

## New Strategies in Chronic Myelogenous Leukemia (CML)

### Introduction

Approximately 80% to 90% of patients with CML in early chronic phase achieve a complete cytogenetic response when treated with imatinib. With a median follow up of 5 years, only approximately 6% of patients have progressed to accelerated or blast phase, and the overall survival is 95%.<sup>1</sup> However, resistance to imatinib occurs in some patients. The most common mechanism of resistance is point mutations of the Bcr-Abl kinase domain which are detected in 30% to 50% of resistant cases. Over 40 different mutations have been reported which vary in their extent of resistance to imatinib.<sup>2</sup> Other mechanisms of resistance include BCR-ABL-dependent (e.g., overexpression and amplification) and BCR-ABL-independent mechanisms (e.g., overexpression of Src-related kinases).<sup>3</sup> Thus, there is interest in developing new agents/strategies which may over-

come or prevent the development of resistance. Targeted approaches have been favored and many have produced significant clinical responses. These are reviewed here by Drs. Hagop Kantarjian and Jorge Cortes. For any further questions please contact either or any leukemia physician.

### Imatinib

The standard dose of imatinib for patients in chronic phase is 400 mg daily. However, in the initial phase I study,<sup>4</sup> no dose limiting toxicity was identified at doses of up to 1000 mg daily and a maximum tolerated dose was not identified. In addition, there was a correlation between dose and response, with most responses occurring at doses above 300 mg daily. In addition, approximately 40% of patients in chronic phase who fail to respond to the standard dose may respond when their dose is increased to 800 mg daily. Some single-arm, phase II studies have suggested that higher doses of imatinib (i.e., 600 to 800 mg daily) used as the starting dose for patients in chronic phase may result in improved responses.<sup>5-</sup>

<sup>8</sup> Using this higher dose, over 90% of patients have achieved a complete cytogenetic response and approximately 25% have achieved undetectable levels of Bcr-Abl by PCR (i.e., "complete" molecular response). Responses occur significantly faster with higher doses. For example, after 6 months of therapy over 85% of patients treated with the high dose have achieved a complete cytogenetic response, compared to 55% with the standard

dose. Higher doses appear to be well tolerated and over 80% of patients have continued receiving the high dose after 12 months of therapy. Although these results are encouraging and appear to be superior to those achieved with standard dose in previous studies, there has not been a direct comparison of standard and high-dose to confirm superiority. In the most recent update of our experience with high-dose imatinib, the rate of complete cytogenetic responses was significantly higher with high-dose compared to a historical population treated with standard-dose imatinib (91% vs 78%;  $p=0.03$ ). The rate of major and complete molecular responses was also significantly higher in the group treated with high-dose imatinib. Most important, event-free survival and survival free from transformation to accelerated or blast phase were significantly superior for those treated with high-dose imatinib as initial therapy.

An ongoing randomized trial of standard- versus high-dose imatinib is currently ongoing. Patients are randomized in a 2:1 ratio to receive 400 mg daily or 800 mg daily as their starting dose.

For information on this study, please contact Dr. Jorge Cortes or any other leukemia physician.

### Management of Myelosuppression

During the course of treat-

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ment with imatinib and other tyrosine kinase inhibitors, 30% to 50% of patients develop grade 3 or 4 anemia, thrombocytopenia or neutropenia. Cytopenias most frequently occur during the first 2 to 3 months of therapy and in many instances they do not recur. This early myelosuppression is managed with a temporary treatment interruption if there is grade  $\geq 3$  neutropenia (absolute neutrophil count  $< 1 \times 10^9/L$ ) or thrombocytopenia (platelets  $< 50 \times 10^9/L$ ). Upon recovery, the tyrosine kinase is restarted at the same dose if counts recover within 2 weeks or at a lower dose if recovery takes  $> 2$  weeks.<sup>9</sup> For the occasional patient with prolonged and recurrent grade 3 myelosuppression, hematopoietic growth factors have been used. Filgrastim (G-CSF) has been reported to improve the neutropenia allowing uninterrupted therapy with imatinib and frequently improving response to therapy.<sup>10</sup> For patients with thrombocytopenia, low dose interleukin-11 (10 mcg/kg, 3-5 times per week) has been reported to improve the platelet count, allow continuation of therapy sometimes with dose escalation, and improve response in some patients.<sup>11</sup> Erythropoietin and darbepoetin have also been reported to improve anemia associated with tyrosine kinase therapy.<sup>12</sup> These are all investigational uses of

these growth factors. Ongoing and future studies for management of imatinib-associated myelosuppression at MDACC include:

1) Low-dose interleukin-11 for patient with recurrent or persistent thrombocytopenia while on imatinib therapy.

2) A study of erythropoietin for imatinib-associated anemia will start in the near future.

For additional information on studies for management of imatinib-associated myelosuppression please contact Dr. Jorge Cortes or any other leukemia physician.

## New tyrosine kinase inhibitors

More potent Bcr-Abl and dual Src/Abl kinase inhibitors are being developed. At least four of them are already in phase I or phase II trials: nilotinib (AMN107; Tassigna<sup>®</sup>), dasatinib (BMS-354825; Sprycel<sup>®</sup>), SKI-606, and INNO-406.

## Nilotinib

Nilotinib was developed following a rational drug design with imatinib as the lead compound. Imatinib fits tightly into the canonical ATP-binding site of the kinase domain and captures a specific inactive conformation of the activation loop of Abl. This close interaction made changes in

the core of imatinib prohibitive. However, the N-methylpiperazine group of imatinib was more amenable to modifications. Nilotinib was developed through replacements of this ring and proved to be approximately 30 times more potent than imatinib in vitro against BCR-ABL, while maintaining similar activity against other kinases.<sup>13</sup> Nilotinib, like imatinib, binds only to the inactive configuration of Bcr-Abl and inhibits the kinase activity of most BCR-ABL mutants tested, except T315I. A phase I study of nilotinib in patients with CML in all phases of the disease who had failed prior imatinib therapy has been reported.<sup>14</sup> Dose levels were 50 to 1200 mg orally daily then 400 to 600 mg orally BID. Significant clinical activity was identified in all CML phases, with hematologic response rates of 50% to 80%, and cytogenetic response rates of 20% to 50%. Responses were observed in most patients carrying BCR-ABL mutants. The maximum tolerated dose is 400 mg twice daily with dose limiting toxicities being myelosuppression, and transient bilirubin elevations.<sup>14</sup> Phase II studies have confirmed the high response rates and favorable toxicity profile of nilotinib after imatinib failure (Table 1).<sup>15</sup>

Based on this experience, we have initiated a study of nilotinib as first line therapy for patients with CML in early chronic phase with the objective to improve the overall molecular response and to achieve responses earlier since early achievement of response has been correlated with improved long-term outcome. The preliminary data in 13 patients treated suggest that indeed the higher potency is translating into better responses, with 93% of patients in complete cytogenetic response after only 3 months of therapy, and 100% at 6 months. This compares favorably to rates

Table 1. Response in phase 2 studies of nilotinib after imatinib failure

Response	Response Percentage		
	Chronic	Accelerated	Myeloid blastic
	N=81	N=25	N=24
• Hematologic	69	40	13
CHR	69	16	4
• Cytogenetic response	68	56	29
Complete	32	16	21
Partial	14	12	8

→ CHR=complete hematologic response

at 6 months of 88% and 56% with high- and standard-dose imatinib, respectively ( $p=.0001$ ). This study continues accrual.

In addition, considering the efficacy of nilotinib after failure to imatinib, there is interest in exploring earlier intervention in patients who have not met the criteria for failure but have a suboptimal response as defined by the recommendations of a panel of CML experts.<sup>16</sup>

There are several ongoing studies with nilotinib in CML at our institution:

1) Nilotinib in patients with newly diagnosed Ph-positive CML in chronic phase.

2) Studies of Nilotinib in hyper-eosinophilic syndrome, mastocytosis, polycythemia vera, AML and MDS, and other hematologic cancers.

3) A phase I study of nilotinib in combination with imatinib will start soon for patients with imatinib failure to test the hypothesis, demonstrated in vitro, that the two agents may be synergistic in preventing the emergence of mutations.

4) A study of nilotinib for patients with suboptimal response to imatinib.

For information, please contact Dr. Hagop Kantarjian, Dr. Jorge Cortes or any other leukemia physician.

## Dasatinib

Dasatinib is an ATP-competitive, dual-specific Src- and Abl-kinase inhibitor. Src activation may play a role in the development and progression of many tumors. Src kinase modulates signal transduction through multiple oncogenic pathways including PDGFR, VEGFR and others. Dasatinib is structurally unrelated to imatinib and is a 100- to 300 times more

potent inhibitor of Bcr-Abl kinase activity. Dasatinib binds to both the inactive and active configurations of Bcr-Abl. The crystallographic structure of the kinase-drug interaction shows dasatinib to make fewer contacts with Abl than does imatinib or nilotinib.<sup>17</sup> It induces significant inhibition of the kinase activity of cells transfected with the wild-type Bcr-Abl as well as 14 of 15 mutants of Bcr-Abl, the exception being T315I.<sup>18</sup> Phase I studies used dasatinib 15 to 180 mg orally daily (mostly in chronic phase post imatinib failure) and 35 to 90 mg orally BID (in accelerated or blast phase after imatinib failure).<sup>19</sup> In chronic phase, 93% achieved CHR and 63% of evaluable patients achieved a cytogenetic response (complete in 35% of all treated). In accelerated phase, a hematologic response was achieved in 81%, and a cytogenetic response in 36%. In blastic phase, a hematologic response was achieved in 61%, and a cytogenetic response in 52%.<sup>19</sup> Responses were observed in patients with a wide variety of mutations. The recommended dose for phase II studies is 70 mg twice daily. DLTs are myelosuppression and occasional pleural effusions. Subsequent phase II studies in all phases of the disease confirmed the significant activity of dasatinib with a favorable toxicity profile (Table 2).

These results led to the approval of dasatinib for patients with CML in all phases of the disease after failure to imatinib, as well as patients with Philadelphia chromosome acute lymphoblastic leukemia (ALL) who have failed other therapies.

Based on these favorable results we have initiated a trial for patients with CML in chronic phase who have received no prior therapy with dasatinib as first-line treatment. Considering the potency relative to imatinib, we are investigating whether dasatinib may induce faster cytogenetic responses and a higher rate of molecular responses at 12 months. Preliminary results in 27 patients suggest that approximately 80% of patients achieve a complete cytogenetic response after 3 months of therapy, results that compare favorably to those achieved with imatinib whether at standard- or high-dose.

Dasatinib is also being explored in settings compatible with a suboptimal response to imatinib. That is, patients who do not meet the definition for imatinib failure but whose response could be improved by earlier intervention with a more potent agent.

Ongoing studies with dasatinib are as follows:

1) Dasatinib as front-line therapy in patients with newly diagnosed Ph-positive CML in chronic phase.

Table 2. Response in phase 2 studies of dasatinib in CML after imatinib failure

Response	Response Percentage			
	Chronic	Accelerated	Myeloid Blastic	Lymphoid Blastic
	N=387	N=174	N=109	N=48
• Hematologic	90	59	49	39
CHR	90	34	25	29
• Cytogenetic response	45	39	44	44
Complete	40	25	25	38
Partial	11	10	6	6

→ CHR = Complete Hematologic Response

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2) Dasatinib in other hematologic malignancies including hypereosinophilic syndrome, mastocytosis, polycythemia vera, myeloid metaplasia, AML-MDS, and others.

3) Dasatinib in combination with chemotherapy (Hyper-CVAD) for patients with Ph-positive ALL.

4) Dasatinib for patients with suboptimal response to imatinib.

For information please contact Drs. Jorge Cortes, Hagop Kantarjian, or any other leukemia physician.

## SKI-606

SKI-606 is another orally available, potent dual Src/Abl kinase inhibitor.<sup>20</sup> Studies in vitro have shown SKI-606 to be approximately 200-fold more potent than imatinib as an inhibitor of Bcr-Abl phosphorylation. In addition, cell lines expressing several of the most common imatinib-resistant Bcr-Abl mutants and primary cells from patients with imatinib-resistant mutations in Bcr-Abl are sensitive to SKI-606. Unlike imatinib, nilotinib and dasatinib, SKI-606 exhibits no significant inhibition of c-kit and PDGFR. This differential selectivity could result in clinical benefit by altering the safety profile as the development of some of the adverse events such as pleural effusions have been attributed to the effect of these agents on PDGFR. SKI-606 has been evaluated in a phase I study in solid tumors with the DLT being diarrhea. No pleural effusions were seen in that study. An ongoing study is evaluating the safety and efficacy of SKI-606 in patients with CML who have failed therapy with imatinib. Preliminary results suggest the drug has significant activity with a very favorable profile, with no DLT observed to date.

An ongoing study with SKI-606 is open for patients in any stage of

the disease that have failed prior therapy with imatinib. Patients resistant or intolerant to other tyrosine kinase inhibitors are also eligible. Preliminary results suggest good tolerance, with no pleural effusions seen, and several patients have achieved complete cytogenetic responses as early as 3 months after the start of therapy. For information on this study please contact Dr. Jorge Cortes or any other leukemia physician.

## INNO-406

INNO-406 (NS-187) is another dual inhibitor of Abl and Src family of kinases (specifically Lyn).<sup>21</sup> INNO-406 is 25-to-55 times more potent than imatinib against the BCR-ABL-positive leukemia cell lines K562 and KU812 and against BaF3 cells over expressing wild-type BCR-ABL (BaF3/wt). The inhibition of PDGFR and c-kit with INNO-406 and imatinib is equivalent. In animal models, INNO-406 is at least 10 times more potent than imatinib, prolonging survival of mice transfected with Bcr-Abl-positive leukemias. Furthermore, INNO-406 has an ability to inhibit the kinase activity of mutated ABL proteins which have been reported to be involved in imatinib-resistance (including L387M, H396R, Q252R, F311L, and E255K), and prolonged survival of mice harboring leukemias with these mutations. These data suggest that INNO-406 would be effective in imatinib-resistant CML patients.

An ongoing phase I study is investigating the use of INNO-406 in patients who have failed therapy with imatinib (and in some instances other tyrosine kinase inhibitors). No dose limiting toxicity has been observed to date. For information on this study please contact Drs. Hagop Kantarjian, Jorge Cortes or any other leukemia physician.

## MK-0457

MK-0457 (VX-680) is a potent multikinase inhibitor with activity against aurora kinases. Two important observations have made this a very attractive agent. First, it is its ability to inhibit Abl and Bcr-Abl, and particularly, the ability to inhibit the T315I mutant of these kinases.<sup>22</sup> The biochemical structure of MK-0457 makes it able to bind and inhibit this kinase despite the presence of this mutation that prevents the inhibitory activity of all other kinase inhibitors tested in the clinic including imatinib, dasatinib and nilotinib. MK-0457 inhibited phosphorylation of Bcr-Abl with the T315I mutation as well as the proliferation of CML cells derived from a patient harboring this mutation.<sup>23,24</sup> The second attractive property of this agent is its ability to inhibit JAK-2, even in the presence of the V617F mutation which is present in all patients with polycythemia vera and a significant percentage of patients with other myeloproliferative disorders. A phase I study of MK-0457 is being conducted and the preliminary analysis has shown responses in some of the patients with CML who had failed imatinib and had the T315I mutation, as well as patients with myeloproliferative disorders with the JAK-2 mutation. Phase II studies of this agent, with particular attention to these patient populations, are starting. For information on this study please contact Drs. Francis Giles, Jorge Cortes or any other leukemia physician.

## Homoharringtonine (HHT)

HHT was effective in patients with CML as a single agent or in combinations.<sup>25,26</sup> HHT may

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be additive or synergistic with imatinib. A study by Marin et al included 10 patients with CML who had achieved at least a cytogenetic response with imatinib but had reached a plateau in transcript levels. In addition to continuing imatinib, SQ HHT 1.25 mg/m<sup>2</sup> twice daily for 5 days was given every 28 days. Seven patients had a decline in Bcr-Abl transcript levels which was greater than 1-log in 5. Two patients not in complete cytogenetic remission at the start of therapy became 100% Ph-negative.<sup>27</sup> In a study at MD Anderson SQ HHT was used to treat patients in chronic phase CML who had failed therapy with imatinib. All 5 evaluable patients achieved CHR and 3 achieved a cytogenetic response (1 complete, 2 minor) (Cortes, personal communication; April 2006). In addition, there is evidence of synergy between imatinib and HHT and this is currently being explored in the clinic. Patients with CML in any stage of the disease who have failed imatinib (or imatinib-naïve if they are in blast phase) receive therapy with HHT intravenously combined with imatinib. Preliminary analysis of the first 13 patients treated show that responses have been achieved in the presence of mutations. As expected, transient myelosuppression occurs in most patients but we have so far seen minimal extramedullary toxicity. Interestingly, some patients who have failed imatinib, nilotinib and dasatinib have shown early evidence of hematologic response. In addition, there is in vitro evidence of activity of HHT in CML cells carrying the T315I obtained from patients who have failed imatinib therapy. Based on this data, the following ongoing studies are available:

1) Intravenous HHT plus imatinib in patients who have failed imatinib therapy. Patients in any phase of

Table 3 Response to vaccinations in CML

Vaccine	No.	Concomitant therapy	Immune*	No. with response	
				Cytogenetic	Molecular
<b>Junction peptide</b>					
Pinilla-Ibarz <sup>31</sup>	12	IFN and/or Hy	3	1	1
Cathcart <sup>28</sup>	14	IFN (5), DLI (3), none (3), imatinib (2)	14	4 (3 IFN, 1 imatinib)	3 (2 DLI)
Bocchia <sup>29</sup>	16	Imatinib (10), IFN (6)	16	14/15 (9/9 imatinib, 5/6 IFN)	9 (4 complete) (6 imatinib, 3 IFN)
<b>PR1</b>					
Qazilbash <sup>30</sup>	10	Imatinib	6	4	4 (1 complete)

\* Immune response determined by different methods

the disease (chronic, accelerated or blastic) are eligible, and patients in blast phase can be imatinib-naïve.

2) Subcutaneous HHT for patients with CML in any stage who have failed imatinib therapy and carry the T315I mutation.

For information on these HHT studies, please contact Dr. Jorge Cortes, or any other leukemia physician.

## Vaccines and Other forms of Immunotherapy

Immune modulation may be partially responsible for the favorable results with IFN- $\alpha$ . Immunomodulation with vaccines in CML is attractive (table 3). Different types of antigens may be used in CML vaccines. One approach is to use tumor-specific antigens. The Bcr-Abl fusion creates a new sequence of amino acids only expressed in leukemic cells. Short peptides containing 8 to 12 amino acids, derived from the fusion region, have been tested. In a phase II trial, by Dr. Sheinberg and his group at Memorial Sloan Kettering, 14 patients received a mixture of 6 fusion peptides: 4 patients had a decrease in Ph-positive cells while continuing IFN- $\alpha$

therapy (n=3) or imatinib (n=1); 3 treated for molecular relapse after stem cell transplant had a transient complete molecular response (2 had concurrent DLI).<sup>28</sup> Using a similar approach, Bocchia et al in Italy vaccinated 16 patients with stable residual disease after at least 12 months of imatinib therapy or 24 months of IFN- $\alpha$  therapy with a CML-specific p210-b3a2 peptide. Among the 10 patients treated with imatinib, 5 of 9 patients with residual Ph-positive metaphases achieved a complete cytogenetic response, and 3 had undetectable levels of Bcr-Abl by PCR. Of the 6 patients treated post IFN- $\alpha$  therapy, 5 improved their cytogenetic response (2 achieved complete cytogenetic response).<sup>29</sup>

A different peptide used for immune stimulation is PR1, a nonapeptide derived from proteinase 3 and presented through HLA-A2.1. Proteinase 3 is expressed in myeloid cells during normal neutrophil maturation and is overexpressed in myeloid malignancies. Cytotoxic T-lymphocytes (CTL) specific for PR1 inhibit colony formation in an HLA-restricted manner. PR1-specific CTL are identified in most patients with CML who responded to IFN- $\alpha$  or allogeneic SCT, but not in non-responding patients or

in patients treated with chemotherapy. In one study, 10 patients with CML were treated with PR1: 1 achieved a complete cytogenetic response, and 3 had cytogenetic improvement.<sup>30</sup>

T-cell cytotoxicity might be particularly important in generating an immune response that can eliminate residual leukemia. A new cell therapy approach to treatment of CML is also being investigated. The strategy is based on the use of lethally irradiated, thus non-proliferating, clonal human T-cell line with MHC non-restricted killer activity against a broad range of tumors. The cell line, TALL-104, can lyse tumors across several species while sparing cells from normal tissues.

There are several studies ongoing with vaccines for patients with CML at M.D. Anderson, some in collaboration with many other centers in the USA. These include:

1) Studies of CMLVAX (junction peptide vaccine) in patients with Ph-positive CML who have received at least 12 months of therapy with imatinib and are in complete cytogenetic remission but have stable or increasing levels of BCR-ABL as determined by real-time PCR.

2) Studies of PR1 vaccine in patients with Ph-positive CML who are HLA-A2 positive who have received at least 12 months of therapy with imatinib and are in complete cytogenetic remission but have stable or increasing levels of BCR-ABL as determined by real-time PCR.

3) A study of TALL-104 for patients with CML who have failed or have a suboptimal response with imatinib therapy.

For information on immune modulation studies, please contact Dr. Jorge Cortes or any other leukemia physician.

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## CLL Treatment Priorities

### 1. Untreated

- Fludarabine + Cytosin + Rituximab + GM-CSF (2006-0267)
- Rituximab + Sargramostin (2004-0102)
- CFAR (2005-0269)
- Kinetic Biomarker (2005-0528)
- Idiotype-KLH + GM-CSF (2005-1013)
- Autologous B Cells (2004-0914)

### 2. Prior Therapy

- Fludarabine + Cytosin + Rituximab (ID99-338)
- CI Campath/SQ Campath (ID02-424)
- Clofarabine (2004-0134)
- Anti CD40 MoAb (2005-0025)
- Dasatinib (2005-0497)
- Forodesine HCL (2005-0290)
- OFAR (2004-0373)
- 5-aza (2006-0428)
- CNF2024 (2005-0452)

### 3. Other

- T-cell LPD:
  - Alemtuzumab + Pentostatin (2004-0408)
  - Forodesine HCL (2004-0800)
- Hairy Cell: 2CDA + Rituximab (2004-0223)

## AML/MDS Treatment Priorities

### 1. Newly Diagnosed

- A. Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17): ATRA + Arsenic Trioxide
- B. Cytogenetic feature: Inv16 or t(8;21): Fludarabine + Ara-C
- C. Age >60
  - 5-aza + Valproic Acid + ATRA (2004-0799)
  - IV Clofarabine (2005-0535)

### 2. Salvage Programs

- Dauno + Ara-C + PKC 412 (2003-0645)
- Clofarabine ± Ida ± Ara-C (ID03-0181)
- Ida + Ara-C + EL625 (2003-0475)
- Arsenic Trioxide + ATRA + Mylotarg (ID00-424) in APL
- Mitoxantrone + Etoposide + Ara-C ± CEP-701 (2003-0719)
- PTK 787 + Gleevec (2004-0248)
- Troxatyl (2005-0283)
- Lenalidomide (2006-0293)
- Cloretazine + Ara-C (2004-0639)
- Low dose Decitabine (2004-0468)
- HuM195/rGel (DM98-342)
- Ara-C ± Clofarabine (2006-0069)
- Ida + Ara-C + AEG (2005-0384)
- Oral Clofarabine (2005-0536)
- 5-aza+Valporic Acid (2005-0177)
- 5-aza + Ara-C (2005-0291)
- Zarnestra + Ara-C (2006-0021)
- CHIR-258 (2005-0674)
- ABT-869 (2005-0474)

### 3. Low Risk MDS and CMML with <10% Blasts

- Cytokine Immunotherapy (2004-0253)
- Low dose Decitabine (ID03-0180)
- Oral SCIO-469 (2004-0790)
- Thymoglobulin + Cyclosporin (2005-0115)
- Deferasirox (2005-0233)
- PR1 vaccine (2005-0913)
- FG-2216 (2005-0721)
- AMG531 (2005-0577)

## 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 + Gleevec (ID01-006)

### 2. Salvage Programs

- Ph+:AMN107 (2004-0251)
- Augmented Hyper CVAD (ID03-0166)
- Liposomal Vincristine (ID01-572)
- L-Annamycin (2004-0675)
- Forodesine HCL (2004-0800)

- IMTOX 19 + 22 (2005-0271)
- Clofarabine + Cytosin (2005-0552)
- 5-aza (2005-0895)

## CML Treatment Priorities

### 1. CML Chronic Phase

- A. Early (Diagnosis < 12 months); no prior IFN
  - BMS-354825 (2005-0422)
  - Imatinib 400/800 (2005-0325)
- B. Early; prior IFN-α or late (Diagnosis >12 months)
  1. No prior IFN-α:
    - High-dose STI571 (ID01-292)
  2. STI571 failures:
    - BMS-354825 (2005-0428)
    - AMN107 (2004-0251)
    - KOS-953 + Gleevec (2004-0282)
    - HHT + Gleevec (2005-0067)
    - SKI-606 (2005-0813)

### 2. CML Accelerated Phase

- AMN107 (2004-0251)
- KOS-953 + Gleevec (2004-0282)
- HHT + Gleevec (2005-0067)
- SKI-606 (2005-0813)
- BMS-354825 (2005-0394)

### 3. CML Blastic Phase

1. Myeloid or undifferentiated
  - BMS-354825 (2005-0394)
  - AMN107 (2004-0251)
  - STI571 + Idarubicin + Ara-C (ID01-300)
  - PTK787 + Gleevec (2004-0248)
  - KOS-953 + Gleevec (2004-0282)
  - HHT + Gleevec (2005-0067)
  - SKI-606 (2005-0813)
2. Lymphoid
  - Hyper CVAD + STI571

### 4. Philadelphia-negative Myeloproliferative Disorders (MF, ET, PV, CEL/HES, Ph-neg CML)

- BMS-354825 (2004-0817)
- Lenalidomide + Prednisone (2005-0206)
- Pegasys (DM03-0109)
- PTK787 + Gleevec (2004-0248)
- ONTAK (2004-0142) (Mastocytosis only)
- Sunitinib (2006-0208)
- STI571 (ID01-167) (HES only)
- 2CDA + Ara-C (DM97-232) (HES only)
- Oral IFN (2004-0919) (ET, PV)
- AMN107 (2004-0251)
- GX15-070MS (2006-0411)
- Velcade (2005-0284)

## Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- XL119 (2003-0909)
- XK469R (2004-0154)
- Fenretinide (2005-0690)
- SAHA + DAC (2005-0723)
- ALIMTA (pemetrexed) (2004-0873)
- SNS-595 (2005-0295)
- CP-4055 (2006-0132)
- MK-0457 (2005-0330)
- RTA 401 (CDDO) (2005-0469)
- AT9283 (2006-0177)
- MPC-2130 (2005-0532)
- FTS (2006-0201)
- Perifosine (2005-0793)
- SAHA + Ida (2005-0031)
- Triciribine (2006-0249)
- PT523 (Talotrexin) (2005-0122)
- GX15-070 MS (2005-0584)
- KW-2449 (2006-0275)
- SJG-136 (2005-0607)
- AVN-944 (2005-0609)
- INNO-406 (2006-0278)
- Sapacitabine (2005-0768)
- LBH-589 (2005-0898)
- MK-0752 (2006-0283)
- MKC-1 (2006-0528)

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