

## New Therapies for Patients with Myeloproliferative Diseases

### Jak2 Inhibitors for Patients with Myelofibrosis

Classic Philadelphia chromosome–negative Myeloproliferative Diseases (MPD) include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (MF). Several independent groups have described almost simultaneously a novel activating somatic point mutation in the gene encoding the cytoplasmic Janus kinase 2 (JAK2), characterized by the substitution of valine to phenylalanine at codon 617 (JAK2V617F), in patients with MPD. This mutation is present in 50% of ET and PMF patients, and 97% of PV patients, and makes the JAK2 protein active and phosphorylated all the time. JAK2 is an important protein inside the cell, as it transmits signals for the cell to grow. It is believed that the JAK2 protein (either mutated or not) is a major reason for the existence and progression of these diseases. It is highly likely, therefore, that a JAK2 inhibitor might positively affect the disease and help the MPD patient. Several clinical trials of JAK2 inhibitors are currently underway for patients with MF and described here.

### Randomized Placebo-controlled Study of the JAK Inhibitor INCB018424

A recently completed Phase I/II study of the oral JAK1/2 inhibitor INCB018424 for patients with MF has accrued more than 150 patients and showed exemplary efficacy in reducing enlarged spleen and liver, reducing white blood cell and platelet counts, and improving patients' quality of life (including weight gain, improved ability to walk, and increased performance status). Results were equal in patients with and without JAKV617F mutation. There have been minimal non-hematologic side effects. The hematologic on-target side effect was primarily thrombocytopenia. Based on these encouraging results, the Phase III approval study of INCB018424 is now open to patients with MF, regardless of the JAK2 mutation status, who have enlarged spleen (>5cm) on physical exam, poor performance status, and not lower than  $100 \times 10^9/L$  platelet count.

#### Selected Inclusion Criteria:

- 1) Age 18 years or older
- 2) Subjects must be diagnosed with PMF, PPV-MF or PET-MF, according to the 2008 World Health Organization criteria irrespective of JAK2 mutation status.
- 3) Subjects with myelofibrosis requiring therapy must be classified as high risk (3 or more prognostic factors) OR intermediate risk level 2 (2 prognostic factors). The prognostic factors, defined by the International Working Group (IWG) are: • Age > 65 yrs • Presence of constitutional symptoms (weight loss, fever, night sweats) • Marked anemia (hemoglobin < 10 g/dL) • Leukocytosis (history of white blood cell count (WBC) >  $25 \times 10^9/L$ ) • Circulating blasts equal to or greater than 1%
- 4) Subjects in whom treatment of MF is indicated based on presence of one or more of the following: a. IWG

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- Prognostic Category of High Risk (3 or more risk factors) b. Palpable spleen at 10 cm or more below the costal margin c. Active symptoms of MF as demonstrated by one symptom score of at least 5 (on a zero to 10 scale) on at least one of the following items OR a score of 3 or greater on at least two of the following items: early satiety, abdominal discomfort, abdominal pain, inactivity, night sweats, pruritis, bone pain.
- 5) Subjects who are refractory, resistant or intolerant to available therapy, or in the investigator's judgment, are not candidates for available therapy.
  - 6) Subjects must have discontinued all drugs used to treat underlying myelofibrosis disease no later than 4 weeks prior to the Baseline visit.
  - 7) ECOG performance status of 0-3
  - 8) Subjects must have a palpable spleen measuring 5 cm or greater below the costal margin.
  - 9) Subjects with peripheral blood blast count of < 10%

**Selected Exclusion Criteria:**

- 1) Subjects in whom MF disease is well controlled with current therapy.
- 2) Females who are pregnant or are currently breastfeeding.
- 3) Any history of platelet counts < 50,000/uL or absolute neutrophil count (ANC) < 500/uL except during either treatment for a myeloproliferative disorder or treatment with cytotoxic therapy for any other reason.
- 4) Inadequate liver or renal function
- 5) Active malignancy over the previous 5 years except treated early stage squamous cell carcinoma of the skin or treated basal cell carcinoma of the skin

**Phase I Study of SB1518 for the treatment of advanced myeloid malignancies (including myelofibrosis)**

SB1518 is an oral JAK2 and FLT3 inhibitor. This is a two-part study, with a dose escalation phase and an expanded cohort at the recommended therapeutic dose. The dose escalation portion of the study has been completed; patients are currently being enrolled in the expanded cohort utilizing the best therapeutic dose.

**Selected Inclusion Criteria:**

- 1) Subjects with histologically confirmed myeloid malignancy who have failed standard therapies or are not candidates for palliative therapies.
- 2) Adequate liver and renal function

- 3) Has a corrected QT interval (QTc)  $\leq$  0.47 seconds using the Bazett Formula
- 4) At least 2 weeks since prior therapy that is considered disease-directed

**Selected Exclusion Criteria:**

- 1) Concurrent malignancy, except those subjects with early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or cervical intraepithelial neoplasia
- 2) Known HIV-positive, known active hepatitis A, B, or C
- 3) Women who are pregnant or lactating

**Phase I/II Open Label Multi-Centre Study of the JAK2 inhibitor AZD1480**

The study is designed as a two-part trial, with a dose escalation phase and an expanded cohort at the recommended therapeutic dose. The dose escalation portion of the study is a classical 3+3 design to determine safety and tolerability; patients are currently being accrued. Efficacy will be determined at the therapeutic dose in the expanded cohort.

**Selected Inclusion Criteria:**

- 1) Age 25 years and over
- 2) Patients with myelofibrosis requiring therapy, including those previously treated by myelofibrosis directed therapy who have subsequently relapsed or are refractory, or if newly diagnosed should be intermediate or high risk according to Lille Scoring System (adverse prognostic risk factors are: Hgb<10g/dL, WBC<4 or >30.0 X 10<sup>9</sup>/L; risk group: 0 factor=low, 1 factor =intermediate, 2 factors=high); or with symptomatic splenomegaly (causing e.g. 5-10% weight loss, significant fever, or significant splenic pain affecting performance status) that is equal to or greater than 10 cm below left costal margin.
- 3) ECOG performance status 0-2

**Selected Exclusion Criteria:**

- 1) Platelet count <50 x 10<sup>9</sup>/L
- 2) Serum creatinine >1.5 x ULN, Serum total bilirubin >1.5 x ULN
- 3) Evidence of established interstitial lung disease on screening High Resolution Computerised Tomography (HRCT)

- 4) Chronic Obstructive Pulmonary Disease (COPD) with FEV1/FVC < 0.7 and spirometric classification Stage 3 or 4, i.e., FEV1 <50% predicted.
- 5) Diffusing capacity of the Lung for Carbon Monoxide (DL(CO) ) corrected for hemoglobin <60% predicted, pulse oximetry < 88% O<sub>2</sub> saturation after a 6-minute flat walk.
- 6) Persistent asthma
- 7) History of pulmonary fibrosis
- 8) Abnormality of cornea
- 9) Previous allogenic bone marrow transplantation

## Pomalidomide for Patients with Myelofibrosis and Anemia

Thalidomide, an agent with putative antiangiogenic (prevents new blood vessel formation) and immunomodulatory (modifies immune system) effects, has activity in MF. Improvements in blood cell counts and reduction in splenomegaly have been reported in selected patients but at the expense of significant side effects, including sedation, neurotoxicity, and constipation. When given with prednisone (corticosteroid), these side effects are diminished and patients can tolerate a prolonged course of therapy; this translates into the improvement of blood cell counts in significant numbers of patients. There is a need for more potent and less toxic analogs of thalidomide. Revlimid is an oral thalidomide analog that has recently been approved as therapy for patients with 2 other bone marrow diseases, myelodysplastic syndrome and multiple myeloma. Clinical trials studying the efficacy and safety of revlimid +/- prednisone in MF have been recently conducted at the MD Anderson and Mayo Clinic and have shown similar results to thalidomide, at the expense of significant myelosuppression in most patients. A new analog with improved activity has been developed, called CC4047 or pomalidomide. This medication was studied in an international multicenter four-arm study a year ago and showed an improvement in anemia in up to 40% of MF patients. A new Phase II open-label single-arm study is currently open at MD Anderson for MF patients with severe anemia. Participants are required to visit MD Anderson monthly for the first 6 months and then every 3 months while on the study.

### **Selected Inclusion Criteria:**

- 1) Myelofibrosis requiring therapy
- 2) Screening total hemoglobin level < 10 g/dL or transfusion-dependent anemia

- 3) Total bilirubin <3x ULN or Direct Bilirubin <2x ULN, Serum creatinine <= 2.0 mg/dL, Absolute neutrophil count >/=1,000/uL, Platelet count >/= 50,000/uL
- 4) No active malignancies with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma (in situ) of the cervix or breast

### **Selected Exclusion Criteria:**

- 1) Known positive status for HIV, hepatitis B carrier, or active hepatitis C infection.
- 2) The use of any therapy within 14 days
- 3) Pregnant or lactating females

## Clinical Trials for Mastocytosis Obatoclax Mesylate (GX15-070)

Obatoclax Mesylate is a pro-apoptotic medication meaning that it acts to induce cell-death in diseased cells. Therefore it is believed that this medication may influence the growth of abnormal mast cells (but not normal mast cells) and cause them to die. Treatment consists of Obatoclax given intravenously over 3 hours on 3 consecutive days every 2 weeks (2 weeks is considered one cycle of therapy). All treatments must be given at M.D. Anderson Cancer Center. For patients responding to therapy, treatment may be continued as long as therapeutic benefit is derived. Patients who show no response after 5 cycles of therapy will be taken off study.

### **Selected Inclusion Criteria:**

- 1) Patients with systemic mastocytosis
- 2) Minimum of two weeks since any major surgery or completion of radiation
- 3) ECOG performance status 0-2
- 4) Adequate liver function

### **Selected Exclusion Criteria:**

- 1) Patients with low blood cell counts (Grade 3 or 4), unless it is known that the low blood cell count is due to systemic mastocytosis.
- 2) Treatment with any conventional (specifically, interferon or cladribine) or investigational medicine for SM within the preceding 4 weeks
- 3) Chronic treatment with systemic steroids

## Multicenter Phase III Study of Masitinib or Placebo in Mastocytosis with Handicap

Masitinib is a potent inhibitor of KIT, an enzyme (tyrosine kinase) that is important in the biology of mastocytosis and is involved in the activation and growth of mast cells. By blocking KIT, masitinib may slow the growth of mast cells, which may relieve disease related symptoms. The study is open for patients with skin mastocytosis and for patients with systemic mastocytosis that have indolent or smouldering type. Handicap means that the mastocytosis symptoms are affecting the patient's health and/or quality of life. This is a multicenter study, but MD Anderson is the only treatment center in the USA participating. If the therapy is proven to be significantly superior to placebo, it is possible that masitinib might be approved by the FDA (Food and Drug Administration). Treatment consists of taking Masitinib or placebo pills daily for 24 weeks. A total of 200 patients will be enrolled: 100 patients will receive Masitinib and 100 will receive a matching placebo. Patients will be treated on an outpatient basis and must return to M.D. Anderson every 4 weeks. The therapy will be provided past 24 weeks if it is beneficial to the patient.

### **Selected Inclusion Criteria:**

- 1) Patient with Smouldering Systemic Mastocytosis, Indolent Systemic Mastocytosis, or Cutaneous Mastocytosis.
- 2) Patient with documented treatment failure of his/her handicap(s) with at least one of the following therapies used at optimized dose: Anti H1, Anti H2, Proton pump inhibitor, Osteoclast inhibitor, Cromoglycate sodium, Antileukotriene, other therapies used for the symptomatic care.
- 3) Handicapped status defined as at least two of the following handicaps, including at least one among pruritus, flushes, depression and asthenia: pruritus score  $\geq 6$ , number of flushes per week  $\geq 7$ , Hamilton rating scale (depression)  $\geq 10$ , number of stools per day  $\geq 4$ , number of mictions per day  $\geq 8$ , Fatigue Impact Scale total score (asthenia)  $\geq 40$ .
- 4) ECOG performance status 0-2
- 5) Patient with adequate organ function
- 6) Age 18 years and older

### **Selected Exclusion Criteria:**

- 1) Previous treatment with any tyrosine kinase Inhibitor (e.g. imatinib or dasatinib).
  - 2) Patient who underwent major surgery within 2 weeks prior to study enrollment.
  - 3)  $< 5$  years free of malignancy, except treated basal cell skin cancer or cervical carcinoma in situ
  - 4) Change in the symptomatic treatment of mastocytosis or administration of any new treatment of mastocytosis within 4 weeks prior to baseline
- Dr. Srdan Verstovsek is the Leukemia Department's MPD Program Leader. He can be reached at [sverstov@mdanderson.org](mailto:sverstov@mdanderson.org) or 713-745-3429, or feel free to contact any Leukemia physician.

## Therapies for Patients with Chronic Lymphocytic Leukemia

### General Update

Advances continue in identifying new, active drugs for patients with CLL and understanding the biology of this disease. The utility of prognostic factors in managing patients with CLL continues to be of interest; prospective studies are ongoing to assess association of prognostic factors with time from diagnosis to first treatment, remission duration, time to becoming refractory, and overall survival. Specific chromosome abnormalities identified by FISH, including 11q deletion and 17p deletion, are associated with high-risk disease and are now being targeted with new treatment strategies. These chromosome abnormalities are associated with short remission duration and resistance to standard treatments; therefore identifying active agents for patients with these abnormalities will be an advance.

Two large phase III clinical trials conducted in Europe, one in frontline and one in salvage therapy, demonstrated the FCR regimen (fludarabine-cyclophosphamide-rituximab) as the superior frontline and salvage regimen compared with FC. The FCR regimen, originally developed at M. D. Anderson, has become the standard frontline treatment and standard salvage regimen for previously treated patients who had not received extensive prior treatment. We continue to work to develop the FCR regimen into a more effective regimen by studying dose modification and the addition of new agents that have a different mechanism of action.

The most notable new agent recently studied at M. D. Anderson, in collaboration with other US and European investigators, has been ofatumumab, a fully human monoclonal antibody that binds to CD20. Ofatumumab binds to a different epitope of CD20 than rituximab and is more efficient at mediating complement-dependent lysis of malignant B cells. Ofatumumab was shown to be active in treating patients who were refractory to both fludarabine and alemtuzumab and patients who were refractory to fludarabine and had bulky (>5cm) lymph nodes. The pivotal trial results were reviewed favorably by ODAC and it is likely the FDA will approve ofatumumab by the end of this year. M. D. Anderson investigators have a number of studies planned with ofatumumab, including in combination with chemotherapy, as single-agent for residual disease, and as single-agent for early treatment of high-risk patients.

## Prognostic Factors

When patients with CLL are evaluated at M. D. Anderson, they undergo prognostic factor evaluation including IgVH mutation status, ZAP-70 and CD38 assessment, cytogenetics by metaphase karyotyping, and FISH analysis. We provide this information, along with all diagnostic information, to our referring physicians. These tests are done to prospectively assess the clinical relevance of these prognostic factors in predicting outcome in CLL and we are working on developing treatments specifically for patients with high-risk features such as 11q deletion and 17p deletion.

## Treatment for Older Patients

Patients older than 65 years have lower tolerance for more myelosuppressive regimens such as FCR. This is reflected in lower complete and overall response rates and shorter survival for these older patients. Clearly, effective treatment that is well-tolerated is needed for this group of patients who actually represent the majority of patients managed by community physicians. To develop new treatments for these patients, we are focusing on the activity and mechanism of action of the immune-modulating agent lenalidomide and monoclonal antibodies for patients older than 65.

## Chemoimmunotherapy

The FCR regimen, developed at M. D. Anderson, is the most active combination for patients in both the frontline and salvage settings. We work to improve on that with novel combinations of chemotherapeutic agents with immunomodulating drugs. Strategies include combining

FCR with GM-CSF (sargramostim), which is an immune-enhancing agent that upregulates expression of CD20 on CLL B-cells and enhances in vivo antibody-dependent cell-mediated cytotoxicity (ADCC) activity. ABT-263 is an oral small molecule inhibitor of anti-apoptotic Bcl-2 family members. We are completing a phase I clinical trial of single-agent ABT-263 and are opening a clinical trial with combined ABT-263 with FCR. For previously treated patients, clinical trials with the FCR backbone include the addition of bevacizumab (anti-VEGF mAb). Ofatumumab, the new, fully human monoclonal antibody (mAb) against CD20, is being evaluated in combination with fludarabine and cyclophosphamide in previously untreated patients.

## New Drug Development

Our research focuses on identifying new and effective drugs that work by different mechanisms of action than traditional purine analogs and alkylating agents. These agents include new nucleoside analogs that work by distinct mechanisms (DNA- and RNA-directed agents), monoclonal antibody against novel antigens, a small-molecule Bcl-2 family member inhibitor, protein kinase inhibitors, a hypomethylating agent, and a cyclin-dependent kinase inhibitor. Because these agents are not approved by the FDA, treatment and follow-up must be done at M. D. Anderson. Plerixafor (Mozobil) is an antagonist of the alpha-chemokine receptor CXCR4 and an agonist of CXCR7 and is FDA-approved for stem cell mobilization. Interactions between CLL cells and the microenvironment are responsible for leukemia cell survival and protection from chemotherapy-induced apoptosis. We are evaluating plerixafor in combination with rituximab for previously treated patients with CLL.

Strategies to eliminate minimal residual disease are also under development including: lenalidomide and the bi-specific (anti-CD3 + anti-CD19) mAb. Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress.

- If you have questions about CLL-focused research, please contact Drs. William Wierda, Susan O'Brien, Michael Keating or Alessandra Ferrajoli. Or feel free to contact any other physician.

## CLL Treatment Priorities

### 1. Untreated

- Fludarabine + Cytosine + Rituximab (FCR) (2008-0431)
- Lenalidomide + Rituximab (2008-0385)

### 2. Prior Therapy

- Fludarabine + Cytosine + Rituximab (ID99-338)
- FCR + Bevacizumab (2005-0992)
- HuMax-CD20 (2006-0314)
- Dasatinib (2005-0497)
- OFAR2 (2006-1026)
- 5-aza (2006-0428)
- Lenalidomide + Rituximab (2007-0208)
- Alemtuzumab (2007-0626)
- ABT-263 (2007-0096)
- GS-9219 (2007-0087)
- 8-Chloro-adenosine (2004-0144)
- AMD 3100 (2008-0725)
- Milatuzumab (2008-0075)

### 3. Minimal Residual Disease

- Alemtuzumab vs Rituximab vs Both (2006-0767)

### 4. Other

- Lenalidomide (2006-0715)
- 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 +/- Gemtuzumab (2006-0706)
- B. Cytogenetic feature: Inv16 or t(8;21): Fludarabine + Ara-C + Gemtuzumab (2007-0147)

### C. Younger Patients:

- IA + Sorafenib (2006-0977)
- IA + SAHA (2007-0835)
- Ida + Ara -C (2006-0813)

### Older Patients:

- Clofarabine + Ara-C + DAC (2007-0039)
- IV Clofarabine (2005-0535)
- Low Dose Decitabine +/- Valproic Acid (2006-0686)

- DAC vs low-dose Ara-C (2005-0647)
- SNS-595 (2007-0965)
- CPX-351 vs. 3+7 (2008-0603)
- Vorinostat + Aza (2007-0685)
- AZD1152 vs low-dose Ara-C (2009-0217)

### 2. Salvage Programs

- Tamibarotene (2007-0512) in APL
- Clofarabine ± Ara-C ± Ida (ID03-0181)
- Lenalidomide (2006-0293)
- HuM195/rGel (DM98-342)
- Ara-C ± Clofarabine (2006-0069)
- Oral Clofarabine (2005-0536)
- FAO (2006-1089)
- Azacitidine (2007-0405)
- DAC + Mylotarg (2008-0288)
- Sapacitabine (2007-0727)
- LY2181308 (2007-0707)
- CPX-351 vs 'Standard' (2008-0679)
- DT388IL3 (2008-0313)
- PMA112509 (2009-0046)
- Voreloxin + Ara-C (2009-0131)
- AZD1152 + Ara-C (2009-0172)
- SAR103168 (2009-0196)

### 3. Maintenance Therapy

- DAC vs Observation (2006-0358)

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

- Decitabine (2007-0883)
- Azacitidine (2007-0405)
- Thymoglobulin + Cyclosporin (2005-0115)
- LBH589 (2007-0713)
- Gimatecan (2006-0943)
- Romiplostim (2008-0249)
- Revlimid + Darbepoetin alfa (2006-0657)
- JNJ-26481585 (2008-0245)
- AR-67 (2008-0530)
- ARRY-614 (2009-0129)

## 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 + Cytosan (2005-0552)
- 5-aza + Hyper CVAD (2005-0895)
- Marquibo (2006-1109)
- Augmented Hyper CVAD (ID03-0166)
- MOAD (2008-0267)
- DT2219ARL (2008-0519)

## CML Treatment Priorities

### 1. CML Chronic Phase

- Dasatinib (2005-0422)
- Nilotinib (2005-0048)
- Bosutinib (2005-0813)
- Dasatinib (2007-0606)
- HHT (2006-0926/2006-0192)

### 2. CML Accelerated Phase

- HHT (2006-0926/2006-0192)
- Bosutinib (2005-0813)

### 3. CML Blastic Phase

- HHT (2006-0926/2006-0192)
- Bosutinib (2005-0813)

### 4. Minimal Residual Disease

- Dasatinib + Ipilimumab (2008-0157)

### 5. T315I Mutations

- XL228 (2007-0502)
- PHA-739358 (2007-0939)
- AP24534 (2008-0046)
- HHT (2006-0192)
- DCC-2036 (2008-0732)

## Myeloproliferative Disorders

- Pomalidomide (2007-0199)(MF)
- Bevacizumab (2008-0025)(MF)
- Pegasys (DM03-0109)
- INCB018424 (2007-0169)
- 2CDA + Ara-C (DM97-232) (HES only)
- TG101348 (2007-0837)(MF)
- AZD1480 (2009-0067)
- Obatoclox (2008-0792)
- Masatinib (2008-0275)

## Phase I/II Agents for Hematologic Malignancies

- BAY-43-9006 (2004-0702)
- AT9283 (2006-0177)
- XL228 (2007-0502)
- Bendamustine (2007-0634)
- SB939 (2007-0848)
- INCB018424 (2007-0925)
- PHA-739358 (2007-0939)
- RO5045337 (2007-0408)
- OPB-31121 (2007-0488)
- ARRY-520 (2007-0879)
- SB1518 (2008-0032)
- AP24534 (2008-0046)
- DCC-2036 (2008-0732)
- IMC-EB10 (2009-0042)
- AS703026 (2009-0915)
- GSK1120212 (2009-0239)

## List of Leukemia Service Attendings

ANDREEFF, MICHAEL	(713) 792-7260	KOLLER, CHARLES	(713) 792-7747
BORTHAKUR, GUTAM	(713) 563-1586	KONOPLEVA, MARINA	(713) 794-1628
BURGER, JAN	(713) 563-1487	KORNBLAU, STEVEN	(713) 794-1568
CORTES, JORGE	(713) 794-5783	MATTIUZZI, GLORIA N.	(713) 745-2723
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JABBOUR, ELIAS	(713) 792-4764	VERSTOVSEK, SRDAN	(713) 745-3429
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