

This issue of the newsletter is meant to update our colleagues about investigational studies available in the Leukemia program at M. D. Anderson Cancer Center which may be relevant to their patient care. Novel agents and approaches continue to be introduced clinically with the potential to change treatment opportunities. We will divide the issue into disease specific programs and present very brief updates of the existing strategies in our overall approach to treatment of Leukemia.

## Chronic Myeloid Leukemia (CML)

### Newly diagnosed CML

The second generation tyrosine kinase inhibitors (TKIs) have demonstrated significant activity in all phases of CML post imatinib failure. Dasatinib (Sprycel; BMS354825), a dual Src-Abl inhibitor was approved by the FDA for this indication in June 2006. Nilotinib (Tasigna; AMN107), a more potent Bcr-Abl inhibitor is expected to receive FDA approval in 2007. We have implemented frontline studies with both of these second generation TKIs for patients with newly diagnosed CML. The preliminary analyses show the superior activity of both agents compared with standard- and high-dose imatinib and a reasonable safety profile. Dasatinib is given as 100 mg single daily dose PO vs 50 mg b.i.d. Nilotinib is given as 400 mg PO bid. The preliminary findings of both studies have been reported at the ASH 2006 (Blood 108:abstracts 2161 & 2172, 2006).

a. Dasatinib in newly diagnosed CML – protocol 2005-0422.

b. Nilotinib in newly diagnosed CML – protocol 2005-0048.

Both studies provide free drug supply and require a minimum initial stay (3-5 days) at M. D. Anderson with 1 day visits q 3 months in year 1 and q 6 months thereafter.

### CML post imatinib failure

We have completed the studies with dasatinib and nilotinib which are now available either commercially or on an expanded access program. We are currently investigating two dual Src-Abl inhibitors in this setting: bosutinib (SKI-606) and INNO-406. The experience with bosutinib is already very encouraging. Among 48 patients in chronic phase CML post imatinib failure treated with bosutinib 400 – 600 mg daily the CHR rate is 84% and the major cytogenetic response rate is 52% (complete in 33%) after a median duration of treatment of only 3 months. Side-effects are minimal including grade 3-4 thrombocytopenia in only 6% and rash in 6%. No pleural effusions or significant myelosuppression have been noted. This has been reported at ASH 2006 (Cortes. Blood 108:abstract 168, 2006). This study of bosutinib in CML post imatinib failure in all phases is open. A phase I study of INNO-406, a Lyn and Abl inhibitor is also open, without any evidence of dose limiting toxicity at doses that are already inducing cytogenetic responses.

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## Chronic Myeloid Leukemia (CML)

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- a. Bosutinib in CML post imatinib failure – protocol 2005-0813.
- b. INNO-406 in CML post imatinib failure – protocol 2006-0278

### CML with T315I mutations

This mutation is notorious for its resistance to existing classical TKIs including imatinib, nilotinib and dasatinib. MK0457, a new multi-kinase inhibitor, including aurora kinase and Abl, was found to have significant activity in CML with T315I mutations. Among 11 patients with CML in transformation with T315I treated with MK0457 at 8-32 mg/m<sup>2</sup> per hour x 5 days, 5 achieved solid objective responses: 1 cytogenetic CR, 2 cytogenetic PRs, 1 minor cytogenetic response and 1 hematologic response. These studies of MK0457 in this setting as well as in acute leukemias and refractory hematologic malignancies are ongoing. Of note, MK0457 is also a notable JAK2 inhibitor and may benefit patients with JAK2 mutations refractory to standard therapy (PV, ET, myelofibrosis).

The preliminary results have been reported at ASH 2006 (Giles. Blood 108:abstract 163, 2006).

Other aurora kinase inhibitors with potent T315I and JAK2 inhibitory activities include AT9283 (IV infusion for 3 days) and KW2449 (oral daily therapy). In addition homoharrington-

nine, an old drug with significant anti-CML activity, has shown activity in the setting of CML T315I. It is currently under investigation in this setting as well as in patients with failure to at least 2 TKIs.

- a. MK0457 in CML T315I and other hematologic malignancies – protocol 2006-0992.
- b. AT9283 in refractory hematologic malignancies – protocol 2006-0177.
- c. KW2449 in refractory hematologic malignancies – protocol 2006-0275.
- d. Homoharringtonine in CML with T315I mutations -- protocol 2006-0192.

### Vaccine and other immune modulating strategies in CML

Vaccines in CML may be helpful in the setting of minimal residual disease to augment the host immunity and eradicate residual disease resistant to TKIs. This may provide the future hope for cure of CML without the need for continued therapy. We are testing 2 vaccines in CML in the setting of significant minimal residual disease (complete cytogenetic response but no major molecular response, i.e. QPCR >0.1 and stable). The two vaccines include the synthetic peptide vaccine (Scheinberg vaccine) and the PR1 vaccine (if HLA A2 positive). The 2 vaccine studies are ongoing in protocols 2005-0392 and 2006-0360.

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## Acute Myeloid Leukemia (AML)

In AML several studies have confirmed the superiority of idarubicin over daunorubicin, and the value of high dose ara-C as consolidation in younger patients. A meta-analysis of different induction studies also indicated that high-dose ara-C induction improves remission duration in AML (Kern and Estey. Cancer 107:116, 2006).

Therefore, in younger AML (age < 60 years) our frontline studies incorporate idarubicin and high-dose cytarabine as the backbone standard of therapy. We are currently investigating the potential value of adding sorafenib (a FLT3 / RAF inhibitor) to induction-consolidation therapy.

In elderly AML, intensive chemotherapy is asso-

ciated with a high induction mortality. Our investigations focus on low intensity targeted strategies in patients who are not candidates for intensive chemotherapy. These strategies include clofarabine (adenosine nucleoside analog), decitabine (a hypomethylating agent), cloretazine (an alkylating agent), and tipifarnib (FTI inhibitor) plus low dose cytarabine.

- Idarubicin + cytarabine + sorafenib in AML < 60 years – protocol 2006-0977 (pending).
- Clofarabine in elderly AML – protocol 2006-0654.
- Cloretazine in elderly AML – protocol 2006-0156.
- Decitabine vs. low-dose ara-C in elderly AML – protocol 2005-0647.

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## Acute Myeloid Leukemia (AML)

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Decitabine + valproic acid in high risk MDS/AML – protocol 2006-0686.

In our studies of APL, we identified the combination of ATRA plus arsenic trioxide (+ mylotarg for high risk APL) to produce excellent results in APL. This is the basis for our ongoing study (Estey. Blood 107:3469, 2006). In AML with favorable karyotypes such as t(8;21) and inversion 16, our FLAG regimen has shown favorable results and continues as our frontline strategy.

ATRA + AS2O3 + mylotarg in APL - protocol

2006-0706.

T(8;21), inversion 16 - protocol 2007-0147 (pending).

For AML in CR (any age), 2 maintenance strategies are being investigated, decitabine and PR1 vaccines.

Decitabine vs. Best standard of care as maintenance for AML in CR1 and for subsequent CRs – protocol 2006-0358.

PR1 vaccine maintenance for AML in CR1 and HLA-A2 positivity – protocol 2006-0904.

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## Myelodysplastic Syndrome (MDS)

Current approved strategies in MDS and CMML include the use of hypomethylating agents (decitabine, azacitidine) for MDS/CMML, and the use of lenalidomide (a thalidomide analog) for low risk MDS transfusion dependence and 5q abnormality. We are investigating several strategies to improve the results beyond the standard of care. These are based on the IPSS/general risk of the MDS.

### Lower risk MDS (IPSS low – intermediate-1; blasts < 10%)

In lower risk MDS we are investigating several approaches including combination of growth factors, immune therapy (rabbit ATG), GX15070 (a Bcl 2 inhibitor shown to stimulate multilineage hematopoiesis), vorinostat (a histone deacetylase inhibitor shown also to stimulate multilineage

hematopoiesis), and low doses of decitabine – azacitidine. In lower risk MDS as well as higher risk MDS with 5q abnormality, lenalidomide based regimens are under investigation.

### Higher risk MDS (IPSS intermediate-2 – high; blasts > 10%)

We are attempting to improve the results of hypomethylating agents using them in combination with histone deacetylase inhibitors. Programs in these MDS subtypes include decitabine + valproic acid, decitabine + vorinostat, azacitidine + MGCD.

For patients who fail on hypomethylating strategies, investigational strategies include clofarabine, PO and IV, sapacitabine (an oral cytosine analog), homoharringtonine, gimatecan (an oral topoisomerase I inhibitor) and other phase I/II agents.

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## Chronic Lymphocytic Leukemia (CLL)

Significant success and advance has been made with combination therapies for patients with CLL, particularly chemoimmunotherapy. Fludarabine, cyclophosphamide, and rituxan (FCR) has produced excellent results and is our backbone of CLL therapy at M. D. Anderson. Efforts are now focused on developing active and well tolerated regimens for patients over 65 years old. Current or planned clinical trials for patients with CLL are indicated below.

### Previously Untreated (treatment indicated)

Age > 65 yrs - Single-agent Lenalidomide - protocol 2005-0175.

Age < 70, beta-2 microglobulin > 3.9 mg/L (high risk) - Fludarabine, Cyclophosphamide, Rituximab, Alemtuzumab (CFAR) - protocol 2005-0269.

Any age - Fludarabine, Cyclophosphamide, Rituximab + GM-CSF (FCR+GM-CSF) - protocol 2006-0267.

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# Chronic Lymphocytic Leukemia (CLL)

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## Previously Treated (treatment indicated)

Chemoimmunotherapy

Randomized FCR +/- Lumiliximab (anti-CD23 mAb) - protocol 2006-0789 (pending).

Fludarabine sensitive - FCR + Bevacizumab – protocol 2005-0992.

Oxaliplatin, Fludarabine, Cytarabine, Rituximab (OFAR2) - protocol 2006-1026 (pending).

## Single-Agent Phase I or II

Fludarabine and Alemtuzumab refractory (or bulky nodes) - Ofatumumab (HuMax CD20; anti-CD20 mAb) - protocol 2006-0314.

Dasatinib (Phase II) - protocol 2005-0497.

5-Azacitidine (Phase II) - protocol 2006-0428.

Anti-CD40 mAb (Phase I) - protocol 2005-0025.

Oral CNF2024 (Hsp90 inhibitor) (Phase I) -

protocol 2005-0452.

Clofarabine (Phase I) - protocol 2004-0134.

SNS-032 (cyclin-dependent kinase inhibitor - Phase I) - protocol 2006-0843 (pending).

Oral Enzastaurin (protein kinase C inhibitor) (Phase II) - protocol 2006-0868 (pending).

## Minimal Residual Disease

Subcutaneous Alemtuzumab - protocol 2003-0834.

Randomized Rituximab vs Alemtuzumab vs Rituximab+Alemtuzumab - protocol 2006-0767 (pending).

## Richter's Transformation

Oxaliplatin, Fludarabine, Cytarabine, Rituximab (OFAR2) - protocol 2006-1026 (pending).

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# Acute Lymphocytic Leukemia (ALL)

Exciting progress has happened in adult ALL. With the hyper-CVAD regimen, the CR rate in adult ALL is 90% with a 5-10 year survival rate of 40-50% (Kantarjian.Cancer 101:2788, 2004). We are now treating adult ALL based on its subtype with protocol specific modifications.

In Ph+ ALL, the hyper-CVAD + imatinib regimen has shown encouraging data with 3 year survival rates of 60% (Thomas.Blood 103:4396, 2004). We are currently attempting to improve these results using the combination of hyper-CVAD + dasatinib (dual Src-Abl inhibitor; 300 times more potent than imatinib).

In Burkitt ALL, hyper-CVAD + rituximab has produced event-free-survival rates of 80-90%. This continues to be our current frontline regimen (Thomas.Cancer 106:1569, 2006).

In T-cell ALL, we have incorporated nelarabine (an active anti-T-All agent) with hyper-CVAD to

improve on the previous positive results (Thomas. Blood 104:1624, 2004).

In adolescent-young adults (age 12-30) with ALL, pediatric dose intensive regimens appear to produce better results than standard adult ALL regimens, although no direct comparisons have been made to the hyper-CVAD regimen. Because of the literature experience, we have initiated a frontline study of augmented BFM (the pediatric protocol for high risk ALL) in our adolescent-young adult patients.

Hyper-CVAD + dasatinib in Ph+ ALL – protocol 2006-0478.

Hyper-CVAD + rituximab in Burkitt ALL – protocol ID02-229.

Hyper-CVAD + nelarabine in T-Cell ALL – protocol 2006-0328 (pending).

Augmented BFM regimen in adolescent-young adults (age 12-30) – protocol 2006-0375.

## Myeloproliferative Disorders (MPD)

The development of novel therapies for patients with MPD has been historically hampered by limited understanding of the abnormal processes and molecular causes of these diseases. The discovery of JAK2 mutation in most MPD patients is a first step in this direction. Agents potentially able to interfere with identified abnormalities in MPD are becoming available. Participation in clinical trials of novel agents is warranted. Available programs are listed below.

### Myeloproliferative Disorder

Therapy	MF	ET	PV	Open to patients
<b>Pegylated interferon (Pegasys)</b>		X	X	X
<b>Revlimid (Lenalidomide) + Prednisone</b>	X			X
<b>Bortezomib (Velcade)</b>	X			X
<b>Dasatinib (Sprycel)</b>	X		X	X
<b>Obatoclax (pan bcl-2 inhibitor)</b>	X			X
<b>Sunitinib (Suniteb)</b>	X			X
<b>GC-1008 (antibody against TGF-<math>\beta</math>)</b>	X			March-April 2007
<b>Pomalidomide (CC-4047)</b>	X			March-April 2007
<b>JAK2 inhibitor</b>	X			April-May 2007

For additional information about the therapies for MPD at M.D. Anderson Cancer Center visit website at <http://www.mdanderson.org/diseases/mpd/> or contact Srdan Verstovsek, MD, PhD, MPD Program Leader, at (713) 745-3429; e-mail [sverstov@mdanderson.org](mailto:sverstov@mdanderson.org).

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*Editor: Hagop Kantarjian, M.D. WebMaster: Charles A. Koller, M.D.  
Associate Editor: Sherry Pierce, R.N. Administrator: Rebecca Wischer*

## List of Leukemia Service Attendings

ANDREEFF, MICHAEL	(713) 792-7260	KANTARJIAN, HAGOP	(713) 792-7026
BERAN, MILOSLAV	(713) 792-2248	KEATING, MICHAEL	(713) 745-2376
BORTHAKUR, GUTAM	(713) 563-1586	KOLLER, CHARLES	(713) 792-7747
BURGER, JAN	(713) 563-1487	KORNBLAU, STEVEN	(713) 794-1568
CABANILLAS, MARIA	(713) 745-0654	MATTIUZZI, GLORIA N.	(713) 745-2723
CORTES, JORGE	(713) 794-5783	O'BRIEN, SUSAN	(713) 792-7543
ESTEY, ELIHU	(713) 792-7544	RAVANDI, FARHAD	(713) 745-0394
ESTROV, ZEEV	(713) 794-1675	THOMAS, DEBORAH	(713) 745-4616
FADERL, STEFAN	(713) 745-4613	TSIMBERIDOU, APOSTOLIA	(713) 792-4259
FERRAJOLI, ALESSANDRA	(713) 792-2063	VERSTOVSEK, SRDAN	(713) 745-3429
FREIREICH, EMIL	(713) 792-2660	VU, KHANH	(713) 745-0655
GARCIA-MANERO, GUILLERMO	(713) 745-3428	WIERDA, WILLIAM	(713) 745-0428
ISSA, JEAN-PIERRE	(713) 745-2260		

### CLL Treatment Priorities

#### 1. Untreated

- Fludarabine + Cytosan + 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 + Cytosan + Rituximab (ID99-338)
- FCR + Bevacizumab (2005-0992)
- Lenalidomide (2005-0175)
- HuMax-CD20 (2006-0314)
- 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)
- Hairy Cell: 2CDA + Rituximab (2004-0223)

### AML/MDS Treatment Priorities

#### 1. Newly Diagnosed

- Acute Promyelocytic Leukemia: cytogenetic feature: t(15;17): ATRA + Arsenic Trioxide +/- Gemtuzumab (2006-0706)
- Cytogenetic feature: Inv16 or t(8;21): Fludarabine + Ara-C
- Others: Ida + Ara -C (2006-0813)
  - IV Clofarabine (2005-0535/2006-0654)
  - Cloretazine (2006-0156)
  - Low Dose Decitabine +/- Valproic Acid (2006-0686)
  - DAC vs low-dose Ara-C (2005-0647)

#### 2. Salvage Programs

- Dauno + Ara-C + PKC 412 (2003-0645)
- Clofarabine ± Ida ± Ara-C (ID03-0181)
- Arsenic Trioxide + ATRA + Mylotarg (ID00-424) in APL
- Mitoxantrone + Etoposide + Ara-C CEP-701 (2003-0719)
- Lenalidomide (2006-0293)
- Cloretazine + Ara-C (2004-0639)
- Low dose Decitabine (2004-0468)
- HuM195/tGel (DM98-342)
- Ara-C ± Clofarabine (2006-0069)
- Ida + Ara-C + AEG (2005-0384)
- Oral Clofarabine (2005-0536)
- 5-aza + Ara-C (2005-0291)
- Zarnestra + Ara-C (2006-0021)
- CHIR-258 (2005-0674)

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- AZD1152 (2006-0285)
- AC220 (2006-0850)

### 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)
- AMG531 (2005-0577)
- Obatocalax Mesylate (2006-0688)

## ALL Treatment Priorities

### 1. Newly Diagnosed or Primary Refractory (one non-hyper-CVAD induction)

- Modified Hyper CVAD (ID02-230)
- Burkitt's: Hyper CVAD + Rituximab (ID02-229)
- PH+: Hyper CVAD + Dasatinib (2006-0478)
- Age <31: Augmented BFM (2006-0375)

### 2. Salvage Programs

- PH+: AMN107 (2004-0251)
- Augmented Hyper CVAD (ID03-0166)
- L-Annamycin (2004-0675)
- Forodesine HCL (2006-0595)
- IMTOX 19 + 22 (2005-0271)
- Clofarabine + Cytosan (2005-0552)
- 5-aza (2005-0895)

## CML Treatment Priorities

### 1. CML Chronic Phase

- BMS-354825 (2005-0422)
- AMN107 (2004-0251)
- Oral AMN107 (2005-0048)
- HHT + Gleevec (2005-0067)
- SKI-606 (2005-0813)
- MK-0457 (2006-0992)
- HHT (2006-0192)

### 2. CML Accelerated Phase

- AMN107 (2004-0251)
- HHT (2006-0192)
- SKI-606 (2005-0813)
- MK-0457 (2006-0992)
- HHT + Gleevec (2005-0067)

### 3. CML Blastic Phase

- GX15-07MS (2005-0584)

- AMN107 (2004-0251)
- ST157 + Idarubicin + Ara-C (ID01-300)
- HHT (2006-0192)
- MK-0457 (2006-0992)
- HHT + Gleevec (2005-0067)
- SKI-606 (2005-0813)

### 4. Minimal Residual Disease

- PR1 Vaccine + Gleevec (2006-0360)
- TALL-104 + Gleevec (2004-0837)
- Synthetic Vaccine (2005-0392)

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

- BMS-354825 (2004-0817)
- Lenalidomide + Prednisone (2005-0206)
- Pegasys (DM03-0109)
- ONTAK (2004-0142) (Mastocytosis only)
- Sunitinib (2006-0208)
- ST571 (ID01-167) (HES only)
- AMN107 (2004-0251)
- GX15-07MS (2006-0411)
- Velcade (2005-0284)
- 2CDA + Ara-C (DM97-232) (HES only)

## Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- Fenretinide (2005-0690)
- SAHA + DAC (2005-0723)
- SNS-595 (2005-0295)
- CP-4055 (2006-0132)
- MK-0457 (2005-0330)
- RTA 401 (CDDO) (2005-0469)
- AT9283 (2006-0177)
- FTS (2006-0201)
- SAHA+ Ida (2005-0031)
- Triciribine (2006-0249)
- PT523 (Talotrexin) (2005-0122)
- GX15-07MS (2005-0584)
- KW-2449 (2006-0275)
- SJG-136 (2005-0607)
- INNO-406 (2006-0278)
- Sapacitabine (2005-0768)
- MGCD0103 + Aza (2005-0659)

*Leukemia*

***INSIGHTS***

The University of Texas  
M. D. Anderson Cancer Center  
1515 Holcombe Boulevard  
Houston, Texas 77030-4009

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