CITY OF HOPE MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HCT

TITLE: Phase I/II study of the combination of Dasatinib with chemotherapy for high risk acute myeloid leukemia (AML) patients

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 12393 **VERSION: 4.0**

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

COH Initial (dated 07/17/2013)	Version: 0.0
COH Amendment v 1.0 (dated 10/04/2013)	Version: 1.0
COH Amendment v 2.0 (dated 03/20/2014)	Version: 2.0
COH Amendment v 3.0 (dated 07/07//2014)	Version: 3.0
COH Amendment v 4.0 (dated 01/22/2016)	Version: 4.0

DISEASE SITE:	Bone Marrow/Blood
STAGE (If applicable):	AML
MODALITY:	Chemotherapy
TYPE:	Phase I/II
PRINCIPAL INVESTIGATOR:	Ahmed Aribi, M.D
COLLABORATING INVESTIGATOR(S):	Anthony Stein, M.D.
PARTICIPATING CLINICIANS:	Monzr Al Malki, M.D., Ibrahim Aldoss, M.D., Haris Ali, M.D., Elizabeth Budde, M.D., Ji-Lian Cai, M.D., PhD, Thai Cao, M.D., Robert Chen, M.D., Len Farol, M.D., Stephen Forman, M.D., Alex Herrera, M.D., Myo Htut, M.D., Chatchada Karanes, M.D., Samer Khaled, M.D., Amrita Krishnan, M.D., Guido Marcucci, M.D., Matthew Mei, M.D., Auayporn Nademanee, M.D., Ryotaro Nakamura, M.D., Nitya Nathwani, M.D., Margaret O'Donnell, M.D., Pablo Parker, M.D., Leslie Popplewell, M.D., Vinod Pullarkat, M.D., Michael Rosenzweig, M.D., Firoozeh Sahebi, M.D., Amandeep Salhotra, M.D., Tanya Siddiqi, M.D., Eileen Smith, M.D., David Snyder, M.D., Ricardo Spielberger, M.D., Jasmine Zain, M.D.
STUDY STATISTICIAN:	Joycelynne M. Palmer, PhD
PARTICIPATING SITES:	City of Hope

Investigators

PRINCIPAL INVESTIGATOR:

Ahmed Aribi, MD
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
Phone: (626) 256-4673 x 62405
Fax: (626) 301-8116
e-mail: aaribi@coh.org

STUDY STATISTICIAN:

Joycelynne M. Palmer, PhD
City of Hope National Medical Center
1500 E. Duarte Road, Bldg 171, Office 1006
Duarte, CA 91010
Phone: (626) 256-4673 x 65266
Fax: (626) 471-7106
e-mail: jmpalmer@coh.org

COLLABORATING INVESTIGATORS:

Ravi Bhatia, M.D.
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
Phone: (626) 256-4673 x62705
Fax: (626) 301-8973
e-mail: rbhatia@coh.org

Anthony Stein, M.D.
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
Phone: (626) 256-4673 x62705
Fax: (626) 301-8973
e-mail: astein@coh.org

AGENT NSC# AND IND#: N/A

COORDINATING CENTER: City of Hope National Medical Center

Experimental Design Schema

Induction Phase

	Screening	Study Treatment Phase							Post Study Treatment Phase	Follow Up
Day of Cycle	**Day -14 to Day 0**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8 to D28**	**Up two years**
Treatment with Cytarabine 200mg/m^2 /day		**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Treatment with Idarubicin 12mg/m^2 /day		**X**	**X**	**X**						
Treatment with Dasatinib*		**X**	**X**	**X**	**X**	**X**	**X**	**X**		

***Dasatinib dose pending to cohort assigment**

Re-Induction Phase#

	Study treatment Phase							Post Study Treatment Phase	Follow Up
Day of Cycle	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8 to D28**	**Up two years**
Treatment with Cytarabine 200mg/m^2 /day	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Treatment with Idarubicin 12mg/m^2 /day	**X**	**X**	**X**						
Treatment with Dasatinib*	**X**	**X**	**X**	**X**	**X**	**X**	**X**		

***Dasatinib dose pending to cohort assigment**

 # Re-induction therapy will start within one week after day 30 bone marrow.

Protocol Synopsis

Protocol Title:
PHASE I/II STUDY OF THE COMBINATION OF DASATINIB WITH CHEMOTHERAPY FOR HIGH RISK ACUTE MYELOID LEUKEMIA (AML) PATIENTS
Brief Protocol Title for the Lay Public (if applicable):
COMBINATION OF DASATINIB WITH CHEMOTHERAPY FOR HIGH RISK ACUTE MYELOID LEUKEMIA
Study Phase:
I/II
Participating Sites:
City of Hope
Rationale for this Study:
AML is the most common acute leukemia in adults and accounts for approximately 80% of cases, with a median age at diagnosis of approximately 65 years. While standard induction chemotherapy (anthracycline plus cytarabine) produces a 50-75% complete remission rate, only a small percentage of younger patients (<60y) achieve a durable remission; the majority of AML patients eventually relapse and die from recurrent disease. AML patients with poor risk cytogenetics, elderly patients with AML, AML secondary to myelodysplasia or myeloproliferative disorder, and therapy-related AML, have an even worse prognosis, with even lower complete remission rates and long-term survival despite aggressive chemotherapy. Clearly there is a need to improve the outcome of poor risk AML patients. Tyrosine kinases play an important role in AML pathogenesis. Pre-clinical studies performed at our center have shown that Src family tyrosine kinases (SFKs) including Lyn, Hck and Fgr are abnormally activated in AML compared to normal hematopoietic stem and progenitor cells. Other studies show that the c-Kit receptor tyrosine kinase is often overactivated in AML and contributes to abnormal growth. The small molecule SFK and c-Kit inhibitor Dasatinib reduces proliferation and survival of AML stem and progenitor cells. Importantly, Dasatinib treatment enhances sensitivity of AML stem/progenitor cells to chemotherapeutic agents, through inhibition of Akt signaling and activation of p53. These results provide a strong rationale to conduct a clinical study to determine the safety and tolerability of combination of Dasatinib with AML standard chemotherapy and its effect on complete remission (CR) rate, overall survival (OS) and event free survival (EFS).
Objectives:
1. Phase I Objectives: 1.1. **Primary:** Of the dose levels studied, to determine the maximum tolerated dose of dasatinib when given in combination with cytarabine and idarubicin for treatment of high risk AML. The selected dose will be used in the phase II study. To describe the safety, tolerability, and toxicity profile of Dasatinib, given in combination with cytarabine and idarubicin. 1.2. **Secondary:** To document complete remission rate (CR) and survival outcomes

(overall, event-free).

2. Phase II Objectives:

2.1. **Primary:** To determine the anti-tumor activity of Dasatinib given in combination with cytarabine and idarubicin, as assessed by complete remission rate (CR) and remission duration.

2.2. **Secondary:** i) To estimate the survival probabilities (overall and event-free) and cumulative incidence of relapse/progression incidence. ii) To describe, summarize all toxicities by organ and severity.

Study Design:

Phase I

The study design is based on a standard 3 + 3 dose escalation design.

Dose level 1 will be the first dose level tested. Initially three subjects will be treated, if 0/3 experiences a dose limiting toxicity (DLT), enter 3 subjects at dose level 2. If 1/3 of the first 3 subjects has DLT, enter 3 more subjects at dose level 1. If none of these 3 additional subjects has DLT, then proceed to dose level 2. If one or more of these 3 additional subjects has DLT, then a dose reduction (to dose level -1) will be applied.

Among the patients treated at dose level 2, if 0/3 or 1/3 of the first 3 subjects experiences DLT, enter 3 more subjects at dose level 2. If ≤ 1/6 subjects on dose level 2 have DLT, dose level 2 will be declared the phase II dose (P2D). If ≥ 2/6 subjects have DLT at dose level 2, dose level 1 will be declared the P2D, assuming at least six patients have been treated at dose level 1 and ≤ 1/6 subjects has DLT.

Assuming a dose reduction is necessary, among the patients treated at dose level -1, if 0/3 or 1/3 on the first 3 subjects has DLT, enter 3 more subjects at dose level -1. If ≤ 1/6 subjects treated on dose level -1 has DLT, dose level -1 will be declared the P2D. If ≥ 2/6 subjects have DLT on dose level -1, then the study will be terminated.

Dose Level	Cytarabine*	Idarubicin#	Dasatinib^
-1	200mg/m^2	12mg/m^2	70mg/day
1	200mg/m^2	12mg/m^2	100mg/day
2	200mg/m^2	12mg/m^2	140mg/day

*: IV QD, days 1-7
#: IV QD, days 1-3
^: PO QD, days 1-7

The phase I study is expected to enroll 9-18 evaluable (a maximum of 18) patients. Toxicities will be monitored, graded, and recorded according to the NCI-Common Terminology Criteria for Adverse Events version 4.0.

Dose limiting toxicity is defined as any of the toxicities listed below that occur from the first dose of dasatinib through the DLT observation period discussed below. Patients must not have persistent leukemia after induction to be considered evaluable for DLTs associated with hematologic toxicity. Patients who have persistent leukemia are still potentially evaluable patients for safety and cohort advancement based on the non-

hematologic DLT criteria below.

Hematologic Toxicities:
For patients without persistent leukemia following induction:
Grade 4 hematological toxicity persisting >42 days following the last dose of dasatinib (i.e., Day 49) not attributable to persistent leukemia with exclusion of chronic cytopenia attributed to preexistent condition such as MDS, MPN, and MF.

Non-Hematologic Toxicities:
For all patients, within the first 28 days:

Any grade 3 or higher non-hematologic toxicity, excluding:

- Anorexia, fatigue, uric acid, fever with or without neutropenia, or bleeding during a period of Grade 4 thrombocytopenia
- Diarrhea, nausea, abdominal bloating, vomiting or mucositis that resolves to ≤ Grade 1 or to baseline within 7 days of onset with optimal medical management
- Elevated AST, ALT, alkaline phosphatase, or bilirubin that returns to ≤ Grade 2 or to baseline within 14 days of onset
- Rash or elevated amylase or lipase that returns to ≤ Grade 2 or to baseline within 7 days of onset
- Infections or complications of infections due to neutropenia
- Electrolyte disturbance that can be corrected with supplementation within 10 days.

Any grade 5 toxicity not due to disease, will be considered a DLT.

~~As of 7/7/14, nine patients have been treated and are evaluable for toxicity evaluation (six treated at dose level 1 and three treated at dose level 2). Under the revised DLT definition, to ensure safety, three additional patients will be treated on dose level 1, for a total of nine.~~

Patients must complete all 7 days of dasatinib or experience a DLT to be evaluable for toxicity. Phase I patients treated at the P2D will count toward the phase II trial accrual goal.

Observed toxicities will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count) severity (by NCI CTCAE v4.0, date of onset, duration, reversibility, and attribution. Tables will be created to summarize these toxicities and side effects. Baseline information (e.g. cytogenetic risk) and demographic information will be presented for all study patients. While not the primary objective of the phase I study, a preliminary estimate of complete remission rate (CR) and remission duration will be reported. Survival probabilities, overall survival (OS) and event-free (EFS) will be estimated.

Phase II
This is a single center phase II trial to determine the anti-tumor activity of Dasatinib given in combination with cytarabine and idarubicin as assessed by complete remission rate (CR) (Cheson et al. 2003), the primary endpoint; secondary endpoints are remission

duration, survival (overall and event-free) and toxicities. Patients with high-risk AML will be eligible. This study will implement a single arm SWOG Phase II two-stage design to study the activity of Dasatinib plus cytarabine and idarubicin (Green SJ, Benedetti J, and Crowely J, 1997).

The phase II portion of the trial is expected to enroll a minimum of 20 and a maximum of 40 patients. The sample size is based on the desire to discriminate a promising remission rate from a disappointing rate (assuming a 20% difference in the two rates) using a type I error rate of 0.05 and power of approximately 80%.

At stage 1, 20 patients will be entered on the study (including the 6 patients treated at the MTD from Phase I). A 2% false-negative rate ruling out the promising CR rate will result in termination of the study, using the Green-Dahlberg rule. At stage 2, 20 additional patients will be entered. At the end of stage 2, the CR rate must rule out the discouraging CR rate with a type I error of 5% to be declared a success. This design incorporates the Green-Dahlberg rule of 2% false – negative error rate in the first stage (Green SJ and Dahlberg S,1992). Accrual is expected to be complete within 18-24 months.

Remission rates will be calculated as the percent of evaluable patients that have a confirmed CR, and exact 95% confidence intervals will be calculated for these estimates. Time to confirmed complete remission, duration of remission, and survival will be estimated using the product-limit method of Kaplan and Meier. Toxicity will be monitored on an ongoing basis. If the percentage of unacceptable toxicities exceeds 25% with 6 or more patients accrued, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee will be mandated. Patient accrual will not resume until approved by the Data Safety Monitoring Committee to do so.

Endpoints:

Phase I: Toxicity

Phase II: Primary-complete response rate (CR); Secondary-response duration, survival (overall and event-free) and toxicities.

Sample Size:

Phase I, Expected: 9, maximum 18

Phase II, Expected: 40 (6 patients brought forward from Phase I trial + 34 additional)

At stage 1, 20 patients will be entered on the study (14 newly enrolled combined with the 6 patients treated at the MTD from Phase I for a total of 20).

At stage 2, 20 additional patients would be entered on the study.

Estimated Duration of the Study

Accrual is expected to be complete within 18-24 months. Combination treatment will be last 1-3 months for each patient.

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

1. Patients diagnosed with AML meeting one of following criteria:
   1.1. Newly diagnosed, age 60 and older
   1.2. High risk cytogenetics and molecular abnormalities (NCCN criteria)
   1.3. Relapsed or refractory to prior chemotherapy

1.4. Secondary AML
2. Any prior chemo therapy must have been completed ≥2 weeks prior to day 1 of study treatment and the participant must have recovered to eligibility levels from prior toxicity.
   2.1. Only one prior regimen is allowed for relapsed AML Patients.
   2.2. Hydroxyurea is allowed prior to day 1 of study treatment to keep WBC below 20 K.
3. Age ≥18 years.
4. Karnofsky performance status ≥60%.
5. Patients must have normal organ function as defined below:
   5.1. Total bilirubin <1.5 X institutional upper limit of normal
   5.2. AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
   5.3. Creatinine <1.5 X institutional upper limit of normal
   5.4. OR Creatinine clearance ≥60 mL/min for patients with creatinine levels above 1.5 X institutional upper limit of normal,
   5.5. EF ≥45%.
6. Ability to understand and sign a written informed consent document.
7. Patients should not be receiving any other investigational agents.

Exclusion Criteria:

1. Patients with clinically significant illnesses which would compromise participation in the study, including, but not limited to: active or uncontrolled infection, immune deficiencies or confirmed diagnosis of HIV infection, active Hepatitis B, active Hepatitis C, or uncontrolled diabetes, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia; or psychiatric illness/social situations that would limit compliance with study requirements.

2. Patients with additional (other than AML) currently active primary malignancy other than curatively treated CIS of the cervix, or basal or squamous cell carcinoma of the skin. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy and disease free from prior malignancies for >2 years

3. Patients with active central nervous system (CNS) disease.

4. Patients with Chronic Myelogenous Leukemia (CML) in Myeloid blasts crisis.

5. Active infections, including opportunistic infections

6. Women of childbearing potential (WOCBP) who have a positive serum pregnancy test within 14 days of the first administration of oral Dasatinib.

Investigational Product Dosage and Administration:

Induction Chemo Therapy

Patients will receive cytarabine 200mg/m^2 /day IV continuously over 168 hours on days

1-7 with idarubicin 12mg/m^2 /day IV slow push days 1-3, and oral Dasatinib (depending on the dose level the patient is assigned to) once daily on days 1 to 7. Patients who are in CR (Complete Remission) on day 30 BM undergo consolidation therapy, and patients with non-responsive disease on day 30 (bone marrow cellularity ≥ 20 % and leukemia blasts ≥ 5%) receive a re-induction therapy. After completion of study therapy, patients will be followed every 2 months for 2 years.
Clinical Observations and Tests to be Performed:
Standard induction chemo-therapy tests and procedure will be used for this study
Statistical Considerations:
See Study Design Section
Sponsor/Licensee:
City of Hope National Medical Center
Case Report Forms
All data will be collected and submitted using electronic case report forms in Medidata Rave EDC.

Table of Contents

Abbreviations

Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease

1.0 Goals and Objectives (Scientific Aims)

1.1 Phase I Objectives:

1.1.1 Primary:

Of the dose levels studied, to determine the maximum tolerated dose of Dasatinib when given in combination with Cytarabine and Idarubicin for treatment of high risk AML patients. The selected dose will be used in the Phase II study.

1.1.2 Secondary:

To document complete remission rate (CR) and survival outcomes (overall, event-free).

1.2 Phase II Objectives:

1.2.1 Primary Endpoints

To determine the anti-tumor activity of Dasatinib when given in combination with Cytarabine and Idarubicin, as assessed by complete remission rate (CR) and remission duration.

1.2.2 Secondary Endpoints:

To estimate the survival probabilities (overall and event-free) and cumulative incidence of relapse/ progression.

To describe and summarize all toxicities by organ and severity.

2.0 Background

2.1 Introduction/Rationale for Development

AML is the most common acute leukemia in adults and accounts for approximately 80% of cases, with a median age at diagnosis is approximately 65 years. While standard induction chemotherapy (anthracycline plus cytarabine) leads to a complete remission rate of roughly 50-75%, only a small percentage of younger patients (<60y) enjoy a durable remission. The majority of AML patients eventually relapse and die from recurrent disease. Newly diagnosed elderly AML patients (>60), poor risk cytogenetics, , as well as AML secondary to myelodysplasia and myeloproliferative disorders, and therapy-related AML, have an even worse prognosis, with even lower complete remission rates and long-term survival despite aggressive chemotherapy. CR rates for these patient subgroups are as follows: high risk cytogenetics <60y, CR rate 50% Mrozek (2012); high risk cytogenetics ≥60y, CR rate 39% Mrozek (2012); newly diagnosed patients, aged 60 and older, CR rate 48% (41-55%) van der Holt (2005); secondary AML, CR rate 24% Leith (1997); relapsed/refractory CR rate 30%.Clearly there is a need to improve the outcome of poor risk AML patients

Tyrosine kinases play an important role in AML pathogenesis. Pre-clinical studies performed at our center have shown that Src family tyrosine kinases (SFKs) including Lyn, Hck and Fgr are abnormally activated in Acute Myeloid Leukemia (AML) compared to normal hematopoietic stem and progenitor cells. Other studies show the the c-Kit receptor tyrosine kinase is often overactivated in AML and contributes to abnormal growth. The small molecule SFK and c-Kit inhibitor Dasatinib reduces proliferation and survival of AML stem and progenitor cells. Importantly, Dasatinib treatment enhances sensitivity of AML stem/progenitor cells to chemotherapeutic agents, through inhibition of Akt signaling and activation of p53. These results provide a strong rationale to conduct a clinical study to determine the safety and tolerability of combination of Dasatinib with AML standard chemotherapy and its effect on complete remission (CR) rate, overall survival (OS) and event free survival (EFS).

2.2 Overview of Proposed Study

This is an open label, Phase I/II study.

2.2.1 Phase I

The study design is based on a standard 3 + 3 dose escalation design.

Dose level 1 will be the first dose level tested. Initially three subjects will be treated, if 0/3 experiences a dose limiting toxicity (DLT), enter 3 subjects at dose level 2. If 1/3 of the first 3 subjects has DLT, enter 3 more subjects at dose level 1. If none of these 3 additional subjects has DLT, then proceed to dose level 2. If one or more of these 3 additional subjects has DLT, then a dose reduction (to dose level -1) will be applied.

Among the patients treated at dose level 2, if 0/3 or 1/3 of the first 3 subjects experiences DLT, enter 3 more subjects at dose level 2. If ≤ 1/6 subjects on dose level 2 have DLT, dose level 2 will be declared the phase II dose (P2D). If ≥ 2/6 subjects have DLT at dose level 2, dose level 1 will be declared the P2D, assuming at least six patients have been treated at dose level 1 and ≤ 1/6 subjects has DLT.

Assuming a dose reduction is necessary, among the patients treated at dose level -1, if 0/3 or 1/3 on the first 3 subjects has DLT, enter 3 more subjects at dose level -1. If ≤ 1/6 subjects treated on dose level -1 has DLT, dose level -1 will be declared the P2D. If ≥ 2/6 subjects have DLT on dose level -1, then the study will be terminated.

Dose Level	Cytarabine*	Idarubicin[#]	Dasatinib^
-1	200mg/m^2	12mg/m^2	70mg/day
1	200mg/m^2	12mg/m^2	100mg/day
2	200mg/m^2	12mg/m^2	140mg/day

*: IV QD, days 1-7
[#]: IV QD, days 1-3
^: PO QD, days 1-7

The phase I study is expected to enroll 9-18 evaluable patients. Toxicities will be monitored, graded, and recorded according to the NCI-Common Terminology Criteria for Adverse Events version 4.0. Patients must complete all 7 days of dasatinib or experience a dose limiting toxicity (DLT) to be evaluable for toxicity. Patients treated during the phase I portion of the trial at the dose selected for the phase II trial will be counted in the phase II trial.

Observed toxicities will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count) severity (by NCI CTCAE v4.0), date of onset, duration, reversibility, and attribution. Tables will be created to summarize these toxicities and side effects. Baseline information (e.g. cytogenetic risk) and demographic information will be presented for all study patients. While not the primary objective of the phase I study, a preliminary estimate of complete remission rate (CR) will be reported. Survival outcomes overall survival (OS), event-free (EFS)) and remission duration will be estimated/summarized to describe the outcome of treated patients.

2.2.2 Phase II

This is a single center phase II trial to determine the anti-tumor activity of Dasatinib when given in combination with cytarabine and idarubicin as assessed by complete remission rate (CR), the primary endpoint; secondary endpoints are response duration, survival (overall and event-free) and toxicities. CR is noted as the objective status on 2 consecutive evaluations at least 7 days apart; the first evaluation to occur on day 14. Patients with high-risk AML will be eligible. This study will implement a single arm

SWOG Phase II two-stage design to study the activity of Dasatinib plus cytarabine and idarubicin (Green SJ, Benedetti J, and Crowely J, 1997). The phase II portion of the trial is expected to enroll a minimum of 20 and a maximum of 40 patients. Accrual is expected to be complete within 18-24 months.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

2.3 Preclinical Studies

2.3.1 2.3.1 Dasatinib

Current treatments for AML can induce clinical remissions, but are associated with a high likelihood of relapse due to persistence of leukemia stem cells (LSC). There is a pressing need for new approaches to eliminate LSC to improve outcomes for AML patients.

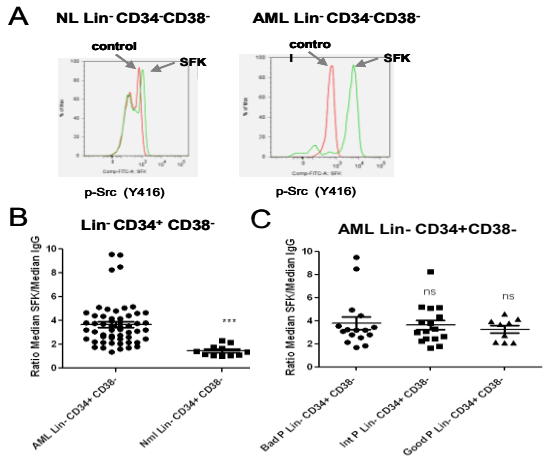

Figure 1. Increased SFK activity in AML LSC. A. Representative FACS plots for p-SFK expression. B. Increased p-SFK levels in AML CD34+CD38- cells. C. Similar levels of p-SFK in good, intermediate and high risk AML cells.

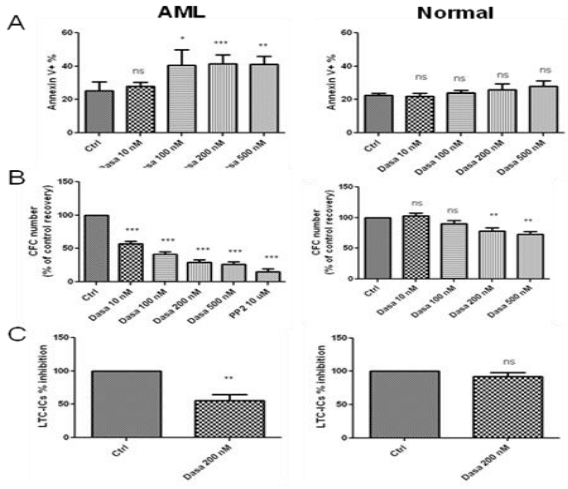

Figure2. Dasatinib treatment inhibits AML progenitor growth in vitro. Treatment with Dasatinib results in increased apoptosis (A), reduced colony growth (B), and reduced LTCIC growth (C) of AML compared to normal CD34+ cells.

Preliminary studies from Dr. Ravi Bhatia's laboratory have shown that AML stem and progenitor cells display higher constitutive SRC-family kinase (SFK) phosphorylation compared to their normal counterparts (Fig 1). No difference in SFK phosphorylation was observed between good, intermediate and poor cytogenetic risk groups, suggesting that SFKs are activated in AML independently of underlying cytogenetic abnormality.

Dasatinib, a dual ABL-SRC inhibitor approved for the treatment of CML, inhibited SFK phosphorylation in AML stem/progenitor cells, and induced significant dose dependent inhibition of AML compared to normal CFC; within the range of plasma drug concentration achieved in patients (Fig 2). Treatment with Dasatinib (200nM) also resulted in reduced growth of AML stem cells in long-term culture-initiating cells (LTC-IC) assays, and a significantly greater increase in apoptosis and significantly greater proliferation inhibition in AML compared to normal progenitor cells.

The combination of Dasatinib (200nM) with Daunorubicin (DNR) or cytarabine (Ara-C), chemotherapeutic agents commonly used for treatment of AML, resulted in significantly greater inhibition of AML CD34+ cell proliferation, survival, and colony growth compared to chemotherapy alone (Fig. 3). This synergistic effect was specific to AML samples and was not observed for normal CD34+ cells. Treatment of AML CD34+ cells with Dasatinib plus chemotherapy resulted in significantly reduced long-term (12 weeks) engraftment of human AML cells following transplantation into immunodeficient mice, indicating significantly enhanced inhibition of AML LSC. In addition, *in vivo* administration of Dasatinib in combination with chemotherapeutic agents in a genetic AML mouse model enhanced elimination of primary AML cells, including AML LSC capable of regenerating leukemia in secondary recipients. The combination of Dasatinib with DNR or Ara-C did not inhibit long term engraftment of normal HSC compared to DNR and Ara-C alone. Studies of underlying mechanisms show that the combination of Dasatinib with DNR enhances p53 activity in AML cells by inhibiting AKT mediated MDM2 phosphorylation. These results indicate that c-Kit and SFK inhibition with Dasatinib significantly enhances the killing of AML LSC by chemotherapeutic agents, while sparing normal stem/ progenitor cells and provide a strong rationale for the proposed clinical trial of Dasatinib in combination with chemotherapy in high-risk AML patients.

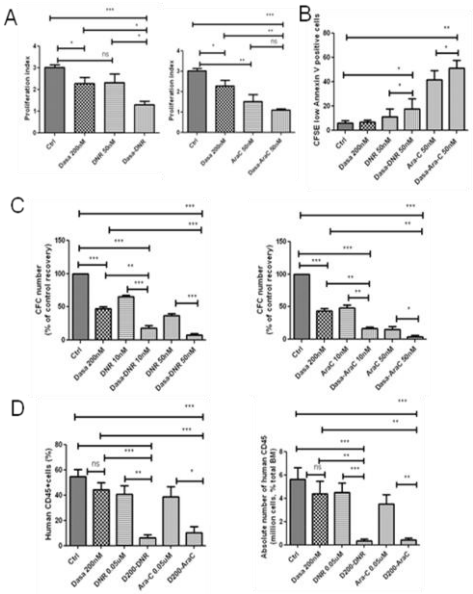

Figure 3. Dasatinib treatment enhances targeting of AML stem/progenitor cells by chemotherapy. Treatment of AML CD34+ cells with a combination of Dasatinib with DNR and Ara-C results in (A) reduced proliferation, (B) increased apoptosis, (C) reduced colony growth, and (D) reduced engraftment in immunodeficient NSG mice, compared to chemotherapy or Dasatinib alone.

2.4 Human Studies

2.4.1 Dasatinib

Dasatinib (BMS-354825, Sprycel®; Bristol Myers Squibb, New York, NY, USA) is a potent, second-generation, small-molecule, multi-target kinase inhibitor of BCR-ABL. This agent exerts greater in vitro activity against non-mutated ABL kinase than imatinib. Dasatinib was initially developed as an inhibitor of the Src family of kinases such as Fyn, Yes, Src, and Lyk, but it also inhibits BCR-ABL, EphA2, platelet-derived growth factor receptor, and c-Kit. \Dasatinib can inhibit the proliferation and kinase activity of wild-type and BCR-ABL mutant cell lines that are resistant to imatinib, except those carrying the T315I mutation. In vivo studies have shown that Dasatinib is 325-fold more potent than imatinib and 16-fold more potent than nilotinib, another BCR-ABL kinase inhibitor, against non-mutated BCR-ABL. In murine models Dasatinib was shown to inhibit leukemic cell growth and to prolong the survival of mice harboring wild-type *BCR-ABL* and M351T, but not the T315I mutant. Dasatinib is a dual-specific Src and Abl inhibitor that can inhibit both the active and inactive conformations of ABL. In June 2006, the Food and Drug Administration approved Dasatinib for the treatment of chronic phase, accelerated phase, or blastic phase CML, resistant or intolerant to imatinib, and for Ph chromosome-positive acute lymphoid leukemia that was resistant or intolerant to prior therapy.

2.4.1.1 Mechanism of action

Dasatinib binds to the ATP-binding site of ABL, but extends in the opposite direction from imatinib. Dasatinib binds the inactive and active conformation of the ABL kinase domain, requires fewer contact points with ABL, and has a greater affinity to the ABL kinase domain compared to imatinib. In vitro, Dasatinib has demonstrated greater than 325-fold activity against *BCR-ABL* wild-type, and the kinase activity of 14 of 15 BCR-ABL imatinib-resistant isoforms has been successfully inhibited at nanomolar concentrations of Dasatinib. The activity of Dasatinib against several *ABL* kinase mutations is explained by the fact that it does not require interaction with some of the residues involved in those mutations. Dasatinib's inhibiting potential against Src family kinase members is greater (IC_{50} 0.5 nmol/L) than its inhibitory activity against ABL (1 nmol/L). At nanomolar concentrations, Dasatinib also inhibits c-KIT, platelet-derived growth factor receptor and EphA2. Dasatinib was also shown to significantly suppress CML colony-forming cells and long-term culture-initiating cells, but it did not significantly alter the level of apoptosis-regulating proteins in CML CD34 + cells. Therefore, Dasatinib suppresses progenitor growth through inhibition of proliferation and a modest increase in apoptosis in dividing progenitors. In addition, Dasatinib did not enhance suppression and targeting of CML primitive and committed progenitors.

2.4.1.2 Pharmacokinetics

Dasatinib is administered orally and peaks from 0.5 to 6 hours after oral dosing. Its half-life is 3 to 5 hours and the absorption is not affected by food intake. Dasatinib is metabolized by the cytochrome P450 (CYP) 3A4 isozyme into active and inactive metabolites. Therefore, concomitant use of Dasatinib with inducers of CYP3A4 can decrease Dasatinib exposure, whereas inhibitors of the 3A4 enzyme, such as antiretrovirals, azole antifungals and macrolides, can increase the toxicity of Dasatinib. Recent data suggest that Dasatinib given orally crosses the blood–brain barrier. The concentrations of Dasatinib found in the cerebrospinal fluid of patients ranged from 1.4 to 20.1 nM, and were consistent with the observed antitumor activity in the central nervous system. The elimination of Dasatinib is primarily via the feces. The concomitant use of H2 blockers and proton pump inhibitors is not recommended since the solubility of Dasatinib depends on intestinal pH, and therefore, anti-acid agents reduce the concentration of Dasatinib by approximately 60%. No clinically relevant data are available for dose modifications based on age, gender or ethnicity, although patients greater than 65 years showed increased fluid retention over younger patients. More importantly, the efficacy of Dasatinib appears to be independent of patient age.

2.4.1.3 Toxicity

Dasatinib is generally well tolerated. The most common non-hematologic adverse events in clinical trials with Dasatinib included gastrointestinal symptoms, such as diarrhea, nausea, vomiting, anorexia, abdominal pain and anorexia; headache; peripheral edema; and pleural effusion. Fewer than 10% of patients reported mucositis, stomatitis, abdominal distention, constipation, colitis, dysphagia, anal fissure, upper gastrointestinal ulcers, pancreatitis and esophagitis. Pleural and pericardial effusion, severe pulmonary edema, pulmonary hypertension, and ascites were less common. Ascites and pleural effusion are usually reversible with temporary dose interruption, diuretics and steroids.

Myelosuppression is common and it is reversible by interruption, reduction or discontinuation of the myelosuppression-inducing Dasatinib dose. Grade 3–4 myelo-suppression is more frequent in patients with accelerated or blastic phase CML and constitutes the most common reason for drug interruption. Thrombocytopenia is more significant than neutropenia and its associated rates of gastrointestinal bleeding and central nervous system hemorrhage are <4% and <1%, respectively, whereas the rate of other severe hemorrhages is approximately 2%. Dasatinib-induced thrombocytopenia associated with hemorrhagic complications suggests that patients receiving anticoagulation or antiplatelet agents should be treated with caution.

Cardiac adverse events are infrequent and include left ventricular dysfunction, cardiac failure, cardiomyopathy, ventricular failure, diastolic dysfunction, and QT-interval prolongation. Skin sequelae

include erythema, erythema multiforme, pustular rash, pruritic rash, skin exfoliation, skin irritation, systemic lupus erythematous, vesicular rash, and maculopapular rash. Fewer than 10% of patients develop acne, alopecia, skin ulcer, pigmentation disorder, panniculitis, photosensitivity, nail disorders, and palmar plantar erythrodysesthesia.

The use of Dasatinib is also associated with hypocalcemia, hypophosphatemia, transaminitis and creatinine elevation. Symptoms from the central nervous system are noted in <10% of patients and include neuropathy, dizziness, dysgeusia, somnolence, tremor, syncope, transient ischemic attack, cerebrovascular disease and seizures. Other toxicities include hypersensitivity, gynecomastia, irregular menses, vertigo, appetite disturbances, increased triglycerides, cholesterol, pyrexia and fatigue.

2.4.1.4 Dasatinib and Chemotherapy Combinations

Ravandi and colleagues examined the efficacy and safety of combining chemotherapy with Dasatinib for patients with newly diagnosed Ph+ ALL. Patients received Dasatinib 100 mg daily for the first 14 days of each cycle of alternating hyper-CVAD, and high-dose cytarabine and methotrexate, for 8 cycles, and patients achieving CR received maintenance Dasatinib, vincristine and prednisone for 2 years, followed by Dasatinib indefinitely. Of 35 patients (median age of 53 years, range, 21-79 years) treated, 33 patients (94%) achieved complete CR. Grade 3 and 4 adverse events included hemorrhage and pleural and pericardial effusions. The estimated 2-year survival was 64%. These results indicate that the combination of chemotherapy with Dasatinib is safe and potentially effective in patients with newly diagnosed Ph+ ALL.

2.4.2 Cytarabine

Cytarabine for Injection USP, commonly known as ara-C, an antineoplastic for intravenous, intrathecal, or subcutaneous administration, contains sterile lyophilized cytarabine (1-ß-D-Arabinofuranosylcytosine). Cytarabine is an odorless, white to off-white, crystalline powder which is freely soluble in water and slightly soluble in alcohol and in chloroform. Cytarabine is a synthetic nucleoside which differs from the normal nucleosides cytidine and deoxycytidine in that the sugar moiety is arabinose rather than ribose or deoxyribose.

2.4.2.1 Cell Culture Studies

Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G**1** phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported.

Extensive chromosomal damage, including chromatoid breaks, has been produced by cytarabine, and malignant transformation of rodent cells in culture has been reported. Deoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

2.4.2.2 Cellular Resistance and Sensitivity

Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase; it is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative. It appears that the balance of kinase and

deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine.

2.4.2.3 Human Pharmacology

Cytarabine is rapidly metabolized and is not effective when taken orally; less than 20% of the orally administered dose is absorbed from the gastrointestinal tract.

Following rapid intravenous injection of cytarabine labeled with tritium, the disappearance from plasma is biphasic. There is an initial distributive phase with a half-life of about 10 minutes, followed by a second elimination phase with a half-life of about 1 to 3 hours. After the distributive phase, more than 80% of plasma radioactivity can be accounted for by the inactive metabolite 1-ß-D-Arabinofuranosyluracil (ara-U). Within 24 hours, about 80% of the administered radioactivity can be recovered in the urine, approximately 90% of which is excreted as ara-U.

Relatively constant plasma levels can be achieved by continuous intravenous infusion.

After subcutaneous or intramuscular administration of cytarabine labeled with tritium, peak plasma levels of radioactivity are achieved about 20 to 60 minutes after injection and are considerably lower than those after intravenous administration.

Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous injection. However, in one patient in whom cerebrospinal levels were examined after 2 hours of constant intravenous infusion, levels approached 40% of the steady-state plasma level. With intrathecal administration, levels of cytarabine in the cerebrospinal fluid declined with a first-order half-life of about 2 hours. Because cerebrospinal fluid levels of deaminase are low, little conversion to ara-U was observed.

2.4.2.4 Adverse Reactions

2.4.2.4.1 Expected Reactions

Because cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis, and reduced reticulocytes can be expected as a result of administration of cytarabine. The severities of these reactions are dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Following 5-day constant infusions or acute injections of 50 to 600 mg/m2, white cell depression follows a biphasic course. Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7 to 9. This is followed by a brief rise which peaks around day 12. A second and deeper fall reaches nadir at days 15 to 24. Then there is a rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at day 5 with a peak depression occurring between days 12 to 15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

2.4.2.4.2 Infectious Complications

Infection - Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

2.4.2.4.3 The Cytarabine (Ara-C) Symdrome

A cytarabine syndrome has been described by Castleberry. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis, and malaise. It usually occurs 6 to 12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated, as well as continuation of therapy with cytarabine.

2.4.2.4.4 Most Frequent Adverse Reactions

anorexia	hepatic dysfunction
nausea	fever
vomiting	rash
diarrhea	thrombophlebitis
oral and anal inflammation or ulceration	bleeding (all sites)

Nausea and vomiting are most frequent following rapid intravenous injection.

2.4.3 Idarubicin

IDAMYCIN® (idarubicin hydrochloride for injection, USP) is a sterile, semi-synthetic antineoplastic anthracycline for intravenous use. Chemically, idarubicin hydrochloride is 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6 trideoxy-α-L-*lyxo*hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxyhydrochloride, (7S-*cis*).

2.4.3.1 Mechanism of Action

Idarubicin hydrochloride is a DNA-intercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II. The absence of a methoxy group at position 4 of the anthracycline structure gives the compound a high lipophilicity which results in an increased rate of cellular uptake compared with other anthracyclines.

2.4.3.2 Pharmacokinetics

Pharmacokinetic studies have been performed in adult leukemia patients with normal renal and hepatic function following intravenous administration of 10 to 12 mg/m2 of idarubicin daily for 3 to 4 days as a single agent or combined with cytarabine. The plasma concentrations of idarubicin are best described by a two or three compartment open model. The elimination rate of idarubicin from plasma is slow with an estimated mean terminal half-life of 22 hours (range, 4 to 48 hours) when used as a single agent and 20 hours (range, 7 to 38 hours) when used in combination with cytarabine. The elimination of the primary active metabolite, idarubicinol, is considerably slower than that of the parent drug with an estimated mean terminal half-life that exceeds 45 hours; hence, its plasma levels are sustained for a period greater than 8 days.

2.4.3.3 Adverse Reactions

Approximately 550 patients with AML have received IDAMYCIN (idarubicin

hydrochloride for injection, USP) in combination with cytarabine in controlled clinical trials worldwide. In addition, over 550 patients with acute leukemia have been treated in uncontrolled trials utilizing IDAMYCIN as a single agent or in combination. The table below lists the adverse experiences reported in U.S. Study 2 (see CLINICAL STUDIES) and is representative of the experiences in other studies. These

adverse experiences constitute all reported or observed experiences, including those not considered to be drug related. Patients undergoing induction therapy for AML are seriously ill due to their disease, are receiving multiple transfusions, and concomitant medications including potentially toxic antibiotics and antifungal agents. The contribution of the study drug to the adverse experience profile is difficult to establish.

The following information reflects experience based on U.S. controlled clinical trials.

2.4.3.3.1 Myelosuppression

Severe myelosuppression is the major toxicity associated with IDAMYCIN therapy, but this effect of the drug is required in order to eradicate the leukemic clone. During the period of myelosuppression, patients are at risk of developing infection and bleeding which may be life-threatening or fatal.

2.4.3.3.2 Gastrointestinal

Nausea and/or vomiting, mucositis, abdominal pain and diarrhea were reported frequently, but were severe (equivalent to WHO Grade 4) in less than 5% of patients. Severe enterocolitis with perforation has been reported rarely. The risk of perforation may be increased by instrumental intervention. The possibility of perforation should be considered in patients who develop severe abdominal pain and appropriate steps for diagnosis and management should be taken.

2.4.3.3.3 Dermatologic

Alopecia was reported frequently and dermatologic reactions including generalized rash, urticaria and a bullous erythrodermatous rash of the palms and soles have occurred. The dermatologic reactions were usually attributed to concomitant antibiotic therapy. Local reactions including hives at the injection site have been reported. Recall of skin reaction due to prior radiotherapy has occurred with IDAMYCIN administration.

2.4.3.3.4 Hepatic and Renal

Changes in hepatic and renal function tests have been observed. These changes were usually transient and occurred in the setting of sepsis and while patients were receiving potentially hepatotoxic and nephrotoxic antibiotics and antifungal agents. Severe changes in renal function (equivalent to WHO Grade 4) occurred in no more than 1% of patients, while severe changes in hepatic function (equivalent to WHO Grade 4) occurred in less than 5% of patients.

2.4.3.3.5 Cardiac

Congestive heart failure (frequently attributed to fluid overload), serious arrhythmias including atrial fibrillation, chest pain, myocardial infarction and asymptomatic declines in LVEF have been reported in patients undergoing induction therapy for AML. Myocardial insufficiency and arrhythmias were usually reversible and occurred in the setting of sepsis, anemia and aggressive intravenous fluid administration. The events were reported more frequently in patients over age 60 years and in those with pre-existing cardiac disease.

2.4.3.3.6 Pregnancy Category D

Idarubicin was embryotoxic and teratogenic in the rat at a dose of 1.2 mg/m2/day or one tenth the human dose, which was nontoxic to dams. Idarubicin was embryotoxic but not teratogenic in the rabbit even at a dose of 2.4 mg/m2/day or two tenths the human dose, which was toxic to dams. There is no conclusive information about idarubicin adversely affecting human fertility or causing teratogenesis. There has been one report of a fetal fatality after maternal exposure to idarubicin during the second trimester. There are no adequate and well-controlled studies in pregnant women. If IDAMYCIN is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid pregnancy.

3.0 Patient Eligibility

3.1 Inclusion Criteria

- Patients diagnosed with AML meeting one of following criteria:
  - Newly diagnosed, age 60 and older
  - High risk cytogenetics and molecular abnormalities (NCCN criteria)
  - Relapsed or refractory to prior chemotherapy
  - Secondary AML

- Any prior chemo therapy must have been completed ≥2 weeks prior to day 1 of study treatment and the participant must have recovered to eligibility levels from prior toxicity.
  - Only one prior regimen is allowed for Relapsed AML patients
    Note one prior regimen is defined as follows:
    - Induction chemotherapy followed by consolidation is considered one regimen
    - Induction chemotherapy followed by re-induction in case of persistent disease followed by consolidation is considered one regimen
  - Hydroxyurea is allowed prior to day 1 of study treatment to keep WBC below 20 K.

- Age ≥18 years.
- Karnofsky performance status ≥60%.
- Patients must have normal organ function as defined below:
  - Total bilirubin <1.5 X institutional upper limit of normal
  - AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
  - Creatinine <1.5 X institutional upper limit of normal
  - OR Creatinine clearance ≥60 mL/min for patients with creatinine levels above 1.5 X institutional upper limit of normal,
  - EF ≥45%.

- Ability to understand and sign a written informed consent document.
- Patients should not be receiving any other investigational agents.

3.2 Exclusion Criteria

- Patients with clinically significant illnesses which would compromise participation in the study, including, but not limited to: active or uncontrolled infection, immune deficiencies or confirmed diagnosis of HIV infection, active Hepatitis B, active Hepatitis C, or uncontrolled diabetes, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled cardiac arrhythmia; or psychiatric illness/social situations that would limit compliance with study requirements.
- Patients with additional (other than AML) currently active primary malignancy other than curatively treated CIS of the cervix, or basal or squamous cell carcinoma of the skin. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy and disease free from prior malignancies for >2 years
- Patients with active central nervous system (CNS) disease.
- Patients with Chronic Myelogenous Leukemia (CML) in Myeloid blasts crisis.

- Active infections, including opportunistic infections

Women of childbearing potential (WOCBP) who have a positive serum pregnancy test within 14 days of the first administration of oral Dasatinib.

3.2 Inclusion of Women and Minorities

The study is open anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 43 subjects (Phase I trial expected number: 9; Phase II trial expected number: 40 (6 patients brought forward from Phase I trial + 34 additional), a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4.0 Screening and Registration Procedures

4.1 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies or procedures were done before informed consent was obtained. Reference is made to Section 10.0 – Study Calendar.

4.2 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

At the time of registration, the original signed and dated patient's Informed Consent with the Experimental Subject's Bill of Rights (for the medical record) and three copies (for the patient, the research record, and the Coordinating Center) must be available. All Institutional, NCI, Federal, and State of California regulations concerning the Informed Consent form will be fulfilled.

4.3 Registration Requirements/Process

- Pre-study laboratory tests, bone marrow biopsy, x-ray, ECHO and other required tests must be completed prior to registration, within the time frame specified in the protocol. Patients must sign an informed consent prior to the study screening.
- A patient failing to meet all protocol requirements may not be registered.
- Once all the pre-study requirements have been fulfilled, and informed consent has been obtained, and the eligibility checklist has been completed. The study coordinator can register the eligible patient into MIDAS.
- Patients must begin protocol therapy within 1 week of registration.

4.4 Randomization and/or Dose Level Assignment

Patients will be assigned to the dose level that is currently open after their eligibility has been confirmed.

5.0 Treatment Program

5.1 Treatment Overview

This combination induction chemotherapy will be used for in-patients only.

5.1.1 Schedule

For a tabular view of the treatment, monitoring, and follow-up schedule, see study calendar in Section 10.

5.2 Planned Duration of Therapy

Induction therapy: Patients will receive cytarabine 200mg/m^2 /day IV continuously over 168 hours on days 1-7, Idarubicin 12mg/m^2 / day IV slow push on days 1-3, and oral Dasatinib (depending on the dose level the patient is assigned to) once daily on days 1 to 7. Patients are in CR (Complete Remission) on day 30 BM will undergo consolidation therapy, and patients with non-responsive disease (bone marrow cellularity ≥ 20 % and leukemia blasts ≥ 5%) will receive a second course of induction therapy. The re-induction therapy will be the same as the first induction therapy and will start within one week after the day 30 bone marrow.

Dose Level	Cytarabine*	Idarubicin#	Dasatinib^
-1	200mg/m^2	12mg/m^2	70mg/day
1	200mg/m^2	12mg/m^2	100mg/day
2	200mg/m^2	12mg/m^2	140mg/day

*: IV QD, days 1-7

#: IV QD, days 1-3

^: PO QD, days 1-7

Dasatinib dose should be given once daily prior to idarubicin dosing to avoid vomiting caused by chemotherapy. Anti-emetics will be used according to standard practices.

Dasatinib can start and does not need to be held for asymptotic, non-clinical significant grade 3 or 4 non-hematologic laboratory electrolyte abnormalities. Continuation of combination treatment is permitted during the electrolyte supplementation.

5.3 Criteria for Removal from Treatment

Reasons that a patient may discontinue treatment:

- Subject's condition no longer requires study treatment
- Intolerable Adverse event(s)
- Protocol violation
- Subject withdrew consent
- Administrative problems
- New cancer therapy
- Death

5.4 Subject Follow-Up

After completion of study therapy, patients will be followed for AEs up to 30 days of last dose of study drugs. Disease status and Survival information will be obtained for every 2 months up to 2 years after the study completion.

5.5 Supportive Care, Other Concomitant Therapy, Prohibited Medications

5.5.1 Supportive Care

All patients will be provided with the best available supportive care.

5.5.2 Other Concomitant Therapy

5.5.2.1 Nausea/Vomiting

Nausea and vomiting will be considered refractory if it does not resolve to ≤ Grade 1 with treatment with a combination of at least 2 antiemetics.

5.5.2.2 Diarrhea

Subjects will not be given anti-diarrhea medication prophylactically. However, if a subject develops diarrhea felt to be related to study medication, anti-diarrhea medication may be instituted for treatment of this side effect, such as diphenoxylate with atropine or loperamide. If diarrhea without blood develops, and does not have an identifiable cause other than agent administration, loperamide 4 mg po after the first unformed stool with 2 mg po with every subsequent unformed stool may be administered. This regimen can be repeated for each diarrheal episode. The occurrence of liquid stools after a 24 hour diarrhea-free period will be considered a new episode. If subject develops blood or mucus in the stool, dehydration or hemodynamic instability, loperamide will be discontinued and the subject will be treated with IV fluids and antibiotics as clinically indicated. Other potentially helpful treatments may also be administered, such as somatostatin analogues, probanthine, etc.

5.5.2.3 Electrolyte Abnormalities

If hypokalemia, hypophosphatemia, or hypomagnesemia occur, the patient may receive oral or IV supplementation to correct the abnormality. If hyponatremia occurs, the patient may receive 0.9% Sodium Chloride intravenously to correct the abnormality.

5.5.2.4 Neutropenia

If clinically indicated, granulocyte growth factors can be administered per physician discretion. Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode.

In the presence of residual leukemia, neutropenia (including febrile neutropenia) is presumed to be due to the underlying disease. Study medications should be re-initiated as soon as the febrile neutropenia is evaluated and appropriate antibiotic therapy is started. Resolved episode of Febrile neutropenia is not in itself a reason to delay treatment.

5.5.2.5 Anemia

Symptomatic anemia should be treated with red blood cell infusion and is recommended if the hemoglobin falls below 8.5G/dL. Use of red blood cell growth factors is allowed per physician discretion.

5.5.2.6 Thrombocytopenia

Thrombocytopenia will be treated as per standard practice. In the absence of bleeding, fever, or a necessary invasive procedure, platelet transfusions should be given for a platelet count ≤10K/uL. In case patient is febrile or has other evidence of infection, platelet transfusions should be given for a platelet count ≤20K/uL. If invasive procedure(s) are planned or the subject develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count above 50K/uL.

5.5.2.7 Antiobiotic Prophylaxis

Patients may receive prophylaxis directed against gram-negative gastrointestinal infections, fungal infection, and/or herpes simplex virus, according to the treating physician's discretion or individual institutional practices.

5.5.2.8 Antiemetics

Antiemetics will be used according to standard practices.

5.5.2.9 Prevention of Tumor Lysis Complications

To prevent occurrence and complications of tumor-lysis-induced hyperuricemia, all patients without known allergy will receive allopurinol 300 mg qd orally prior to beginningof therapy and continuing through the period of maximal tumor lysis (As needed and up to the treating physician's description. Suggested to the time point that WBC≤1,000/uL). For individuals at risk for tumor lysis-induced hyperphosphatemia (e.g. AML subtype M5), it is suggested that amphogel 30 cc q 4 - 6 hours orally can be instituted on admission and continued through the period of maximal tumor lysis (As needed and up to the treating physician's description. Suggested to the time point that WBC≤1,000/uL).

5.5.3 Prohibited Medications

Dasatinib is a CYP3A4 substrate. Systemic administration of a potent CYP3A4 inhibitor is prohibited during the Dasatinib treatment period. If cannot be avoided, alternative agents with less enzyme inhibition potential should be considered, close monitoring for toxicity and a Dasatinib dose reduction should be considered.

Drugs that are CYP3A4 Inducers may decrease Dasatinib plasma concentrations. Systemic administration of a potent CYP3A4 inducer should be avoided during the Dasatinib treatment period. If Dsatinib must be administered with a CYP3A4 inducer, alternative agents with less enzyme induction potential should be considered and used with caution.

Please see Appendix A for the list of CYP3A4 inhibitors and inducers

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. Simultaneous administration of Dasatinib with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of Dasatinib.

Long-term suppression of gastric acid secretion by H2 antagonists or proton pump inhibitors (eg, famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of H2 antagonists or proton pump inhibitors with Dasatinib is not recommended. The use of antacids (at least 2 hours prior to or 2 hours after the dose of Dasatinib) should be considered in place of H2 antagonists or proton pump inhibitors in patients receiving Dasatinib therapy.

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular re-polarization (QT interval). Administer Dasatinib with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Correct hypokalemia or hypomagnesemia prior to Dasatinib administration.

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 28 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- Hydroxyurea is allowed prior to day 1 of study treatment to keep WBC below 20 K.
- Leukopheresis is allowed prior to day 1 of study treatment to keep WBC below 100K/ul
- No other investigational therapy should be given to patients
- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.

5.6 Additional Laboratory Studies

Blood samples will be obtained pre-treatment and after 1 and 3 days of treatment to assess for P-SRC, P-AKT, P-MAPK and P53 expression in leukemia cells using flow cytometry and for expression of p53 target genes (CDKN1A, Necdin, Bax, Puma, Noxa, DR5) by Q-PCR. 40ml peripheral blood sample will be collected into green top tubes (Sodium Heparin) at each time point and send to Dr. Ravi Bhatia laboratory for correlative studies.

BM cells will be obtained at recovery and residual leukemia stem/progenitor cells will be evaluated by isolating CD34+ cells (and where possible CD34+CD38- cells) will be isolated and analysis of selected populations for mutations identified pre-treatment by FISH, PCR or sequencing analysis as appropriate. 20ml bone marrow aspirate sample will be collected into green top tubes (Sodium Heparin) at baseline, and each of disease assessment time point and send to Dr. Ravi Bhatia laboratory for correlative studies.

5.7 Definition of Dose-Limiting Toxicity (DLT)

Dose limiting toxicity is defined as any of the toxicities listed below that occur from the first dose of dasatinib through the DLT observation period discussed below. The list of hematologic and non-hematologic toxicities was constructed after reviewing published toxicity data (including type, frequency and duration) for the Cytarabine/Idarubicin drug combination/regimen and for Dasatinib given as a single agent. Patients must not have persistent leukemia after induction to be considered evaluable for DLTs associated with hematologic toxicity. Patients who have persistent leukemia are still potentially evaluable patients for safety and cohort advancement based on the non-hematologic DLT criteria below.

Hematologic Toxicities:
For patients without persistent leukemia following induction:
Grade 4 hematological toxicity persisting >42 days following the last dose of dasatinib (i.e., Day 49) not attributable to persistent leukemia with exclusion of chronic cytopenia attributed to preexistent condition such as MDS, MPN, and MF.

Non-Hematologic Toxicities:
For all patients, within the first 28 days:
Any grade 3 or higher non-hematologic toxicity, excluding:

- Anorexia, fatigue, uric acid, fever with or without neutropenia, or bleeding during a period of Grade 4 thrombocytopenia
- Diarrhea, nausea, abdominal bloating, vomiting or mucositis that resolves to ≤ Grade 1 or to baseline within 7 days of onset with optimal medical management
- Elevated AST, ALT, alkaline phosphatase, or bilirubin that returns to ≤ Grade 2 or to baseline within 14 days of onset
- Rash or elevated amylase or lipase that returns to ≤ Grade 2 or to baseline within 7 days of onset
- Infections or complications of infections due to neutropenia
- Electrolyte disturbance that can be corrected wit supplementation within 10 days.

Any grade 5 toxicity, not due to disease, will be considered a DLT.

Patients must complete all 7 days of dasatinib or experience a dose limiting toxicity (DLT) to be evaluable for toxicity.

6.0 Dose Delays/Modifications for Adverse Events

6.1 Dose modification for Dasatinib

No dose adjustment needed for hematological toxicity

For Grade 3-4 non-hematological toxicity, Dasatinib dose must be held until Grade < or = 1, then resume to next lower dose level.

If the patient is at the reduced dose level -1, the same Grade 3-4 non-hematological toxicity recurs, patient needs to be discontinued from the study.

Dasatinib does not need to be held for the following grade 3 or 4 toxicities:

- Asymptomatic, non-clinically significant Grade 3 or 4 non-hematologic laboratory electrolyte abnormalities
- Grade 3 or 4 non-hematological toxicities that are unrelated to study drug , had a prior history of medical conditions before the initiation the study treatment,
- Grade 3 nausea, vomiting and diarrhea.

6.2 Dose Modification for Idarubicin

Idarubicin will be given at 12mg/m^2 from days 1-3

- Total bilirubin < 2.5mg/dL no dose reduction
- Total bilirubin ≥2.5mg/dL but < 5mg/dL 50% dose reduction
- Total bilirubin ≥5mg/dL do not administer

6.3 Dose Modification for Cytarabine

Cytarabine will be given at 200mg/m^2 days 1-7. Dose adjustment is not allowed while on the study.

7.0 Data and Safety Monitoring

7.1 Definition of Risk Level

This is a Risk Level 3 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a Phase I/II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

7.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

This study will utilize the Phase I tracking log to monitor data and safety for dose escalation, recording doses administered, and resultant adverse events. The tracking log will contain dose levels administered, DLT-defining adverse events, and documentation that the data from a dose level is complete before dose escalation. Those data and safety elements will be reported to the COH DSMC as applicable within the PMT report, which will be submitted quarterly or semi-annually from the anniversary date of activation, as noted in Table 1 below. Protocol specific data collection will

include the following items: **Patient ID, Dose level, Treatment Courses, and AE summary.**

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

7.3 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death

- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary Malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

7.4 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

8.0 Study Agent Information and Risks

8.1 Dasatinib

Please see section 2.4.1

8.2 Cytarabine

Please see section 2.4.2

8.3 Idarubicin

Please see 2.4.3

9.0 Correlative/Special Studies

Blood samples will be obtained pre-treatment and after 1 and 3 days of treatment to assess for P-SRC, P-AKT, P-MAPK and P53 expression in leukemia cells using flow cytometry and for expression of p53 target genes (CDKN1A, Necdin, Bax, Puma, Noxa, DR5) by Q-PCR. 40ml peripheral blood sample will be collected into green top tubes (Sodium Heparin) at each time point and send to Dr. Ravi Bhatia laboratory for correlative studies.

BM cells will be obtained at recovery and residual leukemia stem/progenitor cells will be evaluated by isolating CD34+ cells (and where possible CD34+CD38- cells) will be isolated and analysis of selected populations for mutations identified pre-treatment by FISH, PCR or sequencing analysis as appropriate. 20ml bone marrow aspirate sample will be collected into green top tubes (Sodium Heparin) at baseline, and each of disease assessment time point and send to Dr. Ravi Bhatia laboratory for correlative studie

10.0 Study Calendar

Study Visit Schedule *

	Screening [1]	Study Treatment Phase							Post Study Treatment Phase [10]	End of Study [11]	Follow Up [12]
Day of Cycle		**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8 to D28**		
Informed consent	X[2]										
Inclusion/exclusion criteria	X										
Treatment with Cytarabine[3]		X	X	X	X	X	X	X			
Treatment with Idarubicin[3]		X	X	X							
Treatment with Dasatinib		X	X	X	X	X	X	X			
Height, Weight, and BSA [4]	X										
Vital Signs	X	X	X	X	X	X	X	X	Weekly	X	
Medical History/Physical Examination/ Karnofsky Performance Status[15]	X	X	X	X	X	X	X	X	Weekly	X	X
12 Lead ECG	X										
Chest X-Ray	X										
Hematology[14]	X	X	X	X	X	X	X	X	2X /Weekly	X	X
Biochemistry[13]	X	X	X	X	X	X	X	X	2X /Weekly	X	
Urinalysis	X										
Serum Pregnancy Test [5]	X										
Echocardiogram[6]	X										
AML Genetic /Molecular Assessments[7]	X										
Bone marrow aspirate/ Biopsy[8]	X								D14 and D30(+/- 3 days)	X	X
Peripheral Blood Sample for Correlative Studies[9]	X	X		X							
Adverse events		X	X	X	X	X	X	X	X	X	
Disease Recurrence and Survival Status											X

* Please note that for all study assessments, more frequent examinations may be performed at physican's discretion, if medically indicated.

1.Screening evaluations must be performed ≤ 14 days prior to D1, administration of Dasatinib, Any screening tests that are performed within 3 days of first dose of Dasatinib do not need have to be repeated on the date of first dose of Dasatinib. Tests done within the appropriate window but prior to informed consent will be accepted if done as standard of care.

2. Informed consent must be obtained ≤ 14 days prior to day 1 of study treatment, administration of Dasatinib

3. 7+3 (Cytarabine+Idarubicin) treatment order will be used City of Hope standard research order.

4. Height, Weight and BSA should be performed as per City of Hope Chemotherapy SOP.

5. Serum Pregnancy test should be performed at the screening for women of childbearing potential.

6. May be used for screening if done within 30 days of study treatment as part of standard of care.

7. Molecular assessments for FLT3, NPM1 and c-Kit should be performed at screening. These tests do not have to be repeated and the result can be used for baseline if done within 30 days of first dose of Dasatinib.

8. Bone marrow aspirate/biopsy should be performed at the screening, Day 14(+/-3 days), then again at Day 30(+/-3days) or at the counts recovery. Cytogenetic and FISH analysis, molecular assessments of chromosomal breakpoints or other genetic abnormalities should be performed based on disease characteristics, institutional practice standards. The bone marrow may be performed ≤ 30 days prior to the first administration of Dasatinib. At each time point, additional 20ml bone marrow aspirate sample are required to be sent to Dr. Bhatia's laboratory for correlative studies.

9. 40ml peripheral blood sample for correlative studies need to be sent to Dr. Bhatia's laboratory at screening and on Day 1 and Day 3 after first dose of Dasatinib.

10. Assessments should be performed weekly at least, defined as every 7 days from Day7 (+/-3 days).

11. EOT assessments should be performed prior to another anti-cancer treatment, unless patient has been withdrawn from study.

12. Patients who achieve a CR and patients who proceed to HSCT (regardless of remission status) should be followed every 2 months (+/- 1 week) thereafter up to 2 years of study treatment completion.

13. Biochemistry tests for Sodium, Potassium, Chloride, Carbon Dioxide, Creatinine, Urea Nitrogen, Calcium, Glucose, Albumin, Bilirubin Total, Phosphatase, Alkaline, Protein Total, ALT/SGPT and AST/SGOT), Magnesium, Uric Acid and other tests that are necessary per patient's medical condition should be performed on the screening, daily for days 1-7. Starting on day 8, biochemistry tests for Sodium, Potassium, Chloride, Carbon Dioxide, Creatinine, Urea Nitrogen, Calcium, Glucose, Bilirubin Total, Uric Acid, Magnesium and other tests that are necessary per patient's medical condition should be performed.

14. Hematology CBC, Platelets and Differential should be performed at screening and on Day 1. CBC and Platelets should be performed daily to counts recover. Differential should be performed every other day until count recover.

15. Karnofsky Performance Status (KPS) is required on the study screening only.

11.0 Endpoint Evaluation Criteria/Measurement of Effect

Toxicities/Adverse Events:

From day 1 to day 30, the highest grade of non-hematologic toxicities will be collected, included start and stop dates.

For hematologic adverse events, from day 1 to day 30, collect every grade change (including start and stop dates) for hematologic toxicities grade 3 and above.

Long-Term AE Monitoring/Data Collection: After the completion of treatment (either one or two cycles of therapy), use the late AE form and report only the worst grade of each AE and ONLY report AE's that are possibly, probably, or definitely related to Dasatinib.

Note: If the patient goes on to receive a second cycle of Dasatinib, report the worst grade of every AE until 30 days post the start date of cycle two.

Overall Survival (OS): Patients are considered a failure for this endpoint if they die, regardless of cause. Endpoint measured as time from start of study therapy until death, or last contact, whichever comes first. Patients will be followed for up 2 years after completion of study treatment.

Event Free Survival (EFS): Patients are considered a failure for this endpoint if they die or if they relapse/progress or receive other anti-leukemia therapy. Endpoint measured as time from start of study therapy until death, relapse/progression, receipt of anti-leukemia therapy, or last contact, whichever comes first. Patients will be followed for up 2 years after completion of study treatment.

Complete remission (CR): Bone marrow blasts ≤5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1.0 x 10^9/L (1000/μL); platelet count ≥100 x 10^9/L (100,000/μL); independence of red cell transfusions

CR with incomplete recovery (CRi): All CR criteria except for residual neutropenia (<1.0 x 10^9/L (1000/μL)) or thrombocytopenia (<100 x 10^9/L (100,000/μL))

Morphologic leukemia-free state: Bone marrow blasts ≤5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required

Partial remission (PR): Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent

Cytogenetic CR (CRc): Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow

Relapse: Bone marrow blasts ≥5 percent; or reappearance of blasts in the blood; or development of extramedullary disease

Resistant disease (RD): Failure to achieve CR or CRi (general practice; phase II/III trials), or failure to achieve CR, CRi or PR (phase I trials); only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination

Death in aplasia: Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia

Death from indeterminate cause: Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available

12.0 Data Reporting/Protocol Deviations

12.1 Data Reporting

12.1.1 Confidentiality and Storage of Records

The original data collection forms will be submitted into Medidata Rave Electronic Data Collection (EDC). Data will be stored in encrypted, password protected, secure computers that meet all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

12.1.2 Subject Consent Form

At the time of registration, the original signed and dated Informed Consent form, HIPAA research authorization form, and the California Experimental Subject's Bill of Rights (for the medical record) and three copies (for the subject, the research record, and the Coordinating Center) must be available. All Institutional, NCI, Federal, and State of California requirements will be fulfilled.

12.1.3 Data Collection Forms and Submission Schedule

All data will be collected and submitted using electronic case report forms in Medidata Rave EDC. Data will be submitted per data collection and submission schedule in Medidata Rave EDC.

12.2 Protocol Deviations

12.2.1 Deviation Policy

This protocol will be conducted in accordance with COH's "Clinical Research Protocol Deviation Policy" located at http://www.coh.org/dsmc/Documents/Institutional%20Deviation%20Policy.pdf.

Deviations from the written protocol that could increase patient risk or alter protocol integrity require prior IRB approval of a single subject exception (SSE) request. In addition, if contractually obligated, the sponsor must also approve the deviation. IRB pre-approved SSE protocol modifications are considered an amendment to the protocol and not a deviation. The submission of a deviation report is not required.

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such deviation does not threaten patient safety or protocol scientific integrity. Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety. These instances are considered to be deviations from the protocol. A deviation report will be submitted to the DSMC/IRB within five days.

12.2.2 Reporting of Deviations

All deviations will be reported to the COH DSMC within five days. The DSMC will forward to report to the IRB following review.

12.2.3 Resolving Disputes

The COH Investigational Drug Service (IDS) cannot release a research agent that would cause a protocol deviation without approval by the PI. Whenever the protocol is ambiguous on a key point, the IDS should rely on the PI to clarify the issue.

In situations where there is misperception or dispute regarding a protocol deviation among the persons involved in implementing the protocol, it is the responsibility of the PI to resolve the dispute and the PI may consult with the DSMC chair (or designee) to arrive at resolution.

13.0 Statistical Considerations

13.1 Study Design

This is an open label Phase I/II study.

13.1.1 Phase I

The study design is based on a standard 3 + 3 dose escalation design.

Dose level 1 will be the first dose level tested. Initially three subjects will be treated, if 0/3 experiences a dose limiting toxicity (DLT), enter 3 subjects at dose level 2. If 1/3 of the first 3 subjects has DLT, enter 3 more subjects at dose level 1. If none of these 3 additional subjects has DLT, then proceed to dose level 2. If one or more of these 3 additional subjects has DLT, then a dose reduction (to dose level -1) will be applied.

Among the patients treated at dose level 2, if 0/3 or 1/3 of the first 3 subjects experiences DLT, enter 3 more subjects at dose level 2. If $\leq$ 1/6 subjects on dose level 2 have DLT, dose level 2 will be declared the phase II dose (P2D). If $\geq$ 2/6 subjects have DLT at dose level 2, dose level 1 will be declared the P2D, assuming at least six patients have been treated at dose level 1 and $\leq$ 1/6 subjects has DLT.

Assuming a dose reduction is necessary, among the patients treated at dose level -1, if 0/3 or 1/3 on the first 3 subjects has DLT, enter 3 more subjects at dose level -1. If $\leq$ 1/6 subjects treated on dose level -1 has DLT, dose level -1 will be declared the P2D. If $\geq$ 2/6 subjects have DLT on dose level -1, then the study will be terminated.

Dose Level	Cytarabine*	Idarubicin#	Dasatinib^
-1	200mg/m^2	12mg/m^2	70mg/day
1	200mg/m^2	12mg/m^2	100mg/day
2	200mg/m^2	12mg/m^2	140mg/day

*: IV QD, days 1-7

#: IV QD, days 1-3

^: PO QD, days 1-7

The phase I study is expected to enroll 9-18 evaluable patients. Toxicities will be monitored, graded, and recorded according to the NCI-Common Terminology Criteria for Adverse Events version 4.0. See section 5.7 for dose limiting toxicity (DLT) definition. Patients must complete all 7 days of dasatinib or experience a DLT to be evaluable for toxicity. Phase I patients treated at the P2D will count toward the phase II trial accrual goal.

Observed toxicities will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count) severity (by NCI CTCAE v4.0), date of onset, duration, reversibility, and attribution. Tables will be created to summarize these toxicities and side effects. Baseline information (e.g. cytogenetic risk) and demographic information will be presented for all study patients. While not the primary objective of the phase I study, a preliminary estimate of complete remission rate (CR) and remission duration will be reported. Survival probabilities, overall survival (OS) and event-free (EFS) will be estimated.

13.1.2 Phase II

This is a single center phase II trial to determine the anti-tumor activity of Dasatinib given in combination with cytarabine and idarubicin as assessed by complete remission (CR) rate, the primary endpoint; secondary endpoints are remission duration, survival (overall and event-free) and toxicities. Patients with high-risk AML will be eligible. This study will implement a single arm SWOG Phase II two-stage design to study the activity of Dasatinib plus cytarabine and idarubicin (Green SJ, Benedetti J, and Crowely J, 1997).

As noted in the background section, the CR rates for these high risk patient subgroups vary from roughly 25 to 50%. We will power this study to be able to detect a 20% increase in the CR rate with approximately 80% power, assuming a type I error of 5%. After 20 patients (up to 24 patients can be accrued to allow for over accrual while previous patients are under evaluation), we will estimate the historical rate for the patient population accrued based on the table below (a weighted average of the historically observed CR rate, weighted by percent of accrual in each group). If the promising rate (20% higher than the weighted estimate of the historical CR rate for the patients accrued) can be ruled out with a 0.02 false negative rate, the study will stop accrual and be declared unpromising. Otherwise, the study will accrue to a total of 40 patients. A new historical (weighted) estimated weight of the CR rate will be calculated based on the number of patients accrued to each group. If that historical CR rate can be ruled out with a 0.05 false positive rate, the study will be declared successful.

For each of the groups below, as examples, we present the operating characteristics based on the above rules. The actual operating characteristics will be determined by the actual accrual patterns.

Observed/expected response rates by high risk group are as follows:

High Risk Group:	**Observed CR Rate:**	**Expected Improvement in CR Rate (20%):**	**-Power/Alpha/Total N -Stage 1/Stage 2 Enrollment -Stop if ≤ n responses Stage 1/ Promising if ≥ n responses Stage 2**
Newly diagnosed patients, aged 60 and older	48%, van der Holt (2005)	From 50% to 70%	.80/.05/40 20/20 10/26
High risk cytogenetics <60y	50%, Mrozek (2012)	From 50% to 70%	.80/.05/40 20/20

			10/26
High risk cytogenetics ≥60y	39%, Mrozek (2012)	From 40% to 60%	.79/.05/40 20/20 6/22
Relapsed/refractory	30%, Becker (2013)	From 30% to 50%	.78/.05/40 20/20 5/18
Secondary AML	24%, Leith (1997)	From 25% to 45%	.79/.05/40 20/20 4/16

Accrual is expected to be complete within 18-24 months.

Remission rates will be calculated as the percent of evaluable patients that have a confirmed CR, and exact 95% confidence intervals will be calculated for these estimates. Time to confirmed complete remission, duration of remission, and survival will be estimated using the product-limit method of Kaplan and Meier. Toxicity will be monitored on an ongoing basis. If the percentage of unacceptable toxicities (using the DLT definition) exceeds 25% with 6 or more patients accrued, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee will be mandated. Patient accrual will not resume until approved by the Data Safety Monitoring Committee to do so.

Evaluation of Response

All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. All patients who meet the eligibility criteria (with the exception of those who received no study medication) will be included in the main analysis of the response rates. An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions will be based on all eligible patients who receive any of the study drug. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported.

13.2 Sample Size Accrual Rate

Phase I, Expected: 9, maximum 18

Phase II, Expected: 14-34 (20-40 including the 6 patients brought forward from Phase I trial)

Annually approximately 50 AML patients, patients who would meet the protocol eligibility criteria, are seen at City of Hope. Based on these numbers, this study expects to accrue 20 patients per year. The study is expected to complete the enrollment phase of the study in 24 months, with an additional 24 months of follow-up after the completion of study treatment for each patient. With the last patient enrolled at approximately month 24, the planned trial activity is scheduled to conclude in month 48.

13.3 Statistical Analysis Plan

See Section 13.1

13.4 Overview and Stopping Rules for Excessive Toxicity

The following table will be consulted as relevant toxicities are encountered following the phase I study. The toxicity/early stopping rule for safety will be assessed for each patient at day 28 post start of dasatinib

treatment. The expected rate of unacceptable toxicity should not be ≥33%. The expected rate of regimen-related death should not be ≥25% (see table below for detailed early stopping rules). Patients with ongoing toxicity (beyond day 28) will be followed until resolution or stability. If more than the specified number of patients has unacceptable toxicity (based on DLT definition) or regimen-related death, we will lower the dose of dasatinib to 70 mg/day. If the dose was already reduced during the phase I study, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee will be mandated. Patient accrual will not resume until approved by the Data Safety Monitoring Committee to do so. The acceptable rate of regimen-related death, defined as <25%, was determined after a review of the induction literature for acute myeloid leukemia, in elderly and high risk populations. In a randomized phase III study of three induction regimens, the treatment related mortality rate among patients who received idarubicin and cytarabine was 22% (Rowe, 2004). Based on this study and preliminary results from an ongoing phase II study of induction chemotherapy (daunorubicin/cytarabine) plus dasatinib (Marcucci, ASH 2013), the investigators believe that the addition of dasatinib to idarubicin/cytarabine should not significantly increase (by more than a few percentage points) the published rate of regimen-related death among patients treated with idarubicin and cytarabine (Rowe, 2004).

# of patients treated at phase II dose	**# of patients with unacceptable toxicity that would halt enrollment[1]**	**Cumulative probability of early stopping given a toxicity rate of:**		
		15%	**33%**	**45%**
6	2	0.22	0.64	0.84
12	4	0.24	0.73	0.92
18	6	0.25	0.78	0.95
24	8	0.25	0.81	0.97
30	10	0.25	0.83	0.98
36	12	0.25	0.84	0.99
[1]: For each unacceptable toxicity, halt enrollment and evaluate if the cumulative # of patients reaches or exceeds the specified limits.				

14.0 Human Subject Issues

14.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

14.2 Recruitment of Subjects

Patients with a diagnosis of de novo acute myeloid leukemia, secondary acute myeloid leukemia, and therapeutic related acute myeloid leukemia, either newly diagnosed or relapsed after treatment will be identified from the new patient services, outpatient clinics or inpatient service of City of Hope Medical Center by physicians in the Department of Hematology. Patients will be recruited for the study by the principal investigator, co-investigators or participating clinicians.

14.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line[SM] website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

14.4 Study location and Performance Sites

This study will be performed at COH.

14.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The records related to subject identity will be kept in a separate research file and will be stored in a locked file cabinet. A coded list will be used to link the subject's identity to the study data. Any information allowing identification of the subjects will not be included in any published report or any computerized records. Data will be presented as aggregate or group data. The principal investigator and co-investigators will be the only one having access to the collected data. The results will not be available to patients, their physicians, insurance carriers or employers.

14.6 Financial Obligations and Compensation

The investigational drug Dasatinib, will be provided free of charge by City of Hope. Should this drug become commercially available during the course of your treatment, the research participant and/or the insurance carrier may be asked to pay for the costs of the drug.

The standard of care drugs Cytarabine, Idarubicin, and induction chemo procedures provided will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. However, neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant, however, financial compensation will not be available.

The research participant will not be paid for taking part in this study.

14.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Research subjects will be afforded sufficient time to consider whether or not to participate in the research.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed

by eligibility testing. The research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

15.0 References

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society. 1999:32–41.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. Washington, DC; Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services, National Institutes of Health; 1992. US Department of Health and Human Services, Public Health Service Publication NIH 92-2621.
3. AMA Council on Scientific Affairs. Guidelines for Handling Parenteral Antineoplastics. JAMA. 1985;253:1590–1591.
4. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. 1987. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia. 1983; 1:426–428.
6. Jones RB, Frank R, Mass T. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA Cancer J Clin. 1983;33:258–263.
7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990; 47:1033–1049.
8. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines). Am J Health-Syst Pharm. 1996;53:1669–1685.
9. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402
10. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics, JAMA, March 15, 1985.
11. National Study Commission on Cytotoxic Exposure — Recommendations for Handling Cytotoxic Agents, Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Ave., Boston, Massachusetts 02115.
12. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Aust 1:426-428, 1983.
13. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A report from the Mount Sinai Medical Center, CA — A Cancer Journal for Clinicians Sept/Oct, 258-263, 1983.
14. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 47:1033-1049, 1990.
15. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), Am J Hosp Pharm, 53:1669-1685, 1996.
16. Rowe JM, Neuberg D, Friedenberg W, Bennett JM, Paietta E, Makary AZ, Liesveld JL, Abboud CN, Dewald G, Hayes FA, Tallman MS, Wiernik PH; Eastern Cooperative Oncology. A phase 3

study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. Blood 103(2):479-85, 2004.