised question whether overexpression of SFK could lead to an acquired resistance to dasatinib. Sensitivity of individual patients’ leukemia cells to TKIs can be carried out by assessment of inhibition of phosphorylation of Crkl and SFK after incubation of patient’s leukocytes with the drug in vitro. We used 10 μM IM or 250 nM dasatinib in vitro and detection with western blot analysis with anti-Crkl 32H4 monoclonal antibody (Cell SignalingTechnology, Beverly, MA) and Phospho-Src Family (Tyr416) Antibody (Cell Signaling Technology Inc., Danvers, MA). By this functional approach we identified several IM-resistant CML cases, where IM failed to inhibit phospho-Crkl and phospho-SFK in vitro; these patients were either in blast crisis or carried a BCR-ABL mutation. In most cases, however, phospho-SFK were inhibited after incubation of the patients’ leukocytes with dasatinib. The exception was a patient with hematological resistance to IM and acquired resistance to dasatinib therapy due to Bcr-Abl-independent activation of SFK. This patient was a 56-year-old female diagnosed with CML in chronic phase. The cytogenetic examination at the time of diagnosis revealed Ph chromosome and an
additional aberration involving derivative chromosomes 2, 3 and 5. After 10 months of IM therapy the BCR-ABL-positive clone was eradicated, but the clinical response to the treatment was unsatisfactory. At the same time the number of cells with the complex additional aberration remained high (>70%). Western blot analysis of the patient's leukocytes revealed overexpression of phospho-SFK suggesting activation of an alternative signaling pathway not inhibited by IM and independent of Bcr-Abl. In vitro sensitivity to dasatinib provided a rationale for switch to dasatinib therapy. Therefore, dasatinib was administered to the patient (2x70 mg daily). However, a rapid development of resistance to dasatinib followed, which corresponded with a loss of inhibition of SFK in in vitro phosphorylation assay. Interestingly, the phenotype of the patient's disease resembles a mouse model of v-src gene induced myeloproliferative disease, characterized by splenomegaly, anemia, and increased numbers of immature erythroid cells (Keller G and Wagner EF, Genes Dev. 1989; 3: 827-37). Our data suggest that the oncogene driving myeloproliferative disease in this patient belongs to SFK. We demonstrate that the detection of activated SFK by immunoblot could lead to recognition of Bcr-Abl-independent and SFK-dependent resistance to dasatinib. This work was supported by Ministry of Education, Youth and Sports of the Czech Republic (project MSM 6198959205) and by CAMELIA Project of the Czech Society of Hematology.
ASH Schedule

Saturday

7:00 am

181 High and Early Rates of Cytogenetic and Molecular Response with Nilotinib 800 Mg Daily as First Line Treatment of Ph-Positive Chronic Myeloid Leukemia in Chronic Phase: Results of a Phase 2 Trial of the GIMEMA CML Working Party Halls B and C (Moscone Center)

9:30 am

Milestones and Monitoring in CML Patients Treated with Imatinib Saturday, December 6, 2008: 9:30 AM Gateway Ballroom - South (Moscone Center) Michael W.N. Deininger, MD Oregon Health and Science University Cancer Institute, Portland, OR

2:30pm

449 Dasatinib Efficacy in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) and Pre-Existing BCR-ABL Mutations Monday, December 8, 2008: 2:30 PM 2009-2011-2022-2024 - West (Moscone Center)

450 Dasatinib Time to and Durability of Major and Complete Cytogenetic Response (MCyR and CCyR) in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Monday, December 8, 2008: 2:45 PM 2009-2011-2022-2024 - West (Moscone Center) Michele Baccarani, MD1

Poster

3225 Dasatinib Dose-Optimization in Chronic Phase Chronic Myeloid Leukemia (CML-CP): Two-Year Data from CA180-034 Show Equivalent Long-Term Efficacy and Improved Safety with 100 Mg Once Daily Dose Poster Board III-307 Neil P. Shah

1095 Dasatinib-Associated Major Molecular Responses Are Rapidly Achieved in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Following Resistance, Suboptimal Response, or Intolerance on Imatinib Saturday, December 6, 2008 Hall A (Moscone Center) Poster Board I-200 Hochhaus

1103 Homo-Harringtonine (Omacetaxine mepesuccinate) Induces a Dramatic and Sustained Reduction of BCR-ABL-T315I mutated Transcripts in Chronic Phase Chronic Myelogenous Leukemia Patients Resistant to Tyrosine Kinase Inhibitors Saturday, December 6, 2008 Hall A (Moscone Center)
Patient Education Material

Franck Nicolini, MD, PhD

1102 The Majority of Chronic Myeloid Leukaemia Patients Who Cease Imatinib after Achieving a Sustained Complete Molecular Response (CMR) Remain in CMR, and Any Relapses Occur Early
Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-207

David M Ross1

970 Allogeneic Myeloablative Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia in the Imatinib Era
Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-75
Jiri Pavlu1, Goldman, Apperley...

973 Results of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Advanced Chronic Myeloid Leukemia (CML) Patients (pts) Who Failed Tyrosine Kinase Inhibitors (TKIs) after Developing BCR-ABL Kinase Domain (KD) Mutations
Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-78
Elias Jabbour1, Jorge Cortes1

1098 Efficacy and Safety of Bosutinib (SKI-606) in Patients with Chronic Phase (CP) Ph+ Chronic Myelogenous Leukemia (CML) with Resistance or Intolerance to Imatinib
Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-203
Jorge Cortes, MD1

1099 Imatinib Long Term Effects (ILTE) Study: An Independent, International Study in CML Patients
Saturday, December 6, 2008
Hall A (Moscone Center)
Poster Board I-204
Carlo Gambacorti-Passerini1

Sunday

Poster

2379 Patient Nonadherence and Treatment Response to Imatinib in Patients with Chronic Myeloid Leukemia: Results from the ADAGIO Study
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-473

2120 Stem Cell Transplant (SCT) for Patients (pts) with Chronic Myeloid Leukemia (CML) Resistant to Tyrosine Kinase Inhibitors (TKI) with BCR-ABL Kinase Domain (KD) Mutation T315I
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-214
Nikolai Velev1

2114 Mutational Analysis of Chronic Phase Chronic Myeloid Leukemia (CML-CP) Clones Reveals Heightened BCR-ABL1 Genetic Instability in Patients Failing Sequential Imatinib and Dasatinib Therapy
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-208
Alfonso Quintas-Cardama, MD

2125 Malignancies Occurring during Therapy with Tyrosine Kinase Inhibitors (TKI) for Chronic Myeloid Leukemia (CML) and Other Hematologic Malignancies
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-219
Dushyant Verma, MD, FACP, Hagop M. Kantarjian

2121 Imatinib Discontinuation Following a Major Molecular Response: Impact of Interferon Alpha and Leukemia Stem Cell Burden (The STOP Study)
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-215
Perttu Koskenvesa, MD1

2112 Association of Pleural Effusion and Bleeding in Patients with Chronic Myelogenous Leukemia Receiving Dasatinib
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-206
Alfonso Quintas-Cardama, MD1, Hagop M. Kantarjian2

3220 Determination of the Activity Profile of Bosutinib, Dasatinib and Nilotinib against 18 Imatinib Resistant Bcr/Abl Mutants
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-302
Sara Redaelli, MS

2119 The Use of 2nd generation Tyrosine Kinase Inhibitors (TKI) after Failure to 2 Prior TKI: Long-Term Follow-up
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-213
Ravin Jain Garg, M.D.1, Hagop M Kantarjian2

2118 Long-Term Mutation Follow-up of Philadelphia-Chromosome Positive Leukemia Patients Treated with Second-Generation Tyrosine Kinase Inhibitors after Imatinib Failure Shows That Newly Acquired Bcr-Abl Kinase Domain Mutations Leading to Relapse Are Mainly Detected during the First Year
Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-212
Simona Soverini1*
**Patient Education Material**

2113 Long Term Follow up of Patients with CML in Chronic Phase Treated with First-Line Imatinib Suggests That Earlier Achievement of a Major Molecular Response Leads to Greater Stability of Response

Sunday, December 7, 2008
Hall A (Moscone Center)
Poster Board II-207
Susan Branford

**Monday**

7:00

182 Efficacy of Dasatinib in Patients (pts) with Previously Untreated Chronic Myelogenous Leukemia (CML) in Early Chronic Phase (CML-CP)
Monday, December 8, 2008: 7:15 AM
Halls B and C (Moscone Center)
Jorge Cortes

183 Randomized Comparison of Imatinib Versus Imatinib Combination Therapies in Newly Diagnosed Chronic Myeloid Leukaemia (CML) Patients in Chronic Phase (CP): First Results of the Phase III (SPIRIT) Trial from the French CML Group (FILMC)
Monday, December 8, 2008: 7:30 AM
Halls B and C (Moscone Center)
Francois Guilhot, MD1

184 Randomized Comparison of Imatinib 400 Mg Vs. Imatinib + IFN Vs. Imatinib + AraC Vs. Imatinib after IFN Vs. Imatinib 800 Mg: Optimized Treatment and Survival. Designed First Interim Analysis of the German CML Study IV
Monday, December 8, 2008: 7:45 AM
Halls B and C (Moscone Center)
Ruediger Hehlmann, MD1

186 International Randomized Study of Interferon Versus STI571 (IRIS) 7-Year Follow-up: Sustained Survival, Low Rate of Transformation and Increased Rate of Major Molecular Response (MMR) in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib (IM)
Monday, December 8, 2008: 8:15 AM
Halls B and C (Moscone Center)
Stephen G O’Brien, MD, PhD

194 Persistence of Leukemia Stem Cells in Chronic Myelogenous Leukemia Patients in Complete Cytogenetic Remission on Imatinib Treatment for 5 Years
Monday, December 8, 2008: 8:15 AM
2001-2003-2014-2016 - West (Moscone Center)
Su Chu, MD

187 Is It Possible to Stop Imatinib in Patients with Chronic Myeloid Leukemia? An Update from a French Pilot Study and First Results from the Multicentre « Stop Imatinib » (STIM) Study
Monday, December 8, 2008: 8:30 AM
Halls B and C (Moscone Center)
Francois-Xavier Mahon
**Patient Education Material**

188 Epidemiological Study on Survival of Chronic Myeloid Leukemia (CML) and Ph+ Acute Lymphoblastic Leukemia (ALL) Patients with T315I Mutation. Final Analysis
Monday, December 8, 2008: 8:45 AM
Halls B and C (Moscone Center)
Franck E Nicolini, MD, PhD

11:00

331 The Initial Molecular Response of Chronic Phase CML Patients Treated with Second Generation ABL Inhibitor Therapy after Imatinib Failure Can Predict Inadequate Response and Provide Indications for Rational Mutation Screening
Monday, December 8, 2008: 11:00 AM
2009-2011-2022-2024 - West (Moscone Center)
Susan Branford,

332 Prediction of Cytogenetic Response to Second Generation TKI Therapy in CML Chronic Phase Patients Who Have Failed Imatinib Therapy and Early Identification of Factors That Influence Survival
Monday, December 8, 2008: 11:15 AM
2009-2011-2022-2024 - West (Moscone Center)
Dragana Milojkovic

333 Molecular Response to First Line Imatinib Therapy Is Predictive for Long Term Event Free Survival in Patients with Chronic Phase Chronic Myelogenous Leukemia – An Interim Analysis of the Randomized German CML Study IV
Monday, December 8, 2008: 11:30 AM
2009-2011-2022-2024 - West (Moscone Center)
Martin C. Müller, MD*

334 Reduction of BCR-ABL Transcript Levels at 6, 12, and 18 Months (mo) Correlates with Long-Term Outcomes on Imatinib (IM) at 72 Mo: An Analysis from the International Randomized Study of Interferon versus STI571 (IRIS) in Patients (pts) with Chronic Phase Chronic Myeloid Leukemia (CML-CP)
Monday, December 8, 2008: 11:45 AM
2009-2011-2022-2024 - West (Moscone Center)
Timothy P Hughes, MD

335 A Phase III, Randomized, Open-Label Study of 400 Mg Versus 800 Mg of Imatinib Mesylate (IM) in Patients (pts) with Newly Diagnosed, Previously Untreated Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Using Molecular Endpoints: 1-Year Results of TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) Study
Monday, December 8, 2008: 12:00 PM
2009-2011-2022-2024 - West (Moscone Center)
Jorge Cortes, MD

445 Significance of Rising Levels of Minimal Residual Disease in Patients with Philadelphia Chromosome-Positive Chronic Myelogenous Leukemia (Ph+ CML) in Complete Cytogenetic Response (CGCR)
Monday, December 8, 2008: 1:30 PM
2009-2011-2022-2024 - West (Moscone Center)
Hagop M Kantarjian

446 Efficacy of Nilotinib (formerly AMN107) in Patients (Pts) with Newly Diagnosed, Previously Untreated Philadelphia Chromosome (Ph)-Positive Chronic Myelogenous Leukemia in Early Chronic Phase (CML-CP)
Patient Education Material

Monday, December 8, 2008: 1:45 PM
2009-2011-2022-2024 - West (Moscone Center)

Jorge Cortes

447 Imatinib (IM) Pharmacokinetic (PK) Exposure and Its Correlation with Clinical Outcome in Patients with Chronic-Phase Chronic Myeloid Leukemia (CML-CP) for 400 Mg and 800 Mg Daily Doses (Tyrosine Kinase Dose Optimization Study [TOPS])
Monday, December 8, 2008: 2:00 PM
2009-2011-2022-2024 - West (Moscone Center)

François Guilhot,

5:00

575 Clonal Hematopoiesis in Philadelphia Chromosome-Negative Bone Marrow Cells of Chronic Myeloid Leukemia Patients Receiving Tyrosine Kinase Inhibitors
Monday, December 8, 2008: 5:00 PM
2001-2003-2014-2016 - West (Moscone Center)

Ron Paquette, MD

Poster

3236 Prevalence of T315I, Dasatinib-Specific Resistant Mutations (F317L, V299L, and T315A), and Nilotinib-Specific Resistant Mutations (P-loop and F359) at the Time of Imatinib Resistance in Chronic-Phase Chronic Myeloid Leukemia (CP-CML)
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-318
Michael W.N. Deininger, MD1

3238 Nilotinib in Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) with Imatinib Resistance or Intolerance: 2-Year Follow-up Results of a Phase 2 Study
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-320
Hagop M Kantarjian

3234 Efficacy and Tolerability of Nilotinib in Chronic Myeloid Leukemia Patients in Chronic Phase (CML-CP) Who Failed Prior Imatinib and Dasatinib Therapy: Updated Results of a Phase 2 Study
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-316
Francis Giles, MD

3217 Clinical Significance of Dose Reductions of Second-Generation Tyrosine Kinase Inhibitors (TKI) in Patients (Pts) with Chronic Myeloid Leukemia (CML)
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-299
Fabio P.S. Santos, MD

3230 Pregnancy Outcomes among Patients with Chronic Myeloid Leukemia Treated with Dasatinib
Patient Education Material

Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-312
Jorge Cortes, MD1

3228 Patients with Chronic Myeloid Leukemia with Variant Philadelphia Chromosome (Ph) Translocations Have a Similar Outcome as Those with Classic Ph When Treated with Imatinib or 2nd Generation TKI
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-310
Nicolas Batty

3224 Dasatinib 140 Mg Once Daily (QD) Demonstrates Equivalent Efficacy and Improved Safety Compared with 70 Mg Twice Daily (BID) in Patients with Accelerated Phase Chronic Myeloid Leukemia (CML-AP): 2-Year Follow-up Data from CA180-035
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-306
Hagop M. Kantarjian, MD1

3239 Safety and Efficacy of Subcutaneous (SC) Omacetaxine Mepesuccinate in Imatinib(IM)-Resistant Chronic Myeloid Leukemia (CML) Patients (pts) with the T315I Mutation – Results of An Ongoing Multicenter Phase II Study
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-321
Jorge Cortes, MD1

3240 Differential Effects of the BCR-ABL-Inhibitors Imatinib, Nilotinib and Dasatinib on NK Cell Reactivity against Chronic Myeloid Leukemia (CML)
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-282
Matthias Krusch, MD

3244 Molecular Responses to Dasatinib and Nilotinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP)
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-326
Alfonso Quintás-Cardama

3222 Management of Chronic Myelogenous Leukemia Using Therapeutic Drug Monitoring of Imatinib: The French Experience of a Centralized Laboratory
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-304
Mathieu Molimard

3195 Effects of Bosutinib (SKI-606) in CML: Kinase Target Profile, Effects on BCR/ABL Mutants, and Synergism with Dasatinib in T315I+ Cells
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-277
Karoline Veronika Gleixner, MD1
3232 Preliminary Clinical Activity in a Phase I Trial of the BCR-ABL/IGF-1R/Aurora Kinase Inhibitor XL228 in Patients with Ph+ Leukemias with Either Failure to Multiple TKI Therapies or with T315I Mutation
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-314
Jorge Cortes, MD1

3219 Randomized Phase II Study of Proteinase 3-Derived PR1 Peptide Vaccine and GM-CSF with or without PEG-Interferon ALFA-2B to Eradicate Minimal Residual Disease in Chronic Myeloid Leukemia
Monday, December 8, 2008
Hall A (Moscone Center)
Poster Board III-301
Alfonso Quintás-Cardama1