However, despite the major advances in therapy, there is room for improving CML management. Presently, there are clinical trials addressing the different stages of the disease. Some of the available clinical trials are reviewed here.

FRONTLINE THERAPY

Nilotinib Studies
In 2005, we initiated a phase II study assessing nilotinib in the frontline setting. This study included 67 patients with Ph+ CML-CP and seven patients with CML-AP. Each patient was diagnosed within 6 months of enrollment and was either untreated or treated with only hydroxyurea, anagrelide, or imatinib 400 mg once daily for a maximum of 1 month prior to study entry. The patients were treated with nilotinib 400 mg twice daily. The primary endpoint of the trial was a major molecular response (MMR) at 12 months defined as a BCR-ABL percentage ratio (International Scale) ≤ 0.1%. The secondary endpoint was a CCyR at 12 months.

At a median follow-up of 17.3 months, evaluable CML-CP patients had achieved a CCyR and MMR of 93% and 81% respectively. Responses were rapid and durable. At 3 and 6 month time points, CCyR was achieved in 78% and 96% of patients respectively. Likewise, MMR was achieved in 42% and 75% of patients.

At 24 months, 93% and 79% of patients maintained CCyR and MMR respectively, and 20% of patients achieved a complete molecular response (CMR), an increase from 11% at 12 months. One patient, who discontinued nilotinib because of intolerance after achieving a CCyR, progressed to blast phase (BP) after an allogeneic stem cell transplant.

In all patients, including the seven patients with CML-AP, grade 3/4 nonhematologic AEs were uncommon. Elevations of bilirubin, lipase, and amylase occurred at rates of 8%, 6%, and 3% respectively. Grade 3/4 hematologic AEs included neutropenia (12%), thrombocytopenia (11%), and anemia (5%).

(continued on page 2)
Based on the results of our trial as well as the GIMEMA trial, a phase 3 randomized, open-label, multicenter study comparing the efficacy and safety of nilotinib with imatinib in patients with newly diagnosed CML, was initiated. The trial included 846 patients randomly assigned 1:1:1 to nilotinib 300 mg twice daily (n = 282), nilotinib 400 mg twice daily (n = 281), or imatinib 400 mg/day (n = 283). MMR at 12 months was the primary endpoint.

The MMR rate at 12 months was significantly higher for nilotinib 300 mg twice daily (44%, P < 0.0001) and nilotinib 400 mg twice daily (43%, P < 0.0001) than for imatinib (22%). The best cumulative MMR rates by 12 months were also significantly higher for nilotinib 300 mg twice daily (55%, P < 0.0001) and nilotinib 400 mg twice daily (51%, P < 0.0001) than for imatinib (27%). Likewise, cumulative rates of CCyR by 12 months were also significantly higher for nilotinib 300 mg twice daily (80%, P < 0.0001) and 400 mg twice daily (78%, P < 0.0005) than for imatinib (65%). Responses were rapidly achieved with nilotinib. Nilotinib dosing schedules of 300 mg twice daily and 400 mg twice daily showed 6 month MMR rate of 33% and 30%; subsequent 9 month MMR rates showed an increase to 43% and 38% respectively. On the other hand, imatinib demonstrated 6 and 9 month MMR rates of 12% and 18% respectively. In addition, more patients achieved undetectable levels of disease (defined as a complete molecular response of ≤ 0.0032% BCR-ABL IS) with nilotinib 300 mg twice daily (13%) and nilotinib 400 mg twice daily (12%) than with imatinib (4%). These higher responses were also associated with significantly fewer progressions with nilotinib than with imatinib.

Grade 3/4 nonhematologic AEs were uncommon across all three arms of ENESTnd, and all occurred at rates of ≤ 1%, except for rash which occurred at a rate of 3% in the nilotinib 400 mg twice daily arm. No instances of QTcF prolongation > 500 msec were observed in any of the treatment arms. Grade 3/4 laboratory abnormalities were uncommon in the nilotinib arms. Rates of grade 3/4 anemia and neutropenia were higher in the imatinib arm of the trial, whereas grade 3/4 thrombocytopenia was more frequently observed in the nilotinib arms.

All efficacy endpoints assessed continued to be superior for nilotinib with a minimum of 24 months of follow-up. Achievement of MMR by 24 months was significantly higher for nilotinib 300 mg twice daily (71%, P < 0.0001) and nilotinib 400 mg twice daily (67%, P < 0.0001) compared with imatinib (44%). Achievement of CMR continued to be significantly higher for nilotinib 300 mg twice daily (26%, P < 0.0001) and nilotinib 400 mg twice daily (21%, P = 0.0004) compared with imatinib (10%). The safety and tolerability profiles of nilotinib and imatinib were unchanged with longer follow-up.

### Nilotinib for Newly Diagnosed CML-CP

<table>
<thead>
<tr>
<th>Phase of Study</th>
<th>Number of Patients (n)</th>
<th>Dose</th>
<th>CCyR %</th>
<th>MMR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>67</td>
<td>400 mg twice daily</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>II</td>
<td>73</td>
<td>400 mg twice daily</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>III</td>
<td>282</td>
<td>300 mg (nilotinib)</td>
<td>80</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>281</td>
<td>400 mg (nilotinib)</td>
<td>78</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>283</td>
<td>400 mg (imatinib)</td>
<td>65</td>
<td>22</td>
</tr>
</tbody>
</table>

### Dasatinib Studies

The design of our dasatinib trial in the frontline setting was similar to the nilotinib phase II study. The dasatinib study included 62 patients with Ph+ CML-CP diagnosed within 6 months of enrollment. The patients were either untreated or treated with only hydroxyurea, anagrelide, or imatinib 400 mg/day for a maximum of 1 month prior to study entry. The dasatinib trial included a 100 mg/day arm (n = 31) and a 50 mg twice daily arm (n = 31). Similar to the nilotinib trial, the primary and secondary endpoints of the dasatinib trial were MMR and CCyR rates at 12 months, and the response definitions were identical to those in the nilotinib trial.

At a median follow-up of 24 months, 98% and 71% of patients evaluable at 12 months had achieved a CCyR and an MMR respectively. Responses were also rapid. At 3 months, CCyR and MMR rates were 81% and 24%, subsequent 6 month data showed an increase to 94% and 63% respectively. At 24 months, CCyR and MMR rates were 84% and 87%. At 12 and 24 months, rates of CMR were respectively 7% and 6% in evaluable patients. Additionally, progression to AP/BP has yet to be seen in the patients. Grade 3/4 nonhematologic AEs were uncommon and included fatigue (6%), joint and muscle pain (6%), and dyspnea (5%). Pleural effusions were
observed in 13% of patients, with only one instance of a grade 3 pleural effusion. Grade 3/4 hematologic AEs included neutropenia (21%), thrombocytopenia (10%), and anemia (6%).

Subsequently, DASISION, a phase 3 randomized, open-label, multicenter study comparing the efficacy and safety of dasatinib 100 mg once daily with that of imatinib, was initiated15. 519 patients with newly diagnosed CML-CP were randomly assigned 1:1 to either dasatinib 100 mg once daily (n = 259) or imatinib 400 mg/day (n = 260). Confirmed CCyR by 12 months was the primary endpoint of the study. The best cumulative MMR rate by 12 months was significantly higher for dasatinib (46%, P < 0.0001) than for imatinib (28%). Best cumulative rates of CCyR by 12 months were also significantly higher for dasatinib (83%, P < 0.001) than for imatinib (72%). Along with these higher response rates, there were fewer progressions to AP/BP with dasatinib (1.9%) than with imatinib (3.5%).

Grade 3/4 nonhematologic AEs were uncommon across both treatment arms. Pleural effusions were mostly grade 1-2 and occurred in 10% of patients treated with dasatinib. Rates of grade 3/4 anemia and thrombocytopenia were higher on dasatinib than imatinib. Overall, discontinuations due to drug-related AEs occurred in 5% of patients in the dasatinib arm and 4% of patients in the imatinib arm.

Dasatinib for Newly Diagnosed CML-CP

<table>
<thead>
<tr>
<th>Phase of Study</th>
<th>Number of Patients (n)</th>
<th>Dose</th>
<th>CCyR %</th>
<th>MMR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>62</td>
<td>100 mg once daily</td>
<td>98</td>
<td>71</td>
</tr>
<tr>
<td>III</td>
<td>259</td>
<td>100 mg (dasatinib)</td>
<td>77</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>260</td>
<td>400 mg (imatinib)</td>
<td>67</td>
<td>28</td>
</tr>
</tbody>
</table>

NEW AGENTS TO TREAT CML POST TKI FAILURE

Multiple strategies to overcome TKI failure are under investigation. Post imatinib failure, nilotinib and dasatinib are both FDA approved and continue to show sustained efficacy, with almost half of patients with imatinib failure being able to achieve a CCyR17,18. However, in patients in whom imatinib has failed because of the presence of the T315I mutation and in patients who have failed 2 TKIs, there are no currently available standard options. For these patients, new agents are being developed and early results seem promising.

Ponatinib (AP24534)

Ponatinib is one of the most promising agents for treatment of T315I mutation. Ponatinib is an orally available multi-TKI designed using a structure-based approach as a pan-BCR-ABL inhibitor19. Ponatinib potently inhibits the enzymatic activity of BCR-ABL-T315I, the native enzyme, and all other tested mutants. It also prevents the emergence of resistant mutants at concentrations of 40 nM. In a phase 1 clinical trial of AP24534 at doses from 2-60 mg in 60 patients with CML (44 with CP, 7 AP and 9 BP), complete hematologic response (CHR) was achieved or maintained in 95% of patients treated in CP; major hematologic responses were also achieved in 35% of patients treated in advanced stages of the disease19. More importantly, 25 of 38 (66%) evaluable patients treated in CP achieved a MCyR, including 20 (53%) CCyR. All 9
patients with T315I mutations in CP achieved MCyR with 89% of them achieving CCyR. The most common drug-related adverse events were elevations of lipase and amylase at a dose of 60 mg daily. Grade 3 or 4 thrombocytopenia occurred in 9% of patients, with no grade 3-4 drug-related neutropenia. Currently, our institution is testing Ponatinib in a phase II, multinational study focusing on patients who have failed dasatinib and/or nilotinib therapies including a subset of patients with the T315I mutation.

DCC-2036
While second generation BCR-ABL inhibitors dasatinib and nilotinib both inhibit many imatinib-resistant mutations, neither drug is effective against the T315I mutation. DCC-2036 is a new tyrosine kinase inhibitor that overcomes imatinib resistance by binding to a different domain on the BCR-ABL protein thus avoiding interaction with the mutated regions most commonly associated with resistance. DCC-2036 retained full potency against the T315I mutant kinase in preclinical studies and therefore warrants testing in patients who have failed prior TKI therapies or who have the T315I mutation and are diagnosed with either Ph+ CML or Ph+ ALL. DCC-2036 is also active against wild type BCR-ABL and other mutants commonly seen after imatinib failure. Early results in our phase I clinical trial of DCC-2036 suggest evidence of clinical benefit.

INCB018424
Abnormalities of Janus Kinase (JAK) function have been associated with a number of hematological disorders. For example, chromosomal translocations resulting in TEL-JAK2 constructs lead to the constitutive activation of STAT5, IL-3-independent cellular proliferation, and leukemogenesis. The translocation t(9;12)(p24;p13) results in the fusion of the kinase catalytic region of JAK2 with the transcription factor TEL generating the constitutively active TEL-JAK2. Similarly, infection with oncogenic viruses such as type I human T-cell lymphotrophic virus and Abelson murine leukemia viruses results in enhanced kinase activity of Jaks, possibly accounting for their leukemogenic potential.

Abnormalities of the JAK-STAT pathways have been described in a variety of leukemias, and their inhibition can be a goal for leukemia therapy. Recent reports suggest that JAK2 activation is critical in maintaining the leukemic stem cell in CML.

INCB018424 phosphate is an inhibitor of the JAKs that is currently being developed for treatment of myeloproliferative disorders. Our current study is examining the potential role of this drug in CML. Patients with CML who are resistant to at least 2 TKIs and have no standard stem cell transplant option are eligible as well as patients with relapse/refractory CML in blast crisis.

Hedgehog Inhibitors
Extensive evidence has been developed for a role for Hedgehog (HH) signaling, including the Smoothened transmembrane protein (Smo), in the maintenance and proliferation of CML stem cells. Using a variety of models, activation of Smo was demonstrated in Bcr-Abl+ cells, and their proliferation was shown to be more dependent on Smo than that of normal hematopoietic stem cells. Conversely, inhibition of HH signaling reduced self-renewal in vitro, in vivo, and in murine retransplantation models. Additionally, reduction of stem cells (defined as clonal progenitors developing during long-term culture) by Smo inhibition was demonstrated in CML patient samples. Recently, the importance of Smo signalling in CML stem cell function was independently demonstrated; constitutive Smo expression increased whereas conditional deletion reduced this population. In a recent preclinical study, the combination of nilotinib plus the Smo inhibitor LDE225 was reported to provide supra-additive inhibition of primitive CML stem cells. Thus, the combination of TKI with HH inhibitor provides an important opportunity to potentially cure patients with CML. The sequential combination of TKI and HH inhibitor is planned at our institution for patients with minimal residual disease and/or suboptimal response to TKI. We are currently conducting a phase I study of the hedgehog inhibitor PF-04449913 for patients with CML (and other hematologic malignancies) who have failed prior therapy. The first portion of the study tests this agent by itself. In the second portion of the study, we will combine this agent with a tyrosine kinase inhibitor.

ERADICATING RESIDUAL DISEASE
Despite extraordinary progress, true cure of CML is not generally achieved by Abl kinase inhibitors. TKIs are potent inhibitors of Bcr-Abl kinases, resulting in rapid reduction of the majority of cells carrying the Ph chromosomal marker. However, suppression of Abl-driven hematopoiesis may be insufficient to eradicate quiescent stem cells. Studies assessing the combination of TKIs with promising agents are to be initiated. If successful, this strategy could lead to the safe, permanent discontinuation of therapy in patients with a good response.
**Omacetaxine**

Omacetaxine (homo-harringtonine), a small molecule inhibitor of ribosomal processes that affects the activity of MCL-1, c-myc, and cyclin D1, acts independently of Bcr-Abl activity\(^2\). This agent has shown activity in patients with the Bcr-Abl T315I mutation and in patients who have failed two TKIs\(^2\). In addition, there is growing evidence suggesting synergy with TKI and potential activity of omacetaxine against the dormant stem cells\(^2\). Therefore, omacetaxine may be additive or synergistic with TKI; such a combination is an attractive strategy to eliminate the leukemic stem cell which is insensitive to all available tyrosine kinase inhibitors. A phase II, single-arm trial combining omacetaxine and TKI in patients with suboptimal response to TKI with persistent minimal residual disease is to be initiated at our institution.

**Hypomethylating agents**

Aberrant DNA methylation can lead to carcinogenesis by silencing tumor suppressor or other critical genes\(^3\). In CML, DNA methylation increases in concert with disease progression\(^3\). Reversal of DNA methylation has been investigated as a target for cancer therapy\(^4\). We have previously shown that decitabine, a hypomethylating agent, has single-agent clinical activity in CML\(^4\), including imatinib-resistant cases. In addition, we showed that combination therapy with decitabine and imatinib was well tolerated and active in advanced phase CML without BCR-ABL kinase mutations\(^4\). Interestingly, we and others have demonstrated that the synergy between decitabine and a TKI such as imatinib depends on residual sensitivity to imatinib\(^4\). Thus, in patients completely resistant to TKI, adding decitabine may not be sufficient to reverse resistance. As such, this synergy may be optimal in patients who were treated with TKI and have persistent minimal residual disease. Such a combination clearly provides a distinct therapeutic approach from TKI alone and may exert an antileukemic effect in CML stem cells that are resistant to all TKIs. A combination single-arm trial is about to be initiated at our institution for patients with persistent minimal residual disease or suboptimal response to TKI therapy.

**PEG-interferon**

Historically, interferon has been a very useful drug in CML, and patients have been cured. Imatinib proved to be superior and better tolerated thus displacing interferon as the initial therapy of CML. However, interferon has important anti-leukemia activity, immunomodulatory properties, and a possible role in eradicating the leukemic stem cell, making it potentially useful for patients with CML. Pegylated interferon is considerably better tolerated than regular interferon. It is administered only once weekly and has better anti-leukemia activity. We are currently exploring the addition of pegylated interferon for the management of minimal residual disease in two settings:

1) Single agent: For patients who have had a good response to tyrosine kinase inhibitors (at least a complete cytogenetic response) but have not achieved a major molecular response or complete molecular response, we will add pegylated interferon at low doses to the ongoing TKI therapy to monitor whether all evidence of disease may be eradicated.

2) Combination with PRI1 vaccine: This vaccine has shown some exciting preliminary results eradicating leukemic cells through a specific immune mechanism. By combining this vaccine with pegylated interferon, we will explore whether a more specific immune recognition leading to eradication may be achieved in patients who have failed to achieve a major molecular response or complete molecular response. The vaccine is added while patients continue with their standard TKI therapy.

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**MONITORING RESPONSE AND RESISTANCE TO THERAPY IN CML**

Several monitoring methods are available to assess response and resistance to therapy in CML: 1) cytogenetics, 2) FISH, 3) qualitative PCR, and 4) mutational studies. Details of advantages and disadvantages of each are detailed in a recent review\(^5\).

A simple way of monitoring patients outside the context of a protocol is as follows:

1) Bone marrow for morphology and cytogenetics pretreatment, at 6 and 12 months to assess imatinib response, then every 1-2 years if stable CCyR

2) Peripheral blood FISH can help assess the cytogenetic response. Additionally, PB FISH can also be used for long-term monitoring (e.g. every 6-12 months) although it would not allow for detection of chromosomal abnormalities in Ph-negative metaphases.

3) In cytogenetic CR, monitor with QPCR every 6 months. Aim for BCR-ABL/ABL ratio of < 0.1% in the international scale (ie, 3-log reduction from standardized baseline). For patients in CCyR, do not react drastically to rises in transcript levels unless consistent with loss of major molecular response (BCR-ABL/ABL ratio > 0.1% in the international scale) and with a 1-log increase. In these cases, resort to lower-risk treatment changes, such as
increasing the imatinib dose, as opposed to higher-risk treatment changes, such as allogeneic transplantation.

4) In standard practice, do not perform mutational analysis at pretreatment or in patients responding to imatinib. Mutational studies are best done only in patients already on imatinib who are demonstrating either cytogenetic or hematologic relapse. About 50% of these patients will show mutations. A T315I mutation should lead to consideration of allogeneic stem cell transplant. The mutations IC50 to a particular agent is a better guide to select therapy. For example, most P-loop mutations respond well to dasatinib while mutations V299L and F317L respond well to nilotinib. Please consult with a CML expert in such situations.

MANAGEMENT OF SIDE EFFECTS

Some of the most common adverse events observed with tyrosine kinase inhibitors and suggested management options are listed in the following table.

Management of the Most Common Nonhematologic Adverse Events Observed During Therapy with Tyrosine Kinase Inhibitors

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>• Antiemetics as needed</td>
</tr>
<tr>
<td></td>
<td>• Take imatinib with food, abundant fluids</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>• Use loperamide or diphenoxylate and atropine</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>• Diuretics as needed</td>
</tr>
<tr>
<td></td>
<td>• Monitor electrolytes if diuretics are used</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>• Steroid-containing cream</td>
</tr>
<tr>
<td></td>
<td>• Surgical management frequently followed by recurrence</td>
</tr>
<tr>
<td>Skin rash</td>
<td>• Symptomatic management (e.g. diphenhydramine), topical or systemic steroids</td>
</tr>
<tr>
<td></td>
<td>• Adequate sun protection</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>• Quinine or tonic water; calcium gluconate</td>
</tr>
<tr>
<td></td>
<td>• Electrolyte replacement as needed</td>
</tr>
<tr>
<td>Arthralgias, bone pain</td>
<td>• Nonsteroidal antiinflammatory agents</td>
</tr>
<tr>
<td></td>
<td>• Nonsteroidal not recommended for patients taking dasatinib</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>• Treatment interruption until recovery to grade 1 or less, then reduce dose</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>• Treatment interruption</td>
</tr>
<tr>
<td></td>
<td>○ Common with nilotinib among patients with Gilbert’s syndrome, with minimal clinical consequences</td>
</tr>
<tr>
<td></td>
<td>• Monitor</td>
</tr>
<tr>
<td>Elevated lipase/amylase</td>
<td>• Clinical evaluation for signs or symptoms of pancreatitis</td>
</tr>
<tr>
<td></td>
<td>○ If no evidence of pancreatitis, continued monitoring</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>• Replacement therapy; monitor closely</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>• Assess before starting therapy and correct any electrolyte abnormalities</td>
</tr>
<tr>
<td></td>
<td>• Avoid coadministration of other agents that may prolong QTc</td>
</tr>
<tr>
<td></td>
<td>• Consider alternative therapies in patients with significant QTc prolongation despite these measures</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>• Treatment interruption, diuretics</td>
</tr>
<tr>
<td></td>
<td>• Corticosteroids may be of benefit to some patients</td>
</tr>
<tr>
<td></td>
<td>• Thoracentesis when unresponsive or with major symptoms</td>
</tr>
</tbody>
</table>
The most common adverse event seen with tyrosine kinase inhibitors is myelosuppression, with grade 3 or 4 neutropenia (absolute neutrophil count $< 1 \times 10^9/L$) and thrombocytopenia (platelet count $< 50 \times 10^9/L$) in up to 30% of patients, and anemia in 5% to 15% of patients. Myelosuppression most often occurs early during the course of therapy (first 2-3 weeks) and is transient. For those patients who develop grade 3 or 4 neutropenia or thrombocytopenia, temporary interruption of therapy is recommended. Therapy can resume once the counts recover to levels above those defining grade 3 cytopenias. If recovery occurs within 2 weeks, treatment can be reinitiated at the same dose; however, a dose reduction is recommended if recovery takes longer than 2 weeks. Hematopoietic growth factors—filgrastim for neutropenia, epoetin alfa for anemia, and oprelvekin for thrombocytopenia—have been reported to benefit patients with recurrent myelosuppression that limits proper administration of therapy. However, the long-term safety of this approach is not known. In the near future, a clinical trial will be initiated investigating the role of eltrombopag, an agonist of the c-mpl receptor, in correcting thrombocytopenia in patients whose CML therapy is limited by recurrent low platelet counts.

ADVANCED PHASE DISEASE

Despite the progress made in CML, the treatment of patients in accelerated or blast phase remains grossly unsatisfactory. Although some patients may respond to the treatment with single-agent TKI, the overwhelming majority of responses are short-lived. This highlights the need to develop additional treatment options for these patients. TKI in combination with standard chemotherapy has been attempted with some success but with considerable toxicity. As the disease progresses, several new genetic and epigenetic phenomena have been described. Of interest is increased methylation of critical genes. Hypomethylating agents have been shown to be active in patients with CML after failure to TKI and to have synergistic activity with TKI. We are initiating a trial in which patients with accelerated or blast phase will receive therapy with decitabine combined with dasatinib. The objective of this trial is to determine whether such a combination may lead to more and more durable responses in this patient population.

THE POTENTIAL FOR CURE

The impact of using more potent agents in the frontline setting in order to discontinue TKI therapy at a later time remains to be determined. The future of CML therapy may include early use of these potent agents, perhaps in combination with new molecules, to help more patients achieve CMR, leading to therapy discontinuation and cure.

For information on any of the clinical trials mentioned in this issue, please contact Drs. Jorge Cortes, Hagop Kantarjian, Elias Jabbour, or Alfonso Quintas-Cardama.

REFERENCES

REFERENCES (continued)


REFERENCES (continued)


CLL Treatment Priorities

1. Untreated
   - Fludarabine + Cytoxan + Rituximab (FCR) (2008-0431)
   - Lenalidomide + Rituximab (2008-0385)

2. Prior Therapy
   - Fludarabine + Cytoxan + Rituximab (ID99-338)
   - FBR (2009-0546)
   - 8-Chloro-adenosine (2004-0144)
   - AMD 3100 (2008-0725)
   - ABT-263 + FCR or BR (2009-0077)
   - Lenalidomide + Ofatumumab (2008-0314)
   - Revlimid (2007-0213)
   - Bafetinib (2010-0175)
   - PCI-32765 (2010-0314)

3. Other

AML/MDS Treatment Priorities

1. Newly Diagnosed
   A. Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17): ATRA + Arsenic Trioxide +/- Idarubicin (2006-0706)
   B. Cytogenetic feature: Inv16 or t(8:21): Fludarabine + Ara-C + Idarubicin (2007-0147)

C. Younger Patients:
   - IA + SAHA (2007-0835)
   - Ida + Ara-C (2006-0813)
   - Clofarabine + IA (2009-0431)
   - Plerixafor + Daunorubicin + Ara-C (2009-0503)
   - BID FA (2009-0781)

Older Patients:
   - Clofarabine + Ara-C + DAC (2007-0039)
   - Vorinostat + Aza (2007-0685)
   - AZD1152 vs low-dose Ara-C (2009-0217)
   - Vidaza + Revlimid (2009-0467)
   - Alternating DAC + Sapacitabine (2009-1002)
   - Sapacitabine (2009-1002)
   - Azacitidine vs Conventional Care (2009-1001)
   - Sorafenib + Azacitidine (2010-0511)

2. Salvage Programs
   - Tamibarotene (2007-0512) in APL
   - Fludarabine + Ara-C + Mylotarg (2009-0781)
   - Lenalidomide (2006-0293)
   - Azacitidine (2007-0405)
   - Sapacitabine (2007-0727)
   - Plerixafor + Sorafenib (2008-0501)
   - DT388IL3 (2008-0313)
   - SAR103168 (2009-0196)
   - Panobinostat (2009-0434)
   - Vidaza + Revlimid (2009-0467)
   - AC220 (2009-0560)
   - Plerixafor + Clofarabine (2009-0536)
   - Oral Panobinostat + Vidaza (2009-0619)
   - PR104 (2009-0772)
   - MK-2206 (2010-0243)
   - SGI-110 (2010-0615)
   - Ara-C +/- Vosaroxin (2010-0692)
   - CIA vs FAI (2010-0788)

3. Low Risk MDS and CMML with <10% Blasts
   - Azacitidine (2007-0405)
   - Thymoglobulin + Cyclosporin (2005-0115)
   - LBH589 (2007-0713)
   - ARRY-614 (2009-0129)
   - Dac +/- Clofarabine (2008-0092)
   - Oral Decitabine (2009-0286)
   - Telintra + Revlimid (2009-0965)
   - Alemtuzumab (2010-0187)
• ON 01910 (2010-0209)

ALL Treatment Priorities

1. Newly Diagnosed or Primary Refractory
   (one non-hyper-CVAD induction)
   A. Modified Hyper CVAD (ID02-230)
   B. Burkitt's: Hyper CVAD + Rituximab
      (ID02-229)
   C. Ph+: Hyper CVAD + Dasatinib (2006-0478)
   D. Age <31: Augmented BFM (2006-0375)
   E. T cell: Hyper CVAD + Nelarabine
      (2006-0328)

2. Salvage Programs
   • Clofarabine + Cytoxan (2005-0552)
   • MOAD (2008-0267)
   • DT2219ARL (2008-0519)
   • RAD001 + Hyper CVAD (2009-0100)
   • CMC-544 (2009-0872)
   • Ponatinib (2010-0570)

CML Treatment Priorities

1. CML Chronic Phase
   • Dasatinib (2005-0422)
   • Nilotinib (2005-0048/2009-0683)

2. CML Blastic Phase
   • Ara-C + Fludarabine (2009-0781)

3. T315I Mutations or Advanced Phases
   • AP24534 (2008-0046/2010-0570)
   • DCC-2036 (2008-0732)

Myeloproliferative Disorders

• Pomalidomide (2007-0199)(MF)
• Pegasys (DM03-0109)
• INCBO18424 (2007-0169)

• 2CDA + Ara-C (DM97-232) (HES only)
• AZD1480 (2009-0067)
• Masatinib (2008-0275)
• LY2784544 (2010-0167)
• SB939 (2010-0319)
• Imetelstat (2010-0672)

Phase I/II Agents for Hematologic Malignancies

• L-Grb2 Antisense (2003-0578)
• SB939 (2007-0848)
• INCBO18424 (2007-0925)
• RO5045337 (2007-0408)
• DCC-2036 (2008-0732)
• AS703026 (2009-0195)
• GSK1120212 (2009-0239)
• Nelarabine (2009-0717)
• Belinostat + Bortezomib (2009-0752)
• LY2523355 (2009-0785)
• ABT348 (2009-0788)
• Thiarabine (2009-1000)
• PF-04449913 (2010-0078)
• TG02 (2010-0244)
• TH-302 (2010-0268)
• ON01910 (2010-0303)
• INCBO18424 (2010-0450)
• KB004 (2010-0509)
Leukemia INSIGHTS

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