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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1203**, "A Randomized Phase III Study of Standard Cytarabine plus Daunorubicin (7+3) Therapy or Idarubicin with High Dose Cytarabine (IA) versus IA with Vorinostat (IA+V) in Younger Patients with Previously Untreated Acute Myeloid Leukemia (AML)". Study Chairs: Drs. G. Garcia-Manero, J.M. Pagel, J.P. Radich and M. Fang.

REVISION #7

Study Chair: Guillermo Garcia-Manero, M.D.
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IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #7

Due to the outcome of the interim analysis conducted by the SWOG Data and Safety Monitoring Committee on May 1, 2015, **Arm 3 (Idarubicin +AraC +Vorinostat) will be permanently closed to accrual, effective immediately.** A minor study re-design is also being implemented to allow more precise estimates of the outcomes of the transplant objective and to clarify the treatment schedule for patients that opt to remain on Arm 3 with or without vorinostat.

IRB Review Requirements:

Institutions **must** update their local consent forms to include the changes to the Model Consent Form **at the time of distribution of this notice**.

Patients currently receiving Arm 3 protocol treatment and patients randomized to Arm 3 who signed a consent form prior to this notice must be informed of the closure of Arm 3 at their next scheduled visit. Please reference the Investigator Letter and Patient Letter distributed with the May 26, 2015 Memorandum.

SWOG considers that the closure of Arm 3 and associated Model Consent Form changes represent an **alteration** in risk/benefit ratio. Therefore, **for all sites utilizing a local IRB**, **accrual of all new patients (to all study arms) remains suspended** until this amendment is approved by your local Institutional Review Board (IRB) and proof of that IRB approval is received by the Coalition for National Cancer Cooperative Groups/CTSU. Submit proof of IRB approval to the following location:

Coalition for National Cancer Cooperative Groups
1818 Market Street
Suite 1100
Philadelphia, PA 19103
FAX: 215/569-0206
E-mail: CTSURegulatory@ctsu.coccg.org

The above-referenced protocol has been modified as follows:

1. The Version Date of the protocol and Model Consent Form have been updated.

2. Page 1, Title Page: Hongli Li, M.S. has replaced Shannon McDonough, M.S. as a Biostatistician on this study.

3. Pages 3-4, Table of Contents: Content has been inserted in Section 7.2 on Page 34 which caused a shift in the page numbers for Section 7.3 and all subsequent sections. The titles for Sections 9.5 and 9.6 have also been updated.

4. Page 6, Schema: The following note has been included under Arm 3 (IA +V): “Permanently closed to accrual, effective TBD”

5. Pages 33 and 34, Section 7.2c:

   - The following paragraph has been inserted at the beginning of the section: "Arm 3 was permanently closed to accrual **effective TBD**. **Effective TBD**, patients previously randomized to Arm 3 have the option to remain on Arm 3 as a medical intervention and must follow the applicable treatment schedule below."
   - Footnote (3) has been added to Arm 3- IA + Vorinostat, "Patients previously randomized to Arm 3 that opt to continue medical treatment with IA + Vorinostat must follow protocol and protocol data submission requirements."
   - "Arm 3-IA" treatment schedule has been added for induction and re-induction for patients previously randomized to Arm 3 wanting to remain on Arm 3 without vorinostat.

6. Page 36, Section 7.4c: "Arm 3-IA" treatment has been added for consolidation for patients previously randomized to Arm 3 wanting to remain on Arm 3 without vorinostat.

7. Pages 39-41, Section 8.2: For clarification, the phrase "during treatment" has been added after "For bilirubin > 5.0 mg/dL" in Sections 8.2c.1, 8.2c.2, 8.2d.1 and 8.2d.2. Similarly, the phrase "during treatment" has been added after "For bilirubin > 3.0 mg/dL" in Sections 8.2d.1 and 8.2d.2.

8. Pages 43-44, and 46-48: Section 9.0:

   - "X"s have been added for "History & Physical Exam" at Weeks 2-4 for both Induction and Re-Induction in Section 9.1. Similarly, "X"s have been added for "History & Physical Exam" in the Wk 2, Wk 3, and Wk 4 columns for Consolidation in Sections 9.2, 9.4, and 9.6.
   - Page 47: The title of the table has been revised to reflect the option for IA treatment alone for patients already registered to Arm 3. "IA + V" has been added to the title of the treatment line and a separate treatment line for "IA" therapy has been added. Footnote "√**"** has also been inserted to clarify that, " Arm 3 was permanently closed to accrual, **effective TBD**. Patients previously randomized to Arm 3 may opt to continue medical treatment with IA or IA + V, and if so, must follow protocol and protocol data submission requirements.". The same changes have also been made to Page 48, for Consolidation therapy for patients previously randomized to Arm 3.

9. Page 50, Section 11.1: The following text has been added to the end of the second paragraph of this section to allow for additional accrual to, and more precise estimates of the outcomes of, the transplant objective:

   In contrast to **S0106**, **S1203** allows patients with complete remission with incomplete blood count recovery (CRi) to register to consolidation (**S0106** required patients to be in complete remission [CR] to register for consolidation). Due to this difference, the accrual rate of high-risk patients in CR has been slower than expected based on **S0106** data. Rather than 13% of patients being eligible for the transplant objective (53/418), the observed rate has been approximately 9%. Given the slower than expected accrual to this objective and the desire to have more precise estimates of outcomes after transplant, accrual to this objective will be open for all patients registered to the trial.

The Model Consent Form has been modified as follows:

1. Page 3, "Why is the study being done?": This section has been revised to remove reference to three treatment combinations and comparison of those combinations, and to include additional information on the transplant objective of the study.

2. Page 5, Schema: The study schema has been updated to remove reference to Arm 3 (IA+Vorinostat) of the study.

3. Page 6, "Induction and Consolidation": The first sentence of this paragraph has been revised to refer to "2" instead of "3" types of induction/consolidation treatments, and the last sentence of this paragraph (which previously referred to Group 3 Induction and Consolidation) has been deleted in its entirety.

4. Page 8, The "Group 3 (often called Arm 3) – IA + Vorinostat" section has been removed in its entirety, and subsequent content/page numbers have been shifted.

5. Pages 11-12: The Group 3 (Vorinostat) risks have been removed in their entirety, and subsequent content/page numbers have been shifted.

6. Page 12: "Are there benefits to taking part in the study?": The second sentence of this paragraph has been removed, and the following text has been included at the end of the third sentence of this paragraph, "and any benefits of matching high-risk AML patients with unrelated stem cell transplant donors."

7. Page 13, "What are the costs of taking part in this study?": The second and third paragraphs of this section (which referred to provision of vorinostat) have been removed in their entirety.

8. Page 14: The website link for more information on clinical trials and insurance coverage at the end of the first sentence of the second paragraph has been updated.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

This study has been approved by the NCI's Central Institutional Review Board.

cc: PROTOCOL & INFORMATION OFFICE
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PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date December 15, 2012

SWOG

A RANDOMIZED PHASE III STUDY OF STANDARD CYTARABINE PLUS DAUNORUBICIN (7+3) THERAPY OR IDARUBICIN WITH HIGH DOSE CYTARABINE (IA) VERSUS IA WITH VORINOSTAT (NSC-701852) (IA + V) IN YOUNGER PATIENTS WITH PREVIOUSLY UNTREATED ACUTE MYELOID LEUKEMIA (AML)

NCT #0180233

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AGENTS:

IND Exempt Agents:
Cytosine Arabinoside (AraC, Cytarabine) (NSC-63878)
Daunorubicin Hydrochloride (Cerubidine) (NSC-82151)
Idarubicin (Idamycin®) (NSC-256439)

NCI Supplied Investigational Agents:
Vorinostat (Zolinza®, Suberoylanilide Hyroxamic Acid, SAHA) (NSC-701852) (IND-117406)

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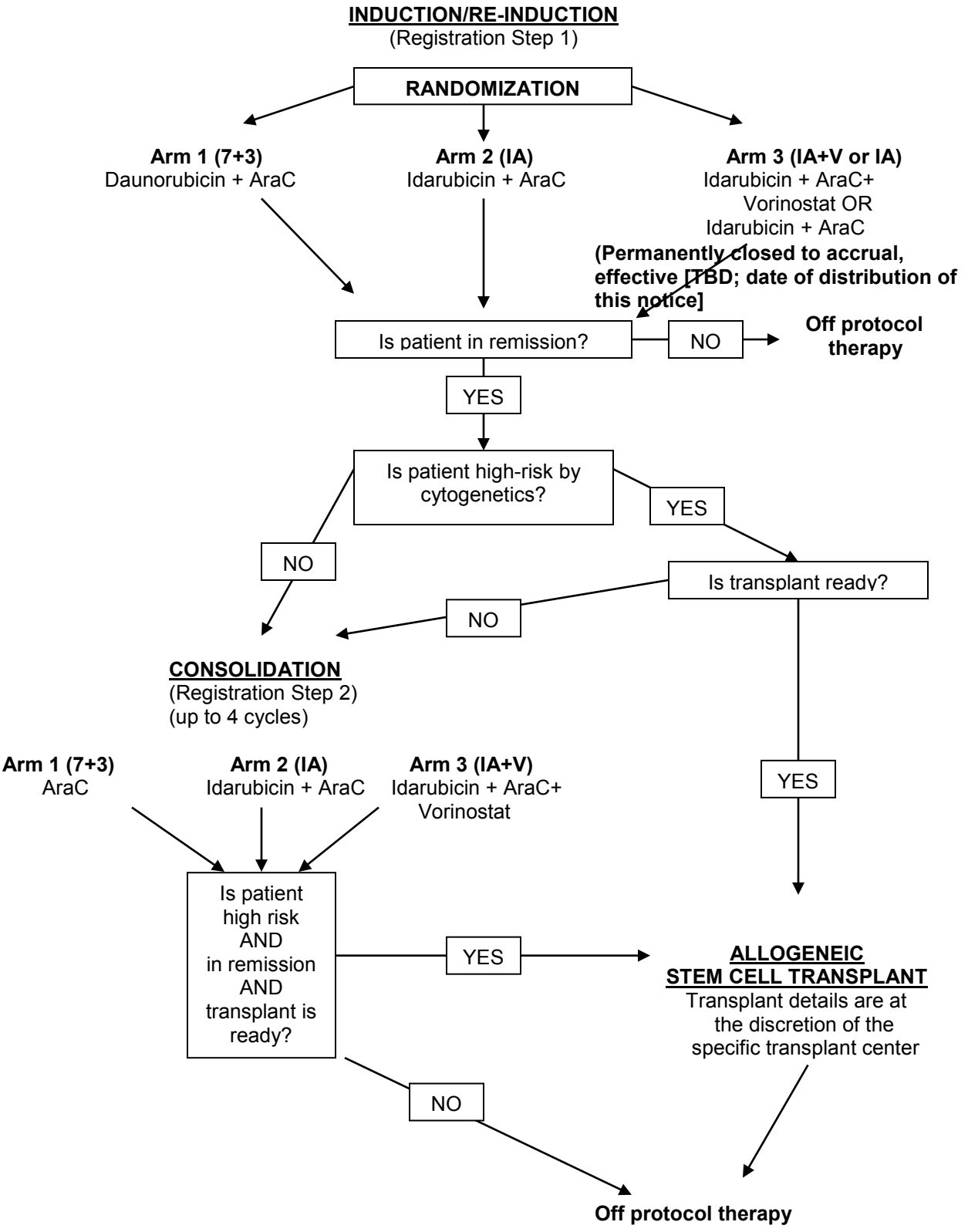
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU Data Operations. Do not copy the CTSU on data submission.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility questions contact the SWOG Data Operations Center by phone at 206/652-2267. For treatment or toxicity related questions contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA


INDUCTION/RE-INDUCTION
(Registration Step 1)
RANDOMIZATION
Arm 1 (7+3)
Daunorubicin + AraC
Arm 2 (IA)
Idarubicin + AraC
Arm 3 (IA+V or IA)
Idarubicin + AraC+
Vorinostat OR
Idarubicin + AraC
(Permanently closed to accrual, effective [TBD; date of distribution of this notice]
Is patient in remission?
NO
Off protocol therapy
YES
Is patient high-risk by cytogenetics?
YES
NO
Is transplant ready?
NO
CONSOLIDATION
(Registration Step 2)
(up to 4 cycles)
Arm 1 (7+3)
AraC
Arm 2 (IA)
Idarubicin + AraC
Arm 3 (IA+V)
Idarubicin + AraC+
Vorinostat
YES
Is patient high risk AND in remission AND transplant is ready?
YES
ALLOGENEIC STEM CELL TRANSPLANT
Transplant details are at the discretion of the specific transplant center
NO
Off protocol therapy

1.0 OBJECTIVES

1.1 Primary Objectives

a. (Chemotherapy): To compare event-free survival (EFS) between patients with AML who receive standard 7+3 or idarubicin and high-dose cytarabine (IA) to patients who receive IA + vorinostat.

b. (Transplant): To determine whether it is possible to get 60% or more of adults with high-risk AML (by cytogenetics) in first complete remission (CR1) to allogeneic hematopoietic cell transplantation (HCT).

1.2 Secondary Objectives

c. (Chemotherapy): To estimate the frequency and severity of toxicities of the three regimens in this patient population.

d. (Transplant): To estimate disease-free survival (DFS) among patients who receive transplant.

e. (Chemotherapy): To compare event-free survival (EFS) between patients who receive standard 7+3 to patients who receive IA.

f. (Chemotherapy/Translational Medicine): To estimate the prevalence of the mutations NPM1, IDH1, IDH2, TET2 and DMT3A and the cytogenetic risk distribution of patients on this study and to evaluate the association between these and overall survival (OS), event-free survival (EFS), disease-free survival (DFS), and complete remission rate .

g. (Chemotherapy): To compare the complete response rate, disease-free survival (DFS), and overall survival (OS) between patients who receive standard 7+3 therapy or IA to patients who receive IA + vorinostat.

1.3 Additional Objectives

h. (Chemotherapy/Translational Medicine): Future planned studies will include testing of histone H3 acetylation, induction of gammaH2AX, analysis of ROS resistance and DNA methylation profiles.

2.0 BACKGROUND

Standard induction therapy for patients with acute myeloid leukemia (AML) consists of the combination of cytarabine (AraC) plus an anthracycline, the so called “7+3” schema. Different doses and schedules of this combination have been used over the last two decades. Recently a combination of AraC 100 mg/m^2 as a daily continuous infusion for seven days with daunorubicin 90 mg/m^2 daily for 3 days has been established to be superior to a combination with lower doses of daunorubicin. *(1)* In that study, complete remission (CR) rates were as follows: favorable cytogenetics 79.5%, intermediate 69.3%, unfavorable 59.3%, FLT-3 wild type (wt) 70.9% and FLT3 mutated (mut) 66.7%. An additional recent study compared induction therapy consisting of idarubicin and cytarabine at a dose of either 200 mg/m^2 by continuous infusion for 7 days or 1,000 mg/m^2 over 3 hours twice daily on Days 1-5. They saw no difference in CR rates, relapse, event free survival (EFS) or overall survival (OS). *(2)* While other regimens have yielded similar results, a combination of daunorubicin at 90 mg/m^2 for 3 days and cytarabine at either 100 or 200 mg/m^2 for 7 days is generally considered to be “standard.”

There is less of a consensus as to what constitutes standard post-remission therapy. The National Comprehensive Cancer Network (NCCN) guidelines and expert reviews generally recommend allogeneic transplant from a matched sibling or alternative donor for patients with poor-risk disease (as determined by cytogenetics), and several cycles of consolidation containing intermediate or high dose cytarabine for patients with good risk disease. Therapy for patients with intermediate risk disease is generally driven by further molecular testing. For patients with a normal karyotype (NK) but FLT3 mutations or without mutations in NPM1, an allogeneic transplant is generally recommended if a matched sibling is available, but it is less certain if alternative donors should be used. For NK patients without FLT3 mutations but with mutations in NPM1, high-dose cytarabine containing regimens are generally recommended, with transplantation reserved until relapse. The optimal cytarabine regimen has recently been revisited, and although 3 gm/m^2 given over 3 hours every 12 hours on Days 1, 3 and 5 is most popular, regimens of 1 or 2 gm/m^2 over 3 hours every 12 hours on Days 1-5 may be equivalent. *(2)* With standard induction and consolidation chemotherapy, approximately 35% of patients can be expected to be alive and disease-free at 3 years.

In addition to a better understanding of optimal dosing of daunorubicin and cytarabine, the last decade has witnessed a remarkable increase in the understanding of the disease, but current therapies still need improvement. A subgroup of the National Cancer Institute (NCI) Leukemia Steering Committee (NCI AML Working Group Subgroup 3) consisting of Harry Erba, Stephen Couban, Deborah Banker, Richard Larson, Wendy Stock, Richard Stone, Steven Gore, Martin Tallman, Eli Estey, Megan Othus, Richard Little and Frederick Appelbaum was charged with developing a strategy for developing the next intergroup clinical trials of upfront therapy for younger patients with AML. This study is one product of this group's work.

Following a series of face-to-face and conference call meetings, the subgroup suggested a general strategy for protocol development. First, it was concluded that it would be optimal if there were a single intergroup protocol that allowed uniform diagnosis, protocol assignment and specimen collection. Such a protocol is currently under discussion. Next, the group concluded that there were several subgroups of AML where targeted therapies were sufficiently developed to be tested as part of up front therapy. These include core binding factor (CBF) AMLs and those associated with FLT3 mutations. Thus, separate protocols dealing with these subgroups are already active or are being developed. However, for the majority of patients, while many potential targets and therapies exist, it was less clear which, if any, were sufficiently mature for a large upfront trial.

In an effort to determine which questions might be addressed, the subgroup felt that a reasonable approach would be to review the literature and invite researchers with clinical data to submit their results for further analysis. The group was particularly interested in Phase II trials of upfront therapy for AML, with the idea that the results of these studies would be compared to those seen with standard therapy. If the results of the comparisons suggested a possible improvement, the regimen might be considered for a Phase III trial, whereas if no advantage was suggested, enthusiasm for further study of the regimen would be considerably less. Data from five regimens were reviewed, including 7+3 with pravastatin, a combination of flavopiridol, cytarabine and mitoxantrone (FLAM), 7+3 with bortezomib, idarubicin with cytarabine (IA), and vorinostat with IA. Data for standard 7+3 came from the recently completed SWOG study **S0106**. The initial analysis focused on CR rates, since analyses of disease-free survival (DFS) and overall survival (OS) were hampered by limited follow-up and variations in post-induction therapies. The CR rate for each of the five regimens was compared to historical data of 7+3 controlling for the risk factors age, performance status, cytogenetic risk, and secondary AML status. Only two of the five regimens had CR rates that were significantly better than the CR rates (controlling for risk factors) from patients treated with 7+3 on **S0106**. Those two regimens were IA ($p=0.009$) and IA + vorinostat ($p < 0.001$). These studies will be presented in more detail below.

Discussions then turned to the structure of the next upfront study. The general consensus favored a randomized Phase III trial with early stopping rules for futility. While some favored a randomized Phase II approach, others noted that such a trial had the disadvantage of not providing definitive conclusions, of requiring considerable delay from the time of its completion until a subsequent definitive trial could be initiated, and that data from the Phase II components would be lost. Thus, a more attractive approach was felt to be a randomized Phase III trial with early interim analysis and strict rules for early stoppage for futility. Admittedly, such an approach carries a risk that a potentially positive study could be stopped early, but this risk was felt to be acceptable and preferable to the shortcomings of a randomized Phase II approach. It was also debated whether to compare 7+3 with IA + vorinostat or include IA as a third arm. The decision to include IA was based on the argument that if IA + vorinostat was positive, there would be no way to determine if vorinostat was the contributing agent. While some felt that a 2 armed study of IA versus IA + vorinostat might be acceptable, others felt that it would be important to include standard 7+3. Ultimately, a three-armed study was decided upon.

Standard induction therapy at MD Anderson (MDA) includes idarubicin 12 mg/m^2 daily for 3 days with continuous infusion AraC at doses of 1.5 gm/m^2 daily for 3 or 4 days depending on age. This approach results in CR rates in excess of 75% in patients with AML younger than 65 years of age. At MDA, patients with favorable karyotypes (i.e. APL and CBF) are treated on other protocols. Over the years there has been a debate as to whether standard 7+3 or MDA IA is a better approach. This has never been formally tested in a randomized clinical trial.

The MDA group has been interested in improving the results of IA by adding a third agent. Examples have included combinations with tipifarnib and more recently sorafenib. *(3,4)* A third combination consisted of the addition of the histone deacetylase inhibitor (HDACI) vorinostat. This work has evolved over the last 5 years from initial Phase I single agent trials and preclinical models to a Phase II study of the combination of IA with vorinostat. In the initial Phase I trial, the maximum tolerated dose (MTD) of vorinostat was defined as 200 mg orally three times a day for 14 days every 21 days. Using this schedule, the drug was well tolerated and associated with an overall response rate (ORR) of 15% in patients with advanced AML. *(5)* Because of the effects of vorinostat on chromatin, it was hypothesized that a combination of vorinostat with a DNA topoisomerase II inhibitor, such as the anthracycline idarubicin, could lead to synergistic anti-leukemia effects. This was confirmed in a series of preclinical models. *(6)* Based on these data, a CTEP sponsored randomized two arm Phase I trial of the combination of idarubicin with vorinostat was conducted. In this trial, two schedules of vorinostat were studied: a 3 day schedule and a classic 14 day schedule based on the initial Phase I trial. In this study, 14 days of vorinostat with idarubicin was too toxic and the dose of idarubicin had to be reduced. In contrast, it was observed that when using vorinostat for 3 days with standard dose idarubicin, the dose of vorinostat could be increased safely to 500 mg orally three times a day for 3 days. *(7)* In parallel with this work, the group at the University of Maryland reported their experience combining AraC, anthracycline and vorinostat. *(8)* These investigators found that the anthracyclines and vorinostat appeared to be synergistic in a sequence independent fashion but demonstrated that for optimal activity vorinostat had to be administered prior to AraC. All this information led to the development of a Phase II study of the combination of vorinostat with IA (IA + vorinostat). The dose of vorinostat was 500 mg orally three times a day for 3 days (Days 1-3) followed on Day 4 by standard IA. In that study (ASH 2010), 75 patients were treated. *(9)* The overall response rate was 86% (including ORR of 93% in diploid patients, 80% in others and 100% in FLT3 mutated patients). The study had a Bayesian design with stopping rules for lack of response rate, excess toxicity/mortality and PFS at 7 months. IA vorinostat was superior in all 3 rules to standard experience with IA. Table 1 summarizes the comparison of IA + vorinostat (IA+V) and IA at MDA (Garcia-Manero, in preparation). Therefore the body of information provided above indicates that IA + vorinostat is safe and very active in patients with newly diagnosed AML and potentially superior to standard IA at MDA.

Table 1: IA + Vorinostat vs. IA at MDA

Response Rates	IA+V (N)	IA+V (%)	IA (N)	IA (%)	P-value
All Patients	75		347		0.015
CR/CRp	64	85%	249	72%	
Otherwise	11	15%	98	28%	
Total	75		347		
Response Rates	IA+V (N)	IA+V (%)	IA (N)	IA (%)	P-value
Diploid Only	29		147		0.055
CR/CRp	27	93%	114	78%	
Otherwise	2	7%	33	22%	
Total	29		147		
Response Rates	IA+V (N)	IA+V (%)	IA (N)	IA (%)	P-value
Miscellaneous Only	29		137		0.039
CR/CRp	27	93%	104	76%	
Otherwise	2	7%	33	24%	
Total	29		137		
Response Rates	IA+V (N)	IA+V (%)	IA (N)	IA (%)	P-value
Only -5/-7	17		63		0.484
CR/CRp	10	59%	31	49%	
Otherwise	7	41%	32	51%	
Total	17		63		
Response Rates	IA+V (N)	IA+V (%)	IA (N)	IA (%)	P-value
FLT3 +	11		32		0.066
CR/CRp	11	100%	24	75%	
Otherwise	0	0%	8	25%	
Total	11		32		

Role of Allogeneic Stem Cell Transplant in Front Line AML

The prognosis of adults with AML can be estimated using a variety of methods, but cytogenetics remains the most common and reproducible. Using cytogenetics, patients can be categorized as having favorable, intermediate or unfavorable (high) risk, the latter group including those with del(5q)/-5, del(7q)/-7, abn3q26 [inv (3)/t(3:3)], abn11q23 rearrangement [except t(9;11)], 17p-, t(6;9), t(9;22), complex (at least 3 unrelated abn), and monosomal karyotype (either a loss of two different chromosomes or loss of one chromosome along with a structural chromosome abnormality other than add, ring and mar). In a previous intergroup trial for adult AML patients age < 61 (**S9034**), the unfavorable risk group made up 30% of all patients, and had a complete response (CR) rate of 54% and an estimated survival at 5 years of 11%, figures that were significantly worse than seen in intermediate or favorable risk patients. *(10)* In this trial, patients with matched siblings were assigned to receive an allogeneic hematopoietic cell transplant in first CR, while those without donors were randomized to autologous transplantation or further chemotherapy. Forty percent of patients randomized to transplant in this trial were actually transplanted. Based on an intent-to-treat analysis, the estimated survival at 5 years from achieving CR was 52% for allogeneic transplantation, 42% for autologous transplantation and 39% for chemotherapy. The advantage of allogeneic transplantation was most obvious for patients with high risk disease, with a 44% survival at 5 years with allogeneic

transplantation versus 15% with chemotherapy. *(11)* Based on these results, as well as those of other single institution studies and large meta-analyses, the recommendation of most experts, including that of the recently published European LeukemiaNet, is that allogeneic transplantation from a matched related donor is recommended for adults age < 61 with high-risk AML in CR1. *(12-15)*

Unfortunately, fewer than 30% of adults will have HLA-matched relatives able to donate. Recent data from the Fred Hutchinson Cancer Research Center (FHCRC) and other centers suggest outcomes after allogeneic HCT from fully matched unrelated donors appear to be similar to that following matched related donor transplantation. *(16)* Depending on ethnicity, matched unrelated donors can be found for anywhere from 25-50% of patients who do not have a matched related donor. Additionally, data recently presented by the groups from Minnesota and the FHCRC show that for patients age < 45, outcomes following double cord transplantation are similar to those seen with either matched related donors or matched unrelated donors. *(17,18)* Given the current criteria for cord blood transplants based on cell dose and degree of mismatch, double cord blood should be available for almost 95% of patients lacking a matched related or matched unrelated donor. Theoretically then, alternative donors should be available for the large majority of high risk AML patients, and outcomes of transplantation should approximate those seen with matched related donors.

However, it takes time, effort and resources to identify potential donors, and there are no prospective data addressing how often this can actually be done. In the prior North American intergroup trial, only 70% of those with matched siblings actually received an allogeneic transplant. While one can reasonably expect that figure to increase with increasing acceptance of transplantation for high risk disease, it remains a question whether alternative donors can be found rapidly enough to treat those without matched family members. Thus, the initial hypothesis to be tested in this trial is that with an organized effort, at least 60% of adults age < 61 with high risk AML in first CR can be treated with an allogeneic transplant, using matched related, matched unrelated or cord blood as the donor source.

All of the studies suggesting roughly equivalent outcomes following matched related, matched unrelated and cord blood transplants were retrospective analyses. These studies were therefore subject to patient selection and other biases, which could dramatically affect outcomes. There are no published prospective studies of the outcome of alternative donor transplants for a large cohort of adult patients with high risk AML identified at diagnosis which would allow for an estimation of the impact of HCT on eventual survival. Thus, a second hypothesis is that by transplanting 60% of adults with high risk AML in first remission, and achieving a 44% DFS at 2 years (as achieved in references *10* and *11*), the overall disease-free survival at 2 years of all high risk patients can be improved from the historic level of 22% to at least 35%.

Rationale for Translational Medicine: Prognostic Significance and Predictive Markers

The following *integrated* studies are planned in order to distinguish genetic and biological subgroups associated with response, and to define mechanisms of actions of these agents.

Mutational analyses of NPM1, IDH1[10], IDH2[10], TET2[11], DNMT3A[12]: Mutations in these genes have been demonstrated in approximately 10-40% of the AML population targeted in his proposal, and have been associated with outcome. It is unknown if the addition of vorinostat will overcome the negative prognostic impact of these mutations. Furthermore mutations in these genes have been proposed to have a significant impact on epigenetic alterations in leukemia and potentially prognosis and response to therapy. *(10-12)* PCR and sequencing of these genes will be performed on pre-treatment specimens obtained from all patients.

The genetics of treatment response: Global gene and miRNA expression have been shown to be associated with survival outcome in AML. *(13)* The **S1203** trial is the perfect complement to the Intergroup AML non-responder project, sponsored by the NCI and approved by CTEP. The non-responder project is using multiple genetic platforms (miRNA, RNA, SNP, methylation) to identify the genetic elements that differentiate primary treatment failure and long-term remission in AML. It is unique in the question asked, the multiple genetic assays used on all samples, and the amount of Intergroup cooperation in performing the assays and analysis. The end product will be a set of bioassays associated with early response, and pathways that may be targetable to convert non-responders into responders. The non-responder protocol will have all assays completed by the end of 2012, and the bioinformatics analysis (the plan devised by Dr. Michael LeBlanc of SWOG, Dr. Lisa McShane of NCI, and Dr. Erich Huang of Sage Bionetworks) will be done by early spring.

The AML non-responder project was promoted with the expectation that validation would take place in the next sets of Intergroup trials. **S1203** is the logical starting place, and we will develop a multi-analyte assay (presumably a combination of mutations, mRNA, miRNA, methylation sites, etc.) to use on the pre-treatment samples from **S1203** as a validation study of predicting initial treatment response. Once the biomarkers are chosen, the statistical plan for this validation will be performed by the above group (currently difficult to do since it is not known what genes/miRNAs/etc will be used, nor is the strength of the association known, which will largely drive the study design).

Measuring HDAC exposure. The induction of histone H3 acetylation is a biomarker of exposure to the HDAC inhibitor. *(1)* This study hypothesizes that the level of H3 acetylation will be associated with treatment response in the vorinostat arm. The assay will be performed by ELISA or Western blot on peripheral blood specimens obtained at baseline and on Day 3.

Measuring DNA damage and ROS pathway. GammaH2AX clusters to genomic areas of DNA damage, and thus the levels of gammaH2AX correlates with the amount of DNA damage induced by vorinostat and idarubicin. *(2) This study hypothesizes that gammaH2AX levels will correlate with disease response, and indeed will be higher in the vorinostat arm.* GammaH2AX will be directly measured by immunocytochemistry and ELISA (Figure 1) on peripheral blood specimens obtained at baseline and by Day 3. *In addition,* Phase II studies from the MDACC suggest that increased levels of Nrf2 and CYYB mRNA are associated with a longer survival (Figure 2). These assays will be measured on peripheral blood specimens obtained at baseline and on Day 3.

Figure 1. Induction of gammaH2AX by vorinostat. Induction of H2AX was measured by immunohistochemistry in cell pellets recovered after treatment with vorinostat and/or idarubicin as indicated.

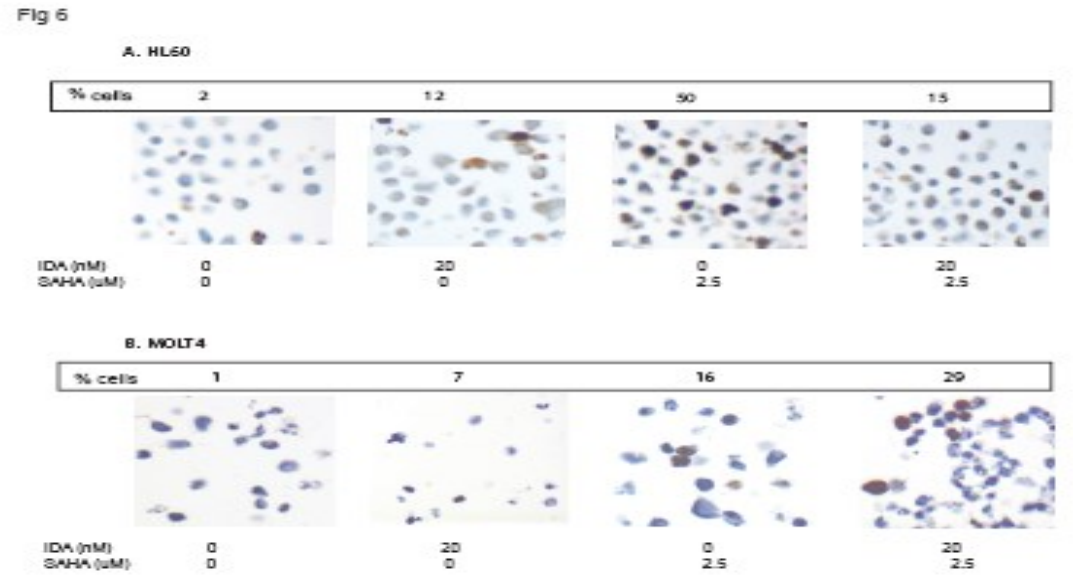
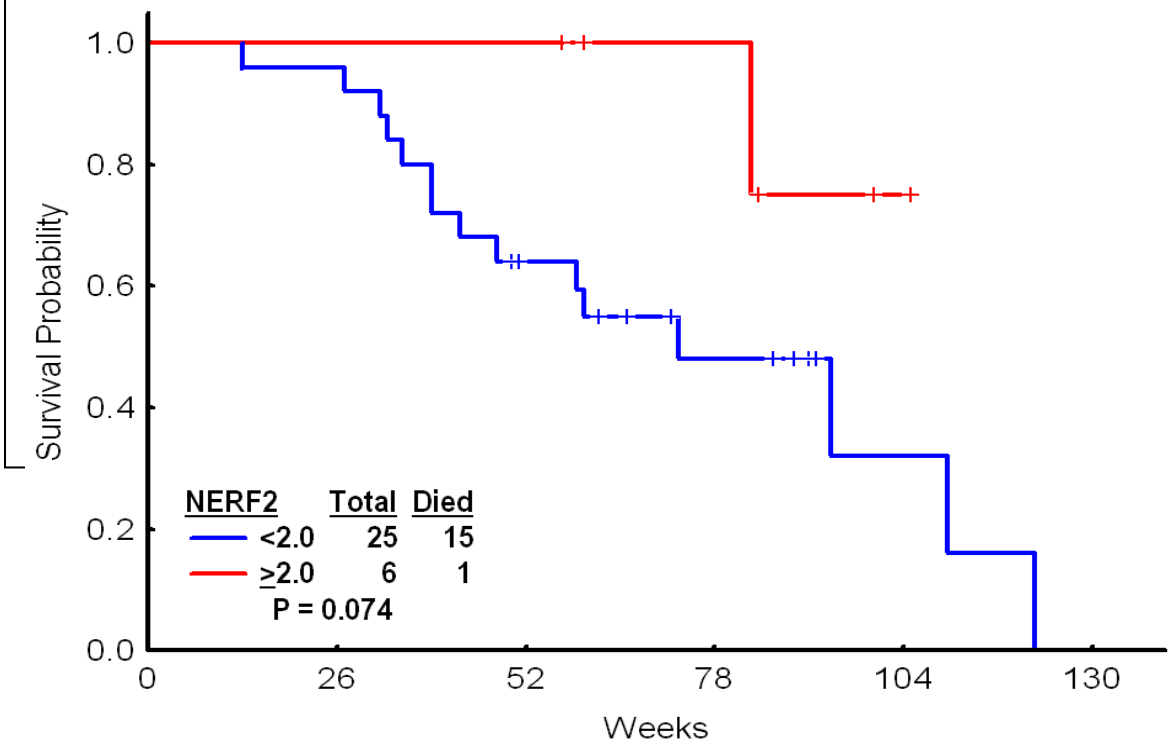


Figure 2. Survival effect of Nrf2 activation in patients with AML treated with vorinostat IA. mRNA levels of Nrf2 were sequentially measured in peripheral blood samples obtained sequentially during induction phase.



Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. SWOG is unaware of any literature supporting an interactive treatment effect by sex or race; therefore, there is no current plan to alter the accrual for separate gender or racial subsets. The Group is committed to the continued accrual of non-white patients to all of its trials at current levels or better, and will explore the effect of treatment by race and sex in these trials. Anticipated accrual to this study by race and ethnicity, based on previous Group trials in this disease type, follows:

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	13	28	41
Not Hispanic or Latino	355	388	743
Total Ethnic	368	416	784
Racial Category			
American Indian or Alaskan Native	0	5	5
Asian	10	11	21
Black or African American	41	41	82
Native Hawaiian or other Pacific Islander	3	3	6
White	314	356	670
Racial Category: Total of all Subjects	368	416	784

3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, AraC, daunorubicin and idarubicin are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, vorinostat is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator Brochures may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 240/276-6575.

3.1 Cytosine Arabinoside (AraC, Cytarabine) (NSC-63878)

a. DESCRIPTION

AraC is chemically 4-amino-1-S-D-arabino-furanosyl-2(1H)-primidinone. AraC is metabolized to its active form, AraCTP. The AraCTP functions as an inhibitor of DNA polymerase. AraC exhibits cell phase specificity, killing cells undergoing DNA synthesis (S phase) and may also block cells from progressing to S phase from G1. Extensive chromosomal damage, including chromatid breaks, occurs. AraC appears to be most effective in tumors with high growth fraction.

AraC can cause fetal harm when administered to pregnant women, however, there are no adequate and well controlled studies in pregnant women.

b. TOXICOLOGY

Human Toxicology: Side effects of AraC include myelosuppression, nausea, vomiting, diarrhea, anorexia, anal ulceration, stomatitis, rash, headache, fever, myalgia, malaise, bone pain, chest pain, hepatic and renal dysfunction, and alopecia. Central nervous system toxicity, i.e., significant cerebral and cerebellar, dysfunction, progression to coma, has been seen with high doses. Severe cardiomyopathy has been reported with high dose AraC in combination with cyclophosphamide. Progressive ascending paralysis has occurred in two patients receiving IV and intrathecal AraC. Marked keratoconjunctivitis has also occurred with high doses.

AraC can cause fetal harm when administered to a pregnant woman, however, there are no adequate and well controlled studies in pregnant women.

c. PHARMACOLOGY

Kinetics: AraC is metabolized by deoxycytidine kinase and related kinases to nucleotide triphosphate, which is an active inhibitor of DNA polymerase. Deoxycytidine prevents or delays cytotoxic activity. The active form is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. The balance of kinase and deaminase levels appears to be an important factor in sensitivity/resistance of the cell to AraC. After IV injection, plasma disappearance of AraC is biphasic. Initial half-life is 10 minutes, delayed half-life is 1 - 3 hours. After 24 hours, 80% is excreted in the urine as its inactive metabolite, AraI. After a single IV administration of AraC, levels in CSF are low. There is little conversion to AraU because of low CSF levels of diaminase. Drug interaction of AraC has been reported with digoxin, gentamycin and fluorocytocine.

Formulation: AraC is supplied as a sterile powder in 100 mg and 500 mg vials for injection. AraC is also available in 1 and 2 gram vials. The drug should be reconstituted with sterile water for injection.

Storage and Stability: The sterile powder should be stored at room temperature 15° - 30°C (59° - 86°). The resulting solution has a stability of 48 hours if stored at ROOM TEMPERATURE. Do not use if even a slight haze develops. The reconstituted solution may be further diluted in 5% dextrose or sodium chloride injection.

Administration: AraC is usually administered by continuous IV infusion, but IV bolus and subcutaneous use have their place in treating certain leukemic responses (i.e., maintenance or remission).

Supplier: AraC is commercially available and therefore should be purchased by a third party. This drug will NOT be supplied by the NCI.

Please refer to the package insert for complete information.

3.2 Daunorubicin Hydrochloride (Cerubidine) (NSC-82151)

a. DESCRIPTION

Daunorubicin (Cerubidine) is the hydrochloride salt of an anthracycline antibiotic produced by a strain of *Streptomyces oeruleorubidus*. It inhibits synthesis of nucleic acids, exhibiting antimitotic and cytotoxic activity.

b. TOXICOLOGY

Human Toxicity: Dose-limiting toxicity includes myelosuppression and cardiotoxicity. Cumulative dose beyond 550 mg/M^2 results in increased risk for CHF. Radiation therapy involving the heart and previous adriamycin administration increases the risk for cardiomyopathy. Hepatic and renal dysfunction may occur. Other reactions include reversible alopecia, nausea and vomiting, anorexia, diarrhea and mucositis. If extravasation occurs during administration, tissue necrosis can result. Rarely, chills, fever, skin rash and anaphylactoid reactions can occur. Because of its teratogenic properties, women of childbearing potential should be advised to avoid pregnancy. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Following IV injection, plasma levels rapidly decline. Subsequently, levels decline slowly with half-life of 18.5 hours. There is no evidence of the drug crossing the blood-brain barrier. Active metabolites are present in the plasma one hour after injection. Twenty-five percent of administered dose is excreted by the kidney and 40% by biliary excretion.

Formulation: The drug is supplied in vials containing 20 mg of daunorubicin as a reddish lyophilized powder. The daunorubicin should be reconstituted with 4 mL of Sterile Water for Injection, USP, or PF 0.9% Sodium Chloride for Injection, USP, to give a final concentration of 5 mg/ml.

Storage and Stability: The drug is stored at room temperature (15°-25°C). The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration. Protect from sunlight.

Administration: When reconstituted with 4 ml of sterile water for injection, USP, each ml contains 5 mg of daunorubicin activity for intravenous administration only.

Supplier: This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.3 Idarubicin HCL (Idamycin®) (NSC-256439)

a. DESCRIPTION

A sterile, synthetic antineoplastic anthracycline for intravenous use. Idarubicin is a DNA-intercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II.

b. TOXICOLOGY

Idarubicin is a potent bone marrow suppressant. Idarubicin should not be given to patients with pre-existing bone marrow suppression induced by previous drug therapy. Deaths due to infection and/or bleeding have been reported during the period of severe myelosuppression. Other warnings include pre-existing heart disease, previous therapy with anthracyclines, previous radiation to the mediastinal-pericardial area, myocardial toxicity typically presenting as CHF, arrhythmias or other cardiomyopathies, in patients with anemia, bone marrow depression, infections, leukemic pericarditis and/or myocarditis, and renal or hepatic impairment. The most common side effects (90% to 100%): infection. Other common side effects include (20% to 90%): nausea, vomiting, hair loss, abdominal cramps, diarrhea, hemorrhage, mucositis, dermatologic, mental status, pulmonary-clinical, fever, headache. Other less common side effects include (10% to 20%): cardiac-clinical. Infrequent side effects include (1% to 10%): Neurologic-peripheral nerves, pulmonary allergy, seizure, cerebellar. Rare side effects include (less than 1%): None reported in this range.

c. PREGNANCY AND LACTATION

Pregnancy Category D- Idarubicin was embryotoxic and teratogenic in the rat. Idarubicin was embryotoxic but not teratogenic in the rabbit. There is no conclusive information about idarubicin adversely affecting human fertility or causing teratogenesis. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from idarubicin mothers should discontinue nursing prior to taking this drug. There has been one case reported of fetal fatality after maternal exposure to idarubicin during the 2nd trimester.

d. PHARMACOLOGY

Kinetics: The plasma concentrations follow a 2 or 3 compartment mode. Idarubicin has a rapid distribution phase with a high volume of distribution reflecting extensive tissue binding. Idarubicin undergoes extensive extrahepatic metabolism and a rapid distribution phase. Idarubicin has a very high volume of distribution. Elimination occurs predominantly by biliary and to a lesser extent by renal excretion. The mean terminal half-life 22 hours when used as a single agent and 20 hours when used in combination. Elimination exceeds 45 hours.

Formulation: Idarubicin is a sterile, red-orange, isotonic parenteral preservative-free solution. It is available in 5mg/5ml, 10mg/10ml and 20mg/20ml single use only vials.

Storage and Stability: Idarubicin should be stored under refrigeration 2° - 8°C (36° to 46°F), and protected from light. The vials are preservative-free and are for single use only.

Administration: Idarubicin should be administered over 10 - 15 minutes into a freely flowing line of NS or D5W. Unless there is specific data do not mix idarubicin with other drugs. Prolonged contact in an alkaline pH will degrade Idarubicin. Precipitation occurs with heparin. Extravasation can cause severe local tissue necrosis. Extravsation may occur with or without an accompanying burning sensation and even if blood returns well on aspiration of the infusion needle. If extravasation occurs terminate infusion immediately and restart in another vein. Treat extravasation with intermittent ice packs (Place ice pack on area of extravasation for 1/2 hour immediately, then for 1/2 hour four times a day for 3 days) and elevate the affected extremity. For more information see package insert and seek further medical treatment as deemed necessary.

Supplier: This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.4 Vorinostat (Zolinza®, Suberoylanilide hydroxamic acid; SAHA)(NSC-701852)(IND-117406)

a. DESCRIPTION

1. Vorinostat is a synthetic antineoplastic agent in the histone deacetylase (HDAC) inhibitor class.

2. Molecular Formula: C14H20N203

3. Molecular Weight: 264.32 g/mol

b. PHARMACOLOGY

Mechanism of Action: Vorinostat inhibits the enzymatic activity of both class I and class II histone deacetylases. These enzymes are responsible for the removal of acetyl groups from lysine residues of proteins and transcription factors. Inhibition of HDAC activity interferes with the stabilization of chromatin structure through the accumulation of acetylated histones. The accumulation results in cell cycle arrest and/or apoptosis of transformed cells.

c. PHARMACOKINETICS

1. Absorption: High-fat meals increase the absorption of vorinostat 33%. Normal Cmax is achieved in 1.5 hours however high fat meals delay peak absorption by approximately 2.5 hours.

2. Distribution: Vorinostat is approximately 71% bound to human plasma protein.

3. Metabolism: Vorinostat is metabolized via glucuronidation and hydrolysis followed by beta-oxidation into 2 inactive metabolites - *O*-glucuronide and 4-anilino-4-oxobutanoic acid. Biotransformation of CYP P450 is negligible from in vitro studies.

4. Elimination: Renal excretion accounts for approximately 50% of Vorinostat elimination. Less than 1% of the dose is recovered as unchanged drug in the urine.

d. TOXICOLOGY

Human Toxicity: The most common dose limiting toxicities (DLTs) include anorexia, dehydration, diarrhea, nausea, vomiting, taste alteration (dysgeusia), fatigue, increased blood creatinine levels, hyperglycemia, hypocalcemia, hypokalemia, and anemia. The majority of these DLTs occurred within the first month on oral vorinostat. At continuous daily dosing of 600 mg every day, 300 mg twice daily, and 400 mg twice daily that exceeded the MTD, the pattern and severity of DLTs were similar. The DLTs were manageable because these toxicities resolved quickly after drug administration was interrupted.

Patient Care Implications: Because vorinostat's dose limiting toxicities are anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake. Encourage patients to seek a nutritional consult.

Treat diarrhea promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If Grade 3 or 4 diarrhea develops, discontinue further treatment with vorinostat.

Patients should not have taken valproic acid, another histone deacetylase inhibitor, for at least 2 weeks prior to study enrollment. Other toxicities by system are as follows:

- CNS: dizziness, headache, shivering, fatigue, fever
- Gastrointestinal: nausea, diarrhea, altered taste sensation, anorexia, constipation and xerostomia
- Cardiovascular: peripheral edema, DVT, PE and QT prolongation
- Renal: increased serum creatinine
- Respiratory: cough, upper respiratory tract infection
- Hematologic: anemia, thrombocytopenia
- Dermatologic: pruritus, alopecia
- Endocrine/Metabolic: hyperglycemia, weight decreased
- Musculoskeletal effects: spasm

Pregnancy and Lactation: Vorinostat is classified as FDA pregnancy category D in all trimesters. Based on animal study results, vorinostat can cause fetal harm when administered to a pregnant woman. If vorinostat is used during pregnancy or if the patient becomes pregnant while on vorinostat, the patient should be informed about the potential hazard to the fetus. It is unknown whether vorinostat is excreted in breast milk and therefore patients should be instructed to avoid breast feeding during treatment.

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Vorinostat (SAHA, NSC 701852)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 702 patients.* Below is the CAEPR for vorinostat (SAHA).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, December 18, 2013[1]

Adverse Events with Possible Relationship to Vorinostat (SAHA, Zolinza) (CTCAE 4.0 Term) [n= 1076]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***

INVESTIGATIONS			
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 3)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypocalcemia		
	Hypokalemia		
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle weakness[3]		***Muscle weakness[3] (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Skin and subcutaneous tissue disorders - Other (skin necrosis)	

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

2 Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

3 Muscle weakness includes Generalized muscle weakness, Muscle weakness left-sided, Muscle weakness lower limb, Muscle weakness right-sided, Muscle weakness trunk, and Muscle weakness upper limb under the

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS SOC.

[4] Prolongation of prothrombin time and International Normalized Ratio have been observed in patients using vorinostat concomitantly with coumarin-derivative anticoagulants.

Also reported on vorinostat (SAHA, Zolinza) trials but with the relationship to vorinostat (SAHA, Zolinza) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (supraventricular arrhythmia); Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Ventricular fibrillation
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (retinal tear)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal hemorrhage; Bloating; Cheilitis; Colitis; Dysphagia; Esophageal hemorrhage; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (duodenitis); Lower gastrointestinal hemorrhage; Mucositis oral; Oral hemorrhage; Oral pain; Small intestinal obstruction; Stomach pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (failure to thrive); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (angioedema)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Vascular access complication; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged[4]; Alkaline phosphatase increased; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased[4]; Investigations - Other (increased lactate dehydrogenase); Lipase increased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (decreased total protein); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Chest wall pain; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (myositis); Myalgia; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
NERVOUS SYSTEM DISORDERS - Abducens nerve disorder; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysphasia; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (Guillain-Barre syndrome); Nervous system disorders - Other (head injury); Nervous system disorders - Other (polyneuropathy); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Euphoria; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Pelvic pain; Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Pharyngeal mucositis; Pleural effusion; Pleuritic pain; Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Purpura; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (brittle nails)
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event; Visceral arterial ischemia

Note: Vorinostat (SAHA, Zolinza) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Drug interactions:

Drug Class	Examples	Outcome
Blood thinning agents	NSAIDs, platelet inhibitors, high dose salicylates, anticoagulants	Increased risk of bleeding
Vaccines	Any live vaccine ie. rotavirus	Potential for infection with live virus
Atypical antipsychotic	Clozapine	Increase possibility of developing myelosuppression
HDAC inhibitor	Valproic Acid	Severe thrombocytopenia and GI bleeding

Drug Class	Examples	Outcome
Anthracyclines	Daunorubicin, doxorubicin	Potential risk for anthracycline cardiac toxicity
Any agent that can cause QT prolongation (list is not inclusive – please check appropriate reference)	Disopyramide, amiodarone, ciprofloxacin, cyclobenzaprine, risperidone, saquinavir, ondansetron, paliperidone, telithromycin, tacrolimus, sunitinib and etc.	Increase risk of QT prolongation
Diuretics, antiviral, antifungal, platinum compound	Acetazolamide, amphotericin B, cisplatin, conivaptan, foscarnet, loop diuretics, methazolamide, thiazide diuretics	Electrolyte abnormalities – hypokalemia and hypomagnesemia

e. DOSING & ADMINISTRATION

1. See treatment plan

2. Vorinostat capsules must be administered whole. Administer doses of vorinostat with food, if possible. Vorinostat should not be given with other HDAC inhibitors.

f. STORAGE AND STABILITY

1. Compatibility information: NA
2. Vorinostat is a cytotoxic drug and appropriate procedures for handling, administering, and destroying the drug should be followed.
3. Store at 20-25°C (68-77°F), excursions permitted between 15°-30°C (59°-86°F).

g. HOW SUPPLIED

1. Vorinostat is supplied as a white, opaque gelatin, size 3 capsule, containing 100 mg of vorinostat. The inactive ingredients contained in each capsule are microcrystalline cellulose, sodium croscarmellose, and magnesium stearate. Vorinostat 100 mg capsules are supplied in bottles containing 120 capsules.

2. Vorinostat is investigational and will be supplied by the NCI

Drug ordering: NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned

protocol number (**S1203**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Note: Initial drug orders must be placed at the time the first patient is being screened for registration. Do not wait until the patient has been registered to order initial supply as it will not arrive in time to treat the patient.

3. Drug Handling and Accountability

Electronic Logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI Oral DARF.

4. Drug Return and/or Disposition Instructions

a. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Oral Drug Accountability Record Form (NCI Oral DARF) available at http://ctep.cancer.gov.

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

b. Drug expiration: If packaging has expiration date, indicate drug expiration date on the NCI Oral DARF under manufacturer and lot # and use the drug lots with shorter expiration dates first.

4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

Acute Myeloid Leukemia (AML) is defined by ≥ 20% myeloblasts in the blood or marrow, with exceptions as in the World Health Organization (WHO) 2009 criteria. *(19)*

NOTE: Acute erythroleukemia (erythroid/myeloid subtype) is defined by the presence in the bone marrow of ≥ 50% erythroid precursors in the entire nucleated cell population and ≥ 20% myeloblasts in the non-erythroid population. Pure erythroid leukemia is defined as a neoplastic proliferation of immature cells committed exclusively to the erythroid lineage (> 80% of the marrow nucleated cells) with no evidence of a significant myeloblastic component.

4.2 Staging Criteria

Staging criteria are not applicable to this protocol.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

All patients who are determined to be high-risk based on cytogenetics or FISH should be considered and referred for potential allogeneic stem cell transplant. High-risk patients may receive transplant at any point after achieving remission (CR or CRi). In order to organize a donor, sites must follow instructions in Section 7.3 at the time of initial registration.

5.1 Registration Step 1 – Induction/Re-Induction

_____ a. Patients must have morphologically confirmed newly diagnosed acute myelogenous leukemia (AML) with blood or bone marrow disease. Patients with only extramedullary disease in the absence of bone marrow or blood involvement are not eligible. Note: This protocol uses WHO diagnostic criteria for AML. Patients with acute promyelocytic leukemia (APL, FAB, M3) or blastic transformation of chronic myelogenous leukemia (CML) are not eligible. Patients with known CBF or FLT3 related leukemias are eligible for this study, but should preferentially be placed on NCI-sponsored protocols specific for these subtypes, if available.

_____ b. Patients must have diagnostic/pre-treatment specimens obtained within 28 days prior to registration submitted as outlined in Section 15.2 for cytogenetic (and FISH if possible) analysis to determine risk status. High risk classification will be defined as del(5q)/-5, del(7q)/-7, abn3q26 [inv(3)/t(3;3)], 11q23 rearrangement [except t(9;11)], 17p-, t(6;9), t(9;22), complex (at least 3 unrelated abn), and monosomal karyotype (either loss of two different chromosomes or loss of one chromosome along with a structural chromosome abnormality other than add, ring and mar). Karyograms and cytogenetics/FISH analysis reports must be submitted for discipline review as outlined in Section 12.0.

_____ c. Patients must be chemo-naïve, i.e., not have received any prior Induction chemotherapy for AML or MDS. Temporary prior measures such as apheresis or hydroxyurea are allowed. Prior anthracycline therapy is allowed, but must not exceed a dose of 200 mg/m^2 daunorubicin or equivalent. Prior ATRA for suspected APL is allowed. Prior methotrexate for CNS involvement is allowed. Patients with prior history of MDS must not have received azacitidine, decitabine, lenalidomide or vorinostat.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Registration Step 1 – Induction/Re-Induction (cont.)

_____ d. Patients must have peripheral blood and bone marrow aspirate specimens obtained within 28 days prior to registration submitted for translational medicine as outlined in Section 15.1. With patient consent, residuals will be banked for future research.

_____ e. Patients must be ≥ 18 and ≤ 60 years of age.

_____ f. Patients must have Zubrod Performance Status ≤ 3 (see Section 10.7).

_____ g. Patients must have either ECHO or MUGA with ejection fraction ≥ 45% within 28 days prior to registration.

_____ h. Patients must not have prolonged QTc interval (> 500 msec) determined by EKG within 28 days prior to registration.

_____ i. Patients must not have cardiac disease defined as: New York Heart Association (NYHA) > Class II (see Appendix 18.2). Patients must not have unstable angina (angina symptoms at rest) or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.

_____ j. Patients must not have any coexisting medical condition that is likely to interfere with study procedures or results, and must be reasonable candidates for intensive chemotherapy, in the opinion of their treating physicians.

_____ k. Patients who are known to be HIV+ are eligible providing they meet all of the following additional criteria within 28 days prior to registration:

- CD4 cells ≥ 500/mm^3
- Viral load of < 50 copies HIV mRNA/mm^3 if on cART or < 25,000 copies HIV mRNA if not on cART
- No zidovudine or stavudine as part of cART

Patients who are HIV+ and do not meet all of these criteria are not eligible for this study.

_____ l. Patients with known Hepatitis B or Hepatitis C infection may be eligible providing they have viral load < 800,000 IU/mL within 28 days prior to registration.

_____ m. Patients must be able to take oral medications.

_____ n. Patients must have a history and physical examination obtained within 28 days prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Registration Step 1 – Induction/Re-Induction (cont.)

_____ o. Patients must not be pregnant or nursing due to the teratogenic potential of the drugs used in this study. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ p. Prior malignancy is allowed providing it does not require concurrent therapy. ***Exception:*** Active hormonal therapy is allowed.

_____ q. Patients must not be receiving valproic acid.

_____ r. All patients must be informed of the investigational nature of this study. Patients or a legally authorized representative must sign and give written informed consent in accordance with institutional and federal guidelines

_____ s. As part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 Registration Step 2 – Consolidation

Patients may be registered for Consolidation provided that they were eligible for the initial Induction/Re-Induction registration and satisfy the following additional criteria.

_____ a. Patients must have achieved morphologic remission (complete remission [CR] or complete remission with incomplete blood count recovery [CRi]) after completion of Induction or Re-Induction therapy (see Section 10.1 for definitions of CR and CRi). Patient must remain in remission until beginning Consolidation and this must be documented by bone marrow and peripheral blood examination within 28 days prior to registration to Step 2.

_____ b. All non-hematologic treatment related toxicities that are deemed clinically significant by the treating physician must have resolved to ≤ Grade 2.

_____ c. Patients must not have received allogeneic stem cell transplant.

6.0 STRATIFICATION FACTORS

A dynamic allocation scheme will be used to balance the randomization on the following two stratification factors *(20)*:

1. Age at registration: < 40 years vs. ≥ 40 years

2. Onset of leukemia: de novo vs. treatment related and/or AML arising from antecedent hematologic disease

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Guillermo Garcia-Manero at 281/380-7813 or Dr. John Pagel at 206/667-1868. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 General Considerations

a. Patients must have the following tests within 28 days prior to treatment to obtain baseline measurements:
- CBC, Differential, Platelets
- Creatinine
- Total bilirubin
- SGPT/SGOT
- If there is a clinical suspicion of CNS involvement, further evaluation with imaging or lumbar puncture

b. Supportive Care

Supportive care for prevention of tumor lysis syndrome (hydration, monitoring, etc.) must be performed per local institutional guidelines. Additional supportive care (e.g. transfusions, prophylactic antibiotics, antifungals and/or antivirals, growth factor support) is also allowed per institutional guidelines. All supportive care must be documented on the Treatment Form.

Co-administration of corticosteroids and corticosteroid-containing eye drops (or equivalent) is recommended for patients receiving high-dose AraC containing regimens. Eye drops should continue for at least 2 days following the last dose of AraC. Methylprednisolone 40-50 mg or dexamethasone 10 mg IV daily may be given with high-dose AraC.

Patients randomized to vorinostat should be counseled about the possibility of diarrhea and should have an anti-diarrheal (e.g., loperamide) readily available (see Section 3.4d).

Antiemetic prophylaxis given per institutional guidelines is recommended for every cycle.

Hospitalization for supportive care during Induction/Consolidation is not required, but is allowed per local institutional guidelines.

7.2 Induction/Re-Induction

a. Arm 1 – 7+3

Induction

Agent	Dose	Route	Day
AraC	100 mg/m^2/day total dose = 700 mg/m^2	Continuous IV	1-7
Daunorubicin[1]	90 mg/m^2/day total dose = 270 mg/m^2	IV Push[2]	1-3

[1] BSA cap 2.5. If daunorubicin is not available because of manufacturing issues, idarubicin at 12 mg/m^2 daily x 3 on Days 1 to 3 can be substituted. This must be noted on the Treatment Summary Form.
[2] Alternatively, daunorubicin may be administered via IV infusion over < 60 minutes.

Patients will have a bone marrow examination approximately 14 days (± 3 days) after the start of Induction chemotherapy. If residual blasts are seen, patients may proceed to Re-Induction as outlined below starting on Day 15 (± 3 days). Patients with clearance of blasts should have a repeat bone marrow examination approximately 28 days (± 3 days) after the start of Induction chemotherapy to confirm CR/CRi. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2. If peripheral counts have not recovered to ANC > 1,000/mm^3 or PLT > 100,000/m^3, the Day 28 bone marrow exam may be delayed for up to 14 days to allow for recovery.

Re-Induction

Agent	Dose	Route	Day[3]
AraC	100 mg/m^2/day total dose = 700 mg/m^2	Continuous IV	1-7
Daunorubicin[1]	45 mg/m^2 /day total dose = 135 mg/m^2	IV Push[2]	1-3

[1] BSA cap 2.5. If daunorubicin is not available because of manufacturing issues, idarubicin at 12 mg/m^2 daily x 3 on days 1 to 3 can be substituted. This must be noted on the Treatment Summary Form.
[2] Alternatively, daunorubicin may be administered via IV infusion over < 60 minutes.
[3] Days are calculated from the start of Re-Induction therapy.

Patients will have a follow-up bone marrow examination approximately 14 days after the start of Re-Induction chemotherapy. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2. If peripheral counts have not recovered to ANC > 1,000/mm^3 or PLT > 100,000/m^3, the Day 14 bone marrow exam may be delayed for up to 14 days to allow for recovery.

b. Arm 2 – IA

Induction

Agent	Dose	Route	Day
AraC	1,500 mg/m^2/day total dose = 6,000 mg/m^2	Continuous IV	1-4
Idarubicin [1]	12 mg/m^2/day total dose = 36 mg/m^2	IV over 15 mins	1-3

[1] BSA cap 2.5

Patients will have a bone marrow examination approximately 28 days (± 3 days) after the start of Induction chemotherapy. If residual blasts remain, patients may proceed to Re-Induction as outlined below at that point. Note: patients on this Arm may not proceed to Re-Induction until Day 28, not Day 15 as in Arm 1. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2. If peripheral counts have not recovered to ANC > 1,000/mm^3 or PLT > 100,000/m^3, the Day 28 bone marrow exam may be delayed for up to 14 days to allow for recovery.

Re-Induction

Agent	Dose	Route	Day [2]
AraC	1,500 mg/m^2/day total dose = 6,000 mg/m^2	Continuous IV	1-4
Idarubicin [1]	12 mg/m^2/day total dose = 36 mg/m^2	IV over 15 mins	1-3

[1] BSA cap 2.5
[2] Days are calculated from the start of Re-Induction therapy.

Patients will have a follow-up bone marrow examination 28 days (± 3 days) after the start of Re-Induction chemotherapy. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2.

c. **Arm 3 – IA + Vorinostat** [3]

Arm 3 was permanently closed to accrual **effective TBD**. **Effective TBD**, patients previously randomized to Arm 3 have the option to remain on Arm 3 as a medical intervention and must follow the applicable treatment schedule below.

Induction

Agent	Dose	Route	Day
Vorinostat [2]	500 mg 3x/day daily dose = 1,500 mg/day total dose = 4,500 mg/cycle	PO	1-3
AraC	1,500 mg/m^2/day total dose = 6,000 mg/m^2	Continuous IV	4-7
Idarubicin [1]	12 mg/m^2/day total dose = 36 mg/m^2	IV over 15 mins	4-6

[1] BSA cap 2.5

[2] Vorinostat is given in divided doses 3 times daily. Missed doses of vorinostat should be skipped. Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

[3] Patients previously randomized to Arm 3 that opt to continue medical treatment with IA + Vorinostat must follow protocol and protocol data submission requirements.

Patients will have a bone marrow examination approximately 28 days (± 3 days) after the start of Induction chemotherapy. If residual blasts remain, patients may proceed to Re-Induction as outlined below at that point. Note: patients on this Arm may not proceed to Re-Induction until Day 28, not Day 15 as in Arm 1. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2. If peripheral counts have not recovered to ANC > 1,000/mm^3 or PLT > 100,000/m^3, the Day 28 bone marrow exam may be delayed for up to 14 days to allow for recovery.

Re-Induction

Agent	Dose	Route	Day[3]
Vorinostat [2]	500 mg 3x/day daily dose = 1,500 mg/day total dose = 4,500 mg/cycle	PO	1-3
AraC	1,500 mg/m^2/day total dose = 6,000 mg/m^2	Continuous IV	4-7
Idarubicin [1]	12 mg/m^2/day total dose = 36 mg/m^2	IV over 15 mins	4-6

[1] BSA cap 2.5

[2] Vorinostat is given in divided doses 3 times daily. Missed doses of vorinostat should be skipped. Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

[3] Days are calculated from the start of Re-Induction therapy.

Patients will have a follow-up bone marrow examination approximately 28 days (± 3 days) after the start of Re-Induction chemotherapy. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2.

Arm 3 – IA *

Induction

Agent	Dose	Route	Day
AraC	1,500 mg/m^2/day total dose = 6,000 mg/m^2	Continuous IV	1-4
Idarubicin [1]	12 mg/m^2/day total dose = 36 mg/m^2	IV over 15 mins	1-3

[1] BSA cap 2.5

* Arm 3 was permanently closed to accrual **effective TBD**. Patients previously randomized to Arm 3 that opt to continue medical treatment with IA must follow protocol and protocol data submission requirements.

Patients will have a bone marrow examination approximately 28 days (± 3 days) after the start of Induction chemotherapy. If residual blasts remain, patients may proceed to Re-Induction as outlined below at that point. Note: patients on this Arm may not proceed to Re-Induction until Day 28, not Day 15 as in Arm 1. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2. If peripheral counts have not recovered to ANC > 1,000/mm^3 or PLT > 100,000/m^3, the Day 28 bone marrow exam may be delayed for up to 14 days to allow for recovery.

Re-Induction

Agent	Dose	Route	Day [2]
AraC	1,500 mg/m^2/day total dose = 6,000 mg/m^2	Continuous IV	1-4
Idarubicin [1]	12 mg/m^2/day total dose = 36 mg/m^2	IV over 15 mins	1-3

[1] BSA cap 2.5

[2] Days are calculated from the start of Re-Induction therapy.

* Arm 3 was permanently closed to accrual **effective TBD**. Patients previously randomized to Arm 3 that opt to continue medical treatment with IA must follow protocol and protocol data submission requirements.

Patients will have a follow-up bone marrow examination 28 days (± 3 days) after the start of Re-Induction chemotherapy. Patients achieving CR or CRi may proceed to allogeneic stem cell transplant or to Consolidation, providing they meet the additional criteria outlined in Section 5.2.

7.3 Allogeneic Stem Cell Transplant

Patients will undergo HLA-typing at the time of study entry. Those with high-risk disease by cytogenetics should be referred for consultation with a transplant team with the goal of conducting an allogeneic transplant while in first remission. The transplantation, including donor selection, will not be guided by this protocol but will be at the discretion of the specific transplant center. However, referral to BMTCTN trial **CTN0903** (for HIV infected patients) or BMTCTN trial **CTN0901** is strongly encouraged. The process for donor identification is outlined in the AML transplant study flow-chart (see Appendix 18.5) and Transplant Donor Search Process (see Appendix 18.6).

Patients will have a buccal swab specimen collected at the time of enrollment to facilitate HLA typing and a preliminary unrelated donor search following a cytogenetic diagnosis of high risk disease.

7.4 Consolidation

For patients receiving Consolidation, therapy should be started as soon as possible (and within 14 days) after recovery from Induction/Re-Induction therapy. Patients must be registered to Step 2 before beginning Consolidation therapy (within 14 days after recovery from Induction/Re-Induction).

Subsequent to Consolidation Cycle 1, cycles will be given at 28 day intervals provided both the ANC has recovered to > 1,000/mm^3 and the platelet count to > 50,000/mm^3. If these levels are not met, at physicians discretion, cycles may be continued at 28 day intervals, provided that the ANC has recovered to > 1,000/mm3 and the platelet count to > 30,000/mm3, where determined that continued protocol therapy is in the best interest of the patient.

Patients may receive up to 4 cycles of Consolidation therapy, depending on transplant availability. Patients who are not classified as high risk will be removed from protocol treatment after completion of Consolidation. Patients who are classified as high risk will remain on protocol treatment for up to one year after documentation of CR or CRi, or until they receive transplant, whichever comes first.

a. Arm 1 – 7+3

Agent	Dose	Route	Day	Schedule*
AraC	3,000 mg/m^2/dose daily dose = 6,000 mg/m^2 total dose = 18,000 mg/m^2	IV over 3 hrs	1, 3, 5	every 12 hours on each day it's given

* Note: One cycle = 28 days

b. Arm 2 – IA

Agent	Dose	Route	Day
AraC	750 mg/m^2/day total dose = 2,250 mg/m^2	Continuous IV	1-3
Idarubicin [1]	8 mg/m^2/day total dose = 16 mg/m^2	IV over 15 mins	1-2

* Note: One cycle = 28 days
[1] BSA cap 2.5

c. **Arm 3 – IA + Vorinostat**

Effective TBD, patients have the option to remain on Arm 3 as a medical intervention with or without vorinostat and must follow the applicable treatment schedule below.

Agent	Dose	Route	Day
Vorinostat [2]	500 mg 3x/day daily dose = 1,500 mg/day total dose = 4,500 mg/cycle	PO	1-3
AraC	750 mg/m^2/day total dose = 2,250 mg/m^2	Continuous IV	4-6
Idarubicin [1]	8 mg/m^2/day total dose = 16 mg/m^2	IV over 15 mins	4-5

* Note: One cycle = 28 days
[1] BSA cap 2.5
[2] Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

Arm 3 – IA [2]

Agent	Dose	Route	Day
AraC	750 mg/m^2/day total dose = 2,250 mg/m^2	Continuous IV	1-3
Idarubicin [1]	8 mg/m^2/day total dose = 16 mg/m^2	IV over 15 mins	1-2

* Note: One cycle = 28 days
[1] BSA cap 2.5
[2] Arm 3 was permanently closed to accrual **effective TBD**. Patients previously randomized to Arm 3 that opt to continue medical treatment with IA must follow protocol and protocol data submission requirements.

7.5 Criteria for Removal from Protocol Treatment

a. Relapse from remission (CR or CRi) (as defined in Section 10.3).

b. Unacceptable toxicity.

c. Patient does not achieve remission (CR or CRi) after Induction or Re-Induction.

d. Patient is not high-risk and completes 4 cycles of Consolidation.

e. Patient receives transplant.

f. Patient is high-risk and does not receive transplant within 1 year of documentation of remission (CR or CRi).

g. The patient may withdraw from the study at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

All patients will be followed until death or 5 years after initial registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 Dose Modifications

a. General considerations

1. Dose modifications will be based on the toxicity requiring the largest dose reduction.

2. Dose modifications may be made for individual drugs if in the judgment of the treating physician, the toxicity is attributable to one drug.

3. All dose reductions must be outlined on the Treatment Form.

4. Concomitant administration of any other therapy for treatment of AML, including systemic retinoids, is prohibited.

5. If any individual drug is permanently discontinued due to toxicity, the patient may remain on protocol treatment with the remaining drugs.

6. Dose modification of AraC or Idarubicin in the setting of renal or hepatic dysfunction will be left to the discretion of the treating physician, but the Study Chair should be notified of any modifications. Any modification should be based on labs obtained the day of drug administration and should follow guidelines below. If dose modifications are required and toxicities subsequently resolve, AraC or Idarubicin may be re-introduced in full dose for the next cycle.

7. Other dose modifications may be acceptable after discussion with the Study Chair. No dose reductions will be made for myelosuppression during Induction

b. Arm 1 – 7+3

1. Induction/Re-Induction

AraC: No dose reductions allowed.

Daunorubicin: No dose reduction allowed during Induction. For Re-Induction, dose reductions may be made in the setting of hepatotoxicity as follows:

For SGPT/SGOT 150-300 U/L OR bilirubin 1.5-3.0 mg/dL, reduce to Dose Level -1. For SGPT/SGOT > 300 U/L OR bilirubin > 3.0-5.0 mg/dL, reduce to Dose Level -2. For bilirubin > 5.0 mg/dL, omit daunorubicin.

Drug	Dose Level 0	Dose Level -1	Dose Level -2
Daunorubicin	45 mg/m^2/day	22.5 mg/m^2/day	11.25 mg/m^2/day

2. Consolidation

No dose reductions allowed for Cycle 1 except in the instance of renal dysfunction. For subsequent cycles, doses of AraC may be reduced to Level -1 for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection

If toxicity persists, AraC dose may be further reduced to Level -2.

Drug	Dose Level 0	Dose Level -1	Dose Level -2
AraC	3,000 mg/m^2/ dose	2,250 mg/m^2/ dose	1,125 mg/m^2/ dose

AraC Dose Modifications for Renal Dysfunction:

- For creatinine greater than 2 mg/dL or calculated creatinine clearance of < 50 mL/min, decrease AraC to 1,000 mg/m^2/dose.
- For creatinine, greater than 3 mg/dL or calculated creatinine clearance of < 30 mL/min, change AraC to 100 mg/m^2/day IV infusion over 24 hours daily for 5 days.

c. Arm 2 - IA

1. Induction/Re-Induction

AraC: No dose reductions allowed for Induction. For Re-Induction, doses of AraC may be reduced to Level -1 for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection

AraC Dose Modifications for Renal Dysfunction:

- For creatinine greater than 2 mg/dL or calculated creatinine clearance of < 50 mL/min, decrease AraC to Level -2.
- For creatinine, greater than 3 mg/dL or calculated creatinine clearance of < 30 mL/min, change AraC to 100 mg/m2/day IV infusion over 24 hours daily for 7 days.

Idarubicin: No dose reduction allowed during Induction. For Re-Induction, doses of idarubicin may be reduced to Level -1 for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection

For Re-Induction, doses of idarubicin may be reduced to Level -2 in the setting of hepatotoxicity: bilirubin 2.6 – 5 mg/dL. For bilirubin > 5.0 mg/dL during treatment, omit idarubicin.

Drug	Dose Level 0	Dose Level -1	Dose Level -2
AraC	1,500 mg/m^2/day	1,125 mg/m^2/day	850 mg/m^2/day
Idarubicin	12 mg/m^2/day	9 mg/m^2/day	6 mg/m^2/day

2. Consolidation

Doses of AraC and/or idarubicin may be reduced to Level -1 for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection
- Bilirubin 2.6 – 5 mg/dL (Idarubicin)

For bilirubin > 5.0 mg/dL during treatment, omit idarubicin.

AraC Dose Modifications for Renal Dysfunction:

- For creatinine greater than 2 mg/dL or calculated creatinine clearance of < 50 mL/min, decrease AraC to Level -2.
- For creatinine, greater than 3 mg/dL or calculated creatinine clearance of < 30 mL/min, change AraC to 100 mg/m2/day IV infusion over 24 hours daily for 5 days.

Drug	Dose Level 0	Dose Level -1	Dose Level -2
AraC	750 mg/m2/day	560 mg/m2/day	375 mg/m2/day
Idarubicin	8 mg/m2/day	6 mg/m2/day	Discontinue

d. Arm 3 – IA + Vorinostat

1. Induction/Re-Induction

AraC: No dose reductions allowed for Induction. For Re-Induction, doses of AraC may be reduced to Level -1 for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection

AraC Dose Modifications for Renal Dysfunction:

- For creatinine greater than 2 mg/dL or calculated creatinine clearance of < 50 mL/min, decrease AraC to Level -2.
- For creatinine, greater than 3 g/dL or calculated creatinine clearance of < 30 mL/min, change AraC to 100 mg/m2/day IV infusion over 24 hours daily for 7 days.

Idarubicin: No dose reduction allowed during Induction. For Re-Induction, doses of idarubicin may be reduced to Level -1 for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection

For Re-Induction, doses of idarubicin may be reduced to Level -2 in the setting of hepatotoxicity: bilirubin 2.6 – 5 mg/dL.

For bilirubin > 5.0 mg/dL during treatment, omit idarubicin.

Vorinostat: No dose reductions allowed for Induction. For Re-Induction, patients may receive vorinostat at Dose Level -1 if they experienced any of the following during Induction:

- Nausea
- Vomiting
- Fatigue
- Grade 3-4 extramedullary toxicity

For bilirubin > 3.0 mg/dL during treatment, discontinue vorinostat.

Drug	Dose Level 0	Dose Level -1	Dose Level -2
AraC	1,500 mg/m^2/day	1,125 mg/m^2/day	850 mg/m^2/day
Idarubicin	12 mg/m^2/day	9 mg/m^2/day	6 mg/m^2/day
Vorinostat	1,500 mg/day	1,200 mg/day	Discontinue

2. Consolidation

AraC/Idarubicin: Doses may be reduced to Level -1 for the following reasons:

- Grade 3-4 non-hematologic toxicity
- Severe life-threatening infection
- Bilirubin 2.6 – 5 mg/dL (idarubicin)

For bilirubin > 5.0 mg/dL during treatment, omit idarubicin.

AraC Dose Modifications for Renal Dysfunction:

- For creatinine greater than 2 mg/dL or calculated creatinine clearance of < 50 mL/min, decrease AraC to Level -2.
- For creatinine, greater than 3 mg/dL or calculated creatinine clearance of < 30 mL/min, change AraC to 100 mg/m2/day IV infusion over 24 hours daily for 5 days.

Vorinostat: For patients who did not have dose reduced for Re-Induction, no dose reductions are allowed for the first cycle of Consolidation. For subsequent cycles, or for patients who had dose reduction during Re-Induction, patients may receive vorinostat at Dose Level -1 if they experienced any of the following:

- Nausea
- Vomiting
- Fatigue
- Grade 3-4 extramedullary toxicity

For bilirubin > 3.0 mg/dL during treatment, discontinue vorinostat.

Dose modification of AraC in the setting of renal or hepatic dysfunction will be left to the discretion of the treating physician, but the Study Chair should be notified of any modifications. Any modification should be based on labs obtained the day of drug administration. If dose modifications are required and toxicities subsequently resolve, AraC may be re-introduced in full dose for the next cycle.

Drug	Dose Level 0	Dose Level -1	Dose Level -2
AraC	750 mg/m^2/day	560 mg/m^2/day	400 mg/m^2/day
Idarubicin	8 mg/m^2/day	6 mg/m^2/day	Discontinue
Vorinostat	1,500 mg/day	1,200 mg/day	Discontinue

8.3 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Guillermo Garcia-Manero at 281/380-7813 or Dr. John Pagel at 206/667-1868.

8.4 Adverse Event Reporting

Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Chair, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDARS

9.1 Arm 1 (7+3) – Induction

	Pre	Induction								Re-Induction #									£
	Tx	D1	D2	D3	D4	D5	D6	D7	Wks 2-4	D1	D2	D3	D4	D5	D6	D7	Wks 2-4	Prog	FU
REQUIRED STUDIES																			
History & Physical Exam &	X				X				X				X				X	X	X
Weight & Performance Status	X																		
Toxicity Notation										XΔ								X	
LABORATORY STUDIES																			
CBC, Diff, Platelets &	X				X				X				X				X	X	X
Serum Creatinine % &	X				X				X				X				X		X
Bilirubin % &	X				X				X				X				X		X
SGOT/SGPT % &	X				X				X				X				X		X
CNS Assessment %	X																		
Disease Assessment/BM Asp/Bx #	X								X								X	X	X
Cytogenetics/FISH ∝	X																	XΩ	
SPECIMEN SUBMISSIONS	X																		
Buccal Swabs/Donor Search *ƒ*		X																	
Peripheral Blood	X			X															
Bone Marrow Aspirate	X																		
X-RAYS/SCANS																			
EKG	X																		
ECHO or MUGA	X																		
TREATMENT																			
AraC		X	X	X	X	X	X	X		X	X	X	X	X	X	X			
Daunorubicin		X	X	X						X	X	X							

\# If Day 14 (± 3 days) marrow exam shows residual blasts, Re-Induction should be considered starting on Day 15 (± 3 days). If blasts are cleared, marrow should be repeated on Day 28 (± 3 days) to confirm CR or CRi. After CR, marrows will be obtained at the discretion of the treating physician for disease assessment.

% Prior to starting treatment; baseline measurements do not affect eligibility (see Section 7.1).

& Weekly, or more often if clinically indicated.

ƒ Upon receipt of swab kit; see Sections 15.3 and 18.6.

Δ Prior to beginning Re-Induction therapy.

∝ See Section 15.2.

Ω Alliance sites only, see Section 15.2b.

£ After off protocol treatment or transplant all indicated assessments will be performed every 3 months for the first year, then every 6 months for the second and third year, then annually until 5 years from initial registration. Additional tests may be performed at the discretion of the treating physician.

9.2 Arm 1 (7+3) – Consolidation

	Pre	Consolidation (1 Cycle) ¶											£
	Tx	D1	D2	D3	D4	D5	D6	D7	Wk2	Wk3	Wk4	Prog	FU
REQUIRED STUDIES													
History & Physical Exam % &	X								X	X	X	X	X
Weight & Performance Status													
Toxicity Notation	X											X	
LABORATORY STUDIES													
CBC, Diff, Platelets &		X								X	X	X	X
Serum Creatinine &		X								X	X		X
Bilirubin &		X								X	X		X
SGOT/SGPT &		X								X	X		X
Disease Assessment/ BM Asp/Bx #												X	X
Cytogenics/FISH												XΩ	
X-RAYS/SCANS													
EKG µ	X												
ECHO or MUGA µ	X												
TREATMENT													
AraC		X		X		X							

After CR or CRi, marrows will be obtained at the discretion of the treating physician for disease assessment.
% Pre-study results do not determine eligibility.
& Weekly, or more often if clinically indicated.
£ After off protocol treatment or transplant all indicated assessments will be performed every 3 months for the first year, then every 6 months for the second and third year, then annually until 5 years from initial registration. Additional tests may be performed at the discretion of the treating physician.
µ Prior to Consolidation treatment, then as indicated.
¶ Up to 4 cycles, or until transplant.
Ω Alliance sites only, see Section 15.2b.

9.3 Arm 2 (IA) – Induction

	Pre	Induction								Re-Induction #									£
	Tx	D1	D2	D3	D4	D5	D6	D7	Wks 2-4	D1	D2	D3	D4	D5	D6	D7	Wks 2-4	Prog	FU
REQUIRED STUDIES																			
History & Physical Exam &	X				X				X				X				X	X	X
Weight & Performance Status	X																		
Toxicity Notation										XΔ								X	
LABORATORY STUDIES																			
CBC, Diff, Platelets &	X				X				X				X				X	X	X
Serum Creatinine % &	X				X				X				X				X		X
Bilirubin % &	X				X				X				X				X		X
SGOT/SGPT % &	X				X				X				X				X		X
CNS Assessment %	X																		
Disease Assessment/ BM Asp/Bx #	X								X								X	X	X
Cytogenetics/FISH ∝	X																	XΩ	
SPECIMEN SUBMISSION																			
Buccal Swabs/Donor Search ƒ					X														
Bone Marrow Aspirate	X																		
Peripheral Blood	X			X															
X-RAYS/SCANS																			
EKG	X																		
ECHO or MUGA	X																		
TREATMENT																			
AraC		X	X	X	X					X	X	X	X						
Idarubicin		X	X	X						X	X	X							

\# If Day 28 (± 3 days) marrow exam shows residual blasts, Re-Induction should be considered starting on Day 29. After CR or CRi, marrows will be obtained at the discretion of the treating physician for disease assessment.

% Prior to starting treatment; baseline measurements do not affect eligibility (see Section 7.1).

& Weekly, or more often if clinically indicated.

ƒ Upon receipt of swab kit; see Sections 15.3 and 18.6.

Δ Prior to beginning Re-Induction therapy.

∝ See Section 15.2.

Ω Alliance sites only, see Section 15.2b.

£ After off protocol treatment or transplant all indicated assessments will be performed every 3 months for the first year, then every 6 months for the second and third year, then annually until 5 years from initial registration. Additional tests may be performed at the discretion of the treating physician.

9.4 Arm 2 (IA) – Consolidation

	Pre	Consolidation (1 Cycle) ¶											£
	Tx	D1	D2	D3	D4	D5	D6	D7	Wk2	Wk3	Wk4	Prog	FU
REQUIRED STUDIES													
History & Physical Exam & %	X								X	X	X	X	X
Weight & Performance Status													
Toxicity Notation	X											X	
LABORATORY STUDIES													
CBC, Diff, Platelets &		X										X	X
Serum Creatinine &		X											X
Bilirubin &		X											X
SGOT/SGPT &		X											X
Disease Assessment/ BM Asp/Bx #												X	X
Cytogenetics/FISH												XΩ	
X-RAYS/SCANS													
EKG µ	X												
ECHO or MUGA µ	X												
TREATMENT													
AraC		X	X	X									
Idarubicin		X	X										

After CR or CRi, marrows will be obtained at the discretion of the treating physician for disease assessment.

% Pre-study results do not determine eligibility.

& Weekly, or more often if clinically indicated.

£ After off protocol treatment or transplant all indicated assessments will be performed every 3 months for the first year, then every 6 months for the second and third year, then annually until 5 years from initial registration. Additional tests may be performed at the discretion of the treating physician.

µ Prior to Consolidation treatment, then as indicated.

¶ Up to 4 cycles, or until transplant.

Ω Alliance sites only, see Section 15.2b.

9.5 Arm 3 (IA+V or IA) – Induction

	Pre	Induction								Re-Induction #									£
	Tx	D1	D2	D3	D4	D5	D6	D7	Wks 2-4	D1	D2	D3	D4	D5	D6	D7	Wks 2-4	Prog	FU
REQUIRED STUDIES																			
History & Physical Exam &	X				X				X				X				X	X	X
Weight & Performance Status	X																		
Toxicity Notation										XΔ								X	
LABORATORY STUDIES																			
CBC, Diff, Platelets &	X				X				X				X				X	X	X
Serum Creatinine % &	X				X				X				X				X		X
Bilirubin % &	X				X				X				X				X		X
SGOT/SGPT % &	X				X				X				X				X		X
CNS Assessment %	X																		
Disease Assessment/ BM Asp/Bx #	X								X								X	X	X
Cytogenetics/FISH ∝	X																	XΩ	
SPECIMEN SUBMISSION																			
Buccal Swabs/Donor Search *ƒ*						X													
Bone Marrow Aspirate	X																		
Peripheral Blood Submission	X			X															
X-RAYS/SCANS																			
EKG	X																		
ECHO or MUGA	X																		
IA + V TREATMENT √																			
Vorinostat		X	X	X						X	X	X							
AraC					X	X	X	X					X	X	X	X			
Idarubicin					X	X	X						X	X	X				
IA TREATMENT √																			
AraC		X	X	X	X					X	X	X	X						
Idarubicin		X	X	X						X	X	X							

\# If Day 28 (± 3 days) marrow exam shows residual blasts, Re-Induction should be considered starting on Day 29. After CR or CRi, marrows will be obtained at the discretion of the treating physician for disease assessment.

% Prior to starting treatment; baseline measurements do not affect eligibility (see Section 7.1).

& Weekly, or more often if clinically indicated.

£ After off protocol treatment or transplant all indicated assessments will be performed every 3 months for the first year, then every 6 months for the second and third year, then annually until 5 years from initial registration. Additional tests may be performed at the discretion of the treating physician.

ƒ Upon receipt of swab kit; see Sections 15.3 and 18.6.

Δ Prior to beginning Re-Induction therapy.

∝ See Section 15.2.

Ω Alliance sites only, see Section 15.2b.

√ Arm 3 was permanently closed to accrual, **effective TBD**. Patients previously randomized to Arm 3 may opt to continue medical treatment with IA or IA + V, and if so, must follow protocol and protocol data submission requirements.

9.6 Arm 3 (IA+V or IA) - Consolidation

	Pre	Consolidation (1 Cycle) ¶											£
	Tx	D1	D2	D3	D4	D5	D6	D7	Wk2	Wk3	Wk4	Prog	FU
REQUIRED STUDIES													
History & Physical Exam & %	X								X	X	X	X	X
Weight & Performance Status													
Toxicity Notation	X											X	
LABORATORY STUDIES													
CBC, Diff, Platelets &		X										X	X
Serum Creatinine &		X											X
Bilirubin &		X											X
SGOT/SGPT &		X											X
Disease Assessment/ BM Asp/Bx #												X	X
Cytogenetics/FISH												XΩ	
X-RAYS/SCANS													
EKG µ	X												
ECHO or MUGA µ	X												
IA + V TREATMENT √													
Idarubicin					X	X							
AraC					X	X	X						
Vorinostat		X	X	X									
IA TREATMENT √													
AraC		X	X	X									
Idarubicin		X	X										

\# After CR or CRi, marrows will be obtained at the discretion of the treating physician for disease assessment.

% Pre-study results do not determine eligibility.

& Weekly during Induction and Consolidation, or more often if clinically indicated.

£ After off protocol treatment or transplant all indicated assessments will be performed every 3 months for the first year, then every 6 months for the second and third year, then annually until 5 years from initial registration. Additional tests may be performed at the discretion of the treating physician.

µ Prior to Consolidation treatment, then as indicated.

¶ Up to 4 cycles, or until transplant.

Ω Alliance sites only, see Section 15.2b.

√ Arm 3 was permanently closed to accrual, **effective TBD**. Patients previously randomized to Arm 3 may opt to continue medical treatment with IA or IA + V, and if so, must follow protocol and protocol data submission requirements.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Remission Definitions

a. Morphologic complete remission (CR): ANC ≥ 1,000/mcl, platelet count ≥ 100,000/mcl, < 5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration).

b. Morphologic complete remission with incomplete blood count recovery (CRi): Same as CR but ANC may be < 1,000/mcl or platelet count < 100,000/mcl.

c. Partial remission (PR): ANC ≥ 1,000/mcl, platelet count > 100,000/mcl, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25%, or marrow blasts < 5% with persistent Auer rods.

10.2 Treatment Failures

Patients who fail to achieve CR, CRi or PR following Induction will be classified according to the type of failure:

a. Resistant Disease: Patient survives ≥ 7 days following completion of initial treatment course and has persistent leukemia in the peripheral blood smear or bone marrow after completion of therapy.

b. Aplasia: Patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow aplastic to hypoplastic (i.e. < 20% cellularity) and without leukemic blasts.

c. Indeterminate:

1. Patient survives < 7 days after completion of initial treatment course.

2. Patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination.

10.3 Relapse from CR or CRi

Reappearance of leukemic blasts in the peripheral blood; or > 5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia); **or** appearance or reappearance of extramedullary disease. If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is > 5% but ≤ 20%, then a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage is > 5% is necessary to establish relapse.

10.4 Event Free Survival (EFS)

EFS is calculated for all patients from the date of initial registration on study until the first of the following events: death from any cause, relapse from remission (CR or CRi) or completion of protocol Induction/Re-Induction therapy without documentation of CR or CRi. Patients last known to be alive and in CR or CRi are censored at the date of last contact.

10.5 Disease Free Survival (DFS)

DFS is calculated for patients who have achieved a CR or CRi. DFS will be measured from the date of CR or CRi until relapse from CR or CRi for death from any cause. Observation is censored at the date of last follow-up for patients last known to be alive without report of relapse.

10.6 Time to Death

Time to death calculated for all patients from date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.7 Performance Status

Patients will be graded according to the Zubrod performance status scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goals

Assuming 10% of registered patients will be ineligible, 784 registered patients will be needed to accrue 705 eligible patients (235 eligible patients per arm).

Based on data from **S0106** (SWOG's most recent trial in this population), it is estimated that 418 patients will need to be registered in order to have 53 patients available for the transplant objective (assuming 10% of registered patients will be ineligible, 27% of eligible patients with be high-risk, and 54% of eligible high-risk patients will achieve CR). Given the estimated accrual rate, it is expected that it will take less than 2.5 years to accrue 418 patients. In contrast to **S0106**, **S1203** allows patients with complete remission with incomplete blood count recovery (CRi) to register to consolidation (**S0106** required patients to be in complete remission [CR] to register for consolidation). Due to this difference, the accrual rate of high-risk patients in CR has been slower than expected based on **S0106** data. Rather than 13% of patients being eligible for the transplant objective (53/418), the observed rate has been approximately 9%. Given the slower than expected accrual to this objective and the desire to have more precise estimates of outcomes after transplant, accrual to this objective will be open for all patients registered to the trial.

If accrual to the randomization associated with the chemotherapy objective (primary objective) is stopped early due to efficacy or futility before 53 eligible patients are registered for the transplant objective (secondary objective), the trial will temporarily suspend accrual while a decision is made by the Study Chairs, the study statistician, CTEP, and the DSMC whether to close the trial or to amend the trial to omit randomization for chemotherapy but continue to accrue patients for the transplant

objective. The decision will take into account the number of patients still needed to reach 53 eligible patients registered for the transplant objective.

11.2 Primary Chemotherapy Objective

The primary goal of this study is to determine whether EFS is improved with IA + vorinostat (IA+V) compared to IA or 7+3 for patients with AML.

EFS estimates from the 7+3 arm of **S0106** (SWOG's most recent trial in this population) indicate that a proportion of patients may be long-term survivors of their disease, in the sense that they will not be observed to fail during the study follow-up. A cure exponential mixture model fit to the 7+3 arm of **S0106** estimated that 35% of patients were long-term survivors and that median EFS for patients who were not long-term survivors was 4.7 months (null). *(19)* This survival model can be written $S(t) = 0.35+0.65*\exp(-\lambda t)$, where $S(t)$ denotes survival at time t and λ is the exponential hazard parameter that corresponds to a median of 4.7 months.

Power and sample size were determined via simulation (5,000 replications) generating survival data from cure exponential mixture models.

IA+V will be considered superior to IA or to 7+3 if EFS is improved with a hazard ratio (HR) of 1.46 from a proportional hazards model (alternative). With a cure exponential model, an HR of 1.46 corresponds to increasing the proportion of long-term survivors from 35% to 45%, and increasing median EFS among patients who are not long-term survivors from 4.7 months to 7.1 months. A 1:1:1 randomization is assumed with 4.5 years of uniform accrual, and an additional year of follow-up after accrual is complete, with administrative censoring at that time. All analyses will be intent-to-treat among eligible patients.

In addition to routine monitoring, five formal interim analyses will be performed. The first two interim analyses will be based on the CR rates. The first analysis will check for harm and the second analysis will test for futility. It is assumed that the null CR rate is 68% (based on 7+3 arm of **S0106**) and the alternative CR rate is 78%. The third, fourth, and fifth interim analyses will be based the HRs comparing 7+3: IA+V and IA: IA+V from a proportional hazards model including covariates for the stratification factors. Interim analyses 3-5 will include both futility and efficacy analyses. The final analysis will also be based on the HRs comparing 7:3 versus IA+V and IA versus IA+V from proportional hazards models including covariates for the stratification factors. For interim and final analyses, two separate regression models will be fit to compare 1) 7:3 versus IA+V and 2) IA versus IA+V.

Up to five interim analyses will be completed. Each interim analysis will test both IA+V versus IA and IA+V versus 7+3. Early termination of an arm or the study will be considered if:

1. Based on the first 60 patients on each arm (about 1 year after trial opens).

    a. If the proportion of CRs with IA+V is observed to be more than 8% less than the proportion of CRs on IA, early termination of the study will be considered.

    b. If the proportion of CRs with 1A+V is observed to be more than 8% less than the proportion of CRs in 7+3, early termination of the study will be considered.

2. Based on the first 100 patients on each arm (about 2 years after trial opens):

   a. if the proportion of CRs with IA+V is observed to be less than the proportion of CRs on IA, early termination of the study will be considered.

   b. if the proportion of CRs with IA+V is observed to be less than the proportion of CRs on 7+3, early termination of the study will be considered.

3. At approximately 40% information (at 61 events on the IA arm, about 2.5 years after trial opens):

   a. if a two-sided test of the alternative hypothesis (HR=1.46) for IA: IA+V is rejected at the 0.05 level (futility test), early termination of the study will be considered.

   b. if a two-sided test of the alternative hypothesis (HR=1.46) for 7+3: IA+V is rejected at the 0.05 level (futility test), early termination of the study will be considered.

   c. if a two-sided test of the null hypothesis (HR=1) for IA: IA+V is rejected at the 0.001 level (efficacy test), early termination of the IA arm will be considered.

   d. if a two-sided test of the null hypothesis (HR=1) for 7+3: IA+V is rejected at the 0.001 level (efficacy test), early termination of the 7+3 arm will be considered.

4. At approximately 60% information (at 91 events on the IA arm, about 3.5 years after the first patient is registered):

   a. if a two-sided test of the alternative hypothesis (HR=1.46) for IA: IA+V is rejected at the 0.02 level (futility test), early termination of the study will be considered.

   b. if a two-sided test of the alternative hypothesis (HR=1.46) for 7+3: IA+V is rejected at the 0.02 level (futility test), early termination of the study will be considered.

   c. if a two-sided test of the null hypothesis (HR=1) for IA: IA+V is rejected at the 0.001 level (efficacy test), early termination of the IA arm will be considered.

   d. if a two-sided test of the null hypothesis (HR=1) for 7+3: IA+V is rejected at the 0.001 level (efficacy test), early termination of the 7+3 arm will be considered.

5. At approximately 80% information (at 121 events on the IA arm, about 4.5 years after the first patient is registered):

   a. if a two-sided test of the alternative hypothesis (HR=1.46) for IA: IA+V is rejected at the 0.02 level (futility test), early termination of the study will be considered.

   b. if a two-sided test of the alternative hypothesis (HR=1.46) for 7+3: IA+V is rejected at the 0.02 level (futility test), early termination of the study will be considered.

c. if a two-sided test of the null hypothesis (HR=1) for IA: IA+V is rejected at the 0.001 level (efficacy test), early termination of the IA arm will be considered.

d. if a two-sided test of the null hypothesis (HR=1) for 7+3: IA+V is rejected at the 0.001 level (efficacy test), early termination of the 7+3 arm will be considered.

The final analysis (at 100% information, 152 events on IA arm, or one year after the last patient is registered) will consist of two two-sided tests of the null hypothesis (HR=1) at the 0.045 level (7+3: IA+V and IA: IA+V).

For the secondary objective of comparing the EFS of 7+3 versus IA, at the time of the final analysis (at 100% information, 152 events on the IA arm, or one year after the last patient is registered), a two-sided test of the hazard ratio of 7:3: IA (versus the null hypothesis of HR =1) will be done using a proportional hazards regression model with the stratification factors included as covariates.

With 235 eligible patients per arm, if IA+V is efficacious (alternative), the probability the trial concludes IA+V is superior to IA is 80%, the probability the trial concludes IA+V is superior to 7+3 is 80%, and the probability the trial concludes IA+V is superior to at least one of IA and 7+3 is 87%.

If IA+V has a CR rate of 78% and IA and 7+3 have CR rates of 68%, but EFS is the same and follows the null in all three arms, the probability the trial will incorrectly conclude that IA+V EFS is superior to IA or to 7+3 is less than 5% (type-1 error) or incorrectly conclude that IA+V EFS is superior to 7+3 is less than 5% (type-1 error).

If IA+V, IA, and 7+3 all follow the null assumptions, the probability the trial will stop early for futility is 97% and the probability the trial will stop for futility within the first two years is 74%.

If there is an interim analysis with at least one significant harm or futility result, the trial will temporarily suspend accrual while a decision is made by the Study Chairs, the study statistician, and the DSMC whether to close the trial or to continue the trial with two arms, IA and 7+3.

If the trial continues with the two arms IA and 7+3, interim monitoring will continue with the following schedule:

1. Based on the first 100 patients on each arm, termination of the study will be considered:

   a. if the proportion of CRs with IA is observed to be less than the proportion of CRs on 7+3.

2. At approximately 40% information (at 61 events on the 7+3 arm), termination of the study will be considered:

   a. if a two-sided test of the alternative hypothesis (HR=1.46) for 7+3: IA is rejected at the 0.05 level (futility test).

   b. if a two-sided test of the null hypothesis (HR=1) for 7+3: IA is rejected at the 0.01 level (efficacy test).

3. At approximately 60% information (at 91 events on the 7+3 arm), termination of the study will be considered:

   a. if a two-sided test of the alternative hypothesis (HR=1.46) for 7+3: IA is rejected at the 0.02 level (futility test).

   b. if a two-sided test of the null hypothesis (HR=1) for 7+3: IA is rejected at the 0.001 level (efficacy test).

4. At approximately 80% information (at 121 events on the 7+3 arm), termination of the study will be considered:

   a. if a two-sided test of the alternative hypothesis (HR=1.46) for 7+3: IA is rejected at the 0.02 level (futility test).

   b. If a two-sided test of the null hypothesis (HR=1) for 7+3: IA is rejected at the 0.01 level (efficacy test)

Additionally, the following will be performed: compare the 1-year, 2-year and 3-year EFS and OS rates between patients who receive standard 7+3 or IA to patients who receive IA + V; compare the complete response rate, DFS, and OS between patients who receive standard 7+3 therapy versus IA; and compare the 1-year, 2-year and 3-year EFS and OS rates between patients who receive standard 7+3 versus IA.

11.3 Transplant Objective

The goal of the transplant objective is to determine whether it is possible to conduct allogeneic HCT on 60% or more of adults with high-risk AML in first complete remission (alternative). If 40% or fewer of high-risk patients in CR can be transplanted, the proposed transplant support system will not be considered feasible (null). A one-sided binomial test compared to the null transplant rate will be conducted.

Fifty-three eligible high-risk patients in CR will provide 89% power for this test with a critical level of 4%

11.4 Translational Medicine Objective

Objectives:

1. To define the prevalence and prognostic implication of known AML-associated mutations.

2. To evaluate the prognostic significance of histone H3 acetylation (measured pre-treatment and at Day 3) among patients treated with vorinostat.

3. To evaluate the prognostic significance of gammaH2Ax (measured pre-treatment and at Day 3).

4. To evaluate the prognostic significance Nrf2 and CYYB mRNA levels (measured pre-treatment and at Day 3).

5. To investigate potential predictive markers based on mRNA and miRNA expression.

6. To investigate potential predictive markers based on DNA methylation.

The total sample size for **S1203** is planned to be 705 eligible patients (235 eligible patients per arm). Given historical specimen submission, it is expected that 90% of eligible patients will provide pre-treatment peripheral blood specimens (n=633 total, 211/arm). Historically SWOG has not requested Day 3 specimens, so all calculations will be conservatively done assuming that specimens will be received from 50% of patients (n=351 total, 117/arm). If more patients have Day 3 specimens available, power for associated analyses will be higher.

Objectives 1-4: Each biomarker will be binary. Overall survival (OS, primary endpoint), event-free survival (EFS), and relapse-free survival (RFS) will be estimated using the Kaplan-Meier method. Univariate associations will be assessed with the log-rank test. Regression modeling will use the Cox model. Associations with complete remission (CR) will be assessed using Fisher's exact test and regression models will use logistic regression. Regression modeling will control for the known pre-treatment prognostic variables including age, performance status, white blood cell count, marrow blasts, cytogenetic risk, and FLT3-ITD and will stratify for treatment arm.

Power calculations are provided for the overall survival endpoint. In the following calculations, it is assumed (based on the most recent SWOG study in this population, **S0106**) that median OS for all patients is 3.4 years. Following the design assumptions of **S1203**, it is assumed that patients will be accrued over a period of 4.5 years and that there will be at least one year of follow-up on all patients. Calculations are done assuming a one-sided test with a significance level of 0.05. Calculations for each objective are outlined below.

Objective 1: Calculations done for each gene. For each gene patients will be classified as mutant (mut) or wild-type (WT). All genes will be tested in all patients with samples. Prevalence for each gene can be estimated within +/- 4%. Historical prevalences are assumed for power calculations. It is assumed that 633 patients will have pretreatment samples available and provide power for one-sided tests.

- **NPM1**: Calculations assume 25% prevalence. If median OS is 3.1 years in the NPM1-WT cohort, this project will have 90% power to detect an improvement in OS to 4.7 years in the NPM-mut cohort (corresponds to a hazard ratio [mut/WT] of 1.52).

- **IDH1/2:** Calculations assume 10% prevalence. If median OS is 2.1 years in the IDH1/2-mut cohort, this project will have 91% power to detect an improvement in OS to 3.6 years in the IDH1-WT cohort (corresponds to a hazard ratio [WT/mut] of 1.71)
- **TET2:** Calculations assume 8% prevalence. If median OS is 2.1 years in the TET2-mut cohort, this project will have 91% power to detect an improvement in OS to 3.58 years in the TET2-WT cohort (corresponds to a hazard ratio [WT/mut] of 1.7).

- **DNMT3A:** Calculations assume 20% prevalence. If median OS is 2.5 years in the TET2-mut cohort, this project will have 90% power to detect an improvement in OS to 3.7 years in the TET2-WT cohort (corresponds to a hazard ratio [WT/mut] of 1.48).

Objective 2: Tests of histone H3 acetylation will only be done on patients on the vorinostat arm. The biomarker will be binary (yes/no). To be conservative, the study assumes that 211 patients will have pre-treatment samples and 117 patients will have Day 3 samples. If more patients have Day 3 samples available, power for associated analyses will be higher.

At pre-treatment, if 25% of patients have histone H3 acetylation, and median OS is 2.95 years among patients without histone H3 acetylation, this project will have 80% power to detect an improvement in OS to 5.6 years in the cohort with histone H3 acetylation (corresponds to a hazard ratio [yes/no] of 1.9).

At Day 3, if 50% of patients have histone H3 acetylation, and median OS is 2.3 years among patients without histone H3 acetylation, this project will have 91% power to detect an improvement in OS to 5.25 years in the cohort with histone H3 acetylation (corresponds to a hazard ratio [yes/no] of 2.28).

An exploratory analysis will be done on patients with both pretreatment and Day 3 samples (assume 117 patients will have both). OS will be estimated among the possible four groups of patients based on combinations of histone H3 acetylation at each time point (yes/yes, no/no, yes/no, no/yes).

Objectives 3 and 4: Tests of gammaH2Ax, Nrf2, and CYYB will be done all patients. The biomarkers will be categorized into high versus low based on the observed median value of the data set. The study assumes that 633 patients will have pre-treatment samples and 351 patients will have Day 3 samples. One set power calculations is done assuming the same characteristics for each biomarker.

At pre-treatment, if 25% of patients have low levels of the biomarker, and median OS is 3.15 years among patients with low biomarker levels, this project will have 81% power to detect an improvement in OS to 4.5 years in the cohort with high biomarker levels (corresponds to a hazard ratio [high/low] of 1.42).

At Day 3, if 50% of patients have low levels of the biomarker, and median OS is 2.75 years among patients with low biomarker levels, this project will have 90% power to detect an improvement in OS to 4.3 years in the cohort with high biomarker levels (corresponds to a hazard ratio [high/low] of 1.56).

An exploratory analysis will be done on patients with both pretreatment and Day 3 samples (assume 351 patients will have both). OS will be estimated among the possible four groups of patients based on combinations of each biomarker at each time point (high/high, low/low, high/low, low/high).

Objectives 5 and 6: Will use bioinformatics personnel and algorithms from the SAGE group based at FHCRC to build prediction models. The models will be provided to a SWOG Leukemia Committee statistician to apply to validation data.

11.5 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

In addition to the above DSMC review, toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician, and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

Cytogenetics/FISH Review

All patients registered to this study will undergo central cytogenetics/FISH review by the SWOG Leukemia Cytogenetics Committee. The purpose of this review is to verify the cytogenetic diagnosis of acute myeloid leukemia and determination of risk status. Diagnostic karyograms, FISH images and local cytogenetics and FISH reports and the **S1203 Mutational Analysis and Cytogenetics Report Form** (see Section 15.2) must be submitted within 28 days after registration via MediData Rave® (see Section 14.3). Failure to submit these items will make the patient ineligible.

Karyogram/FISH images (.ppt/.pptx, gif or .jpeg files) will be submitted as follows:

- if only normal cells are present: submit two karyograms of the normal
- if an abnormal clone is present: submit two karyograms of each abnormal clone
- if a mixture of normal and abnormal clonal cells is present: only two karyograms representing each abnormal clone need to be submitted
- If any non-clonal abnormalities (except random loss) are present: submit one karyogram of each non-clonal cell

Institutional cytogenetics and FISH reports must be of diagnostic/pre-treatment bone marrow. Cytogenetics/FISH studies from peripheral blood will be accepted ONLY if marrow aspirations were dry tap.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than one working day prior to planned start of treatment).

NOTE: If a patient was assigned a SWOG patient ID prior to registration, that patient ID must be used at the time of study registration. For questions about entering a previously assigned patient ID please contact the SWOG Data Operations Center at 206/652-2267.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

1. Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1203** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Click on the SWOG link to expand, then select **S1203**. Click on the Site Registration Documents link.

2. Requirements for **S1203** Site Registration:

   - CTSU IRB Certification (for sites not participating via the NCI CIRB)
   - CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

   Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

   CTSU Regulatory Office
   1818 Market Street, Suite 1100
   Philadelphia, PA 19103
   Phone: 1-866-651-2878
   Fax: 215-569-0206
   E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4. Checking Your Site's Registration Status:

   Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)
   - Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   - Click on the Regulatory tab at the top of your screen
   - Click on the Site Registration tab
   - Enter your 5-character CTEP Institution Code and click on Go

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

  1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

  2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG Registration Policies will Not be Permitted

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, regardless of Group affiliation, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table on Page 3.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS AFTER INITIAL REGISTRATION (STEP 1)

Submit the following:

Onstudy Form

Pathology Report

Radiology reports from all scans performed to assess disease at baseline

See Section 15.0 for specimen submission requirements.

b. WITHIN 28 DAYS AFTER INITIAL REGISTRATION (STEP 1)

Submit the following:

Institutional Cytogenetics and FISH Reports from lab

Karyogram Images

Mutational Analysis and Cytogenetic Report Form

c. WITHIN 14 DAYS AFTER COMPLETION OF INDUCTION, RE-INDUCTION AND EACH CYCLE OF CONSOLIDATION TREATMENT

Submit the following:

S1203 Treatment Form

S1203 Adverse Event Summary Form

d. WITHIN 14 DAYS AFTER EACH RESPONSE ASSESSMENT

Submit the following:

AML Disease Assessment Form documenting results from the assessment

Pathology Report

If bone marrow is performed; bone marrow report, flow cytometric report and cytogenetic report, as applicable.

e. WITHIN 14 DAYS AFTER GOING OFF INDUCTION/RE-INDUCTION TREATMENT

Submit the Off Treatment Notice indicating off treatment for Step 1

f. (HIGH RISK PATIENTS) EVERY 3 MONTHS FOR THE FIRST YEAR OR UNTIL TRANSPLANT

1. Submit the **S1203** High Risk Transplant Form if HTC performed and not previously reported.

   OR

2. Submit the **S1203** High Risk Follow-Up Form if HTC not performed but may be done in the future.

g. WITHIN 14 DAYS AFTER REGISTRATION FOR CONSOLIDATION (STEP 2)

Submit the **S1203** Consolidation Eligibility Form

h. WITHIN 14 DAYS AFTER GOING OFF CONSOLIDATION TREATMENT

Submit the Off Treatment Notice indicating off treatment for Step 2

i. WITHIN 14 DAYS AFTER PROGRESSION/RELAPSE

Submit the AML Disease Assessment Form (if the patient was still on protocol treatment) or Leukemia Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

j. EVERY 3 MONTHS FOR THE FIRST YEAR, EVERY 6 MONTHS FOR THE SECOND AND THIRD YEARS, THEN ANNUALLY UNTIL FIVE YEARS FROM THE INITIAL REGISTRATION

Submit the following:

Follow-Up Form

Leukemia Late Effects Form (if prior to treatment for progression or relapse or a second primary and prior to non-protocol treatment, the patient experiences any severe [≥ Grade 3] long-term toxicity that has not previously been reported)

k. WITHIN 4 WEEKS AFTER KNOWLEDGE OF DEATH

Submit the Notice of Death **and a final S1203** Treatment Form and **S1203** Adverse Event Summary Form (if the patient was still on protocol treatment) or Leukemia Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

Specimen Submission Overview

	SWOG (and other Groups not affiliated with ECOG-ACRIN or Alliance)	**ECOG-ACRIN**	**Alliance**
Translational Medicine	via SWOG to Lab #200 (Section 15.1)	via SWOG to Lab #200 (Section 15.1)	via SWOG to Lab #200 (Section 15.1) AND *Prior to 1/15/*14: CALGB 20202 (Section 15.5b) *As of 3/1/14*: Temporarily Closed
Cytogenetic	Local CLIA-approved laboratory (Section 15.2)	Local CLIA-approved laboratory (Section 15.2)	*Prior to 7/1/14* CALGB-8461 (Section 15.2b) *As of 7/1/14* Local CLIA-approved laboratory (Section 15.2)
HLA Typing	CIBMTR (Section 15.3)	CIBMTR (Section 15.3)	CIBMTR (Section 15.3)
Banking	via SWOG to Lab #200 (Section 15.2)	*Prior to 1/15/14*: E3903 (Section 15.4) *As of 1/15/14:* via SWOG to Lab #200 (Section 15.2)	*Prior to 3/1/14*: CALGB 9665 (Section 15.5c) *As of 3/1/14*: CALGB 9665 Temporarily Closed; submit via SWOG to Lab #200 (Section 15.2)

All sites, regardless of Group affiliation, **must** submit specimens for protocol-specific translational medicine as outlined in Section 15.1 and for cytogenetic risk analysis as outlined in Section 15.2. Because these specimens are being used to meet protocol objectives (See Sections 1.1b, 1.2f and 1.3h), **these submissions are to be prioritized over Group-specific additional correlative specimen submissions** outlined in Sections 15.4 and 15.5.

15.1 Correlative Studies and Banking (REQUIRED FOR ALL GROUPS)

Specimens for correlative studies must be submitted to the SWOG Specimen Repository – Leukemia Division, Lab #200. (Required) Indicated correlative studies to be performed when funding is finalized.

a. Specimens (peripheral blood and bone marrow aspirate) must be submitted at the following times (see Section 9.0):

1. Peripheral blood

a. Pretreatment (within 28 days prior to registration)

b. After treatment on Day 3*

* If day 3 peripheral blood draw falls on a weekend or holiday making overnight shipment impossible, blood should be held in a refrigerator (4°C) until specimen can be shipped. Blood should be stored in purple top EDTA tubes or in the institution's prepared shipping media tubes. Proper storage conditions ensure specimen viability when shipment will be delayed. Reminder: Specimens can be received by the repository on Saturdays.

2. Bone marrow aspirate

a. Pretreatment (within 28 days prior to registration)*

* If the pre-treatment/diagnostic bone marrow aspiration is a dry tap, then an additional 25 ml of blood can be submitted in place of bone marrow aspirate. If there is not enough bone marrow remaining after diagnostic testing to submit marrow, or the pre-treatment/diagnostic bone marrow is not available for submission for any other reason, and if the peripheral blood absolute blast count is ≥ 1,000 blasts per microliter, then an additional 25 ml of peripheral blood can be submitted in place of a repeat bone marrow aspirate.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://swog.org/members/clinicaltrials/specimens/LeuSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. Residual specimens will be banked at the repository for future research only with patient consent.

NOTE: In instances when a pre-treatment specimen must be submitted before the patient is consented to **S1203**, sites may consent patients to specimen submission only using local IRB approved specimen submission consent forms. For sites that do not have local specimen submission consents, a template has been included in Appendix 18.9. Please note the requirement in the consent instructions for sites to obtain a SWOG patient ID from the Data Operations Center (206/652-2267) to be used on the specimen label.

15.2 Cytogenetics and FISH (REQUIRED FOR ALL PATIENTS)

Specimens for cytogenetic (and FISH if possible) analysis must be submitted to the site's preferred local CLIA-approved laboratory, regardless of Group affiliation. (Required)

a. Diagnostic/pre-treatment specimens (bone marrow aspirate, or peripheral blood if dry tap) obtained within 28 days prior to registration must be submitted for cytogenetic (and FISH if possible) analysis. Use of SWOG approved laboratories is encouraged, but not mandatory.

b. Specimen collection and submission instructions and a list of approved laboratories can be accessed on the SWOG Cytogenetics webpage (www.swog.org/Members/ClinicalTrials/Specimens/Cytogenetics.asp).

c. The **S1203** Cytogenetics Lab Report Form must be submitted to the laboratory along with the specimen. The laboratory will then return the completed form with the results. The lab will also need to send .ppt/.pptx, .gif or .jpeg files of the karyograms for the institution. E-mail contact information for the Data Manager must be provided to the lab performing the cytogenetics studies. The Institution will complete the Mutational Analysis and Cytogenetics Report Form Medidata Rave® using the information and ppt/pptx/jpeg/gif files provided by the lab.

NOTE: Only abnormal FISH results should have images submitted; submission of normal FISH images is not necessary.

15.3 Buccal Swab for Transplant Donor Identification (REQUIRED FOR ALL PATIENTS)

Buccal swab specimens for use in HLA typing for donor identification must be submitted to the Center for International Blood and Marrow Transplant Research (CIBMTR). (Required)

a. Specimens (buccal swabs) must be collected at the time of registration (as soon as specimen collection kit is received) for every patient enrolled and submitted per the instructions provided in the specimen collection kit **within 14 days after kit receipt**. A shipping label will be provided as part of the kit.

b. Specimens collection kits are provided for this submission. The SWOG Transplant Investigator will be notified at the time of patient registration, and will prompt the CIBMTR to ship kits directly to the registering site. Kits will consist of 4 cotton swabs, label set for the swabs, collection/submission instructions, unrelated donor search request form (capturing information required to optimize the search process including weight, sex, race/ethnicity and birth month/year) and a postage paid envelope to ship the specimens to CIBMTR. Specimens should be submitted at the time of collection per the provided instructions. For a detailed description of the transplant donor search process, see Appendix 18.6.

c. Residual specimens and specimens from patients who are not determined to have high risk disease will be destroyed.

NOTE: This specimen submission will NOT utilize the SWOG Specimen Tracking System.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent (hereinafter referred to as "Agent"), vorinostat, used in this protocol is provided to the NCI under a Clinical Trials Agreement (CTA) between Merck (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_proeprty) contained within the terms of award apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to the Collaborator and should be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agent, each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP option Collaborator

(http://ctep.cancer.gov/industryCollaborations2/intellectual_proeprty.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to the Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to the Collaborator for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentation must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator. No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines describe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.
When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1 or 16.2, as applicable.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in Arm 3 of this study is vorinostat. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Vorinostat (Arm 3)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP-IND:**

1) **Group-specific instructions.**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

2) For this study, the adverse events listed below do **not** require expedited reporting via CTEP-AERS:

- ≤ Grade 4 myelosuppression
- ≤ Grade 4 fatigue
- ≤ Grade 4 infection

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used in this study are AraC, daunorubicin and idarubicin. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210-614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on this study who have received only the commercial drugs listed in 16.1g above within 30 days of the last administration of the commercial agent(s).

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. Reporting Secondary Malignancies, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/dosc/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

    - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
    - (if available) a copy of the cytogenetics report

    SWOG
    ATTN: SAE Program
    4201 Medical Drive, Suite 250
    San Antonio, Texas 78229

    NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (This *includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration*:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

18.2 New York Heart Association Classifications

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.3 Intake Calendar

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: _____ **Year:** _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

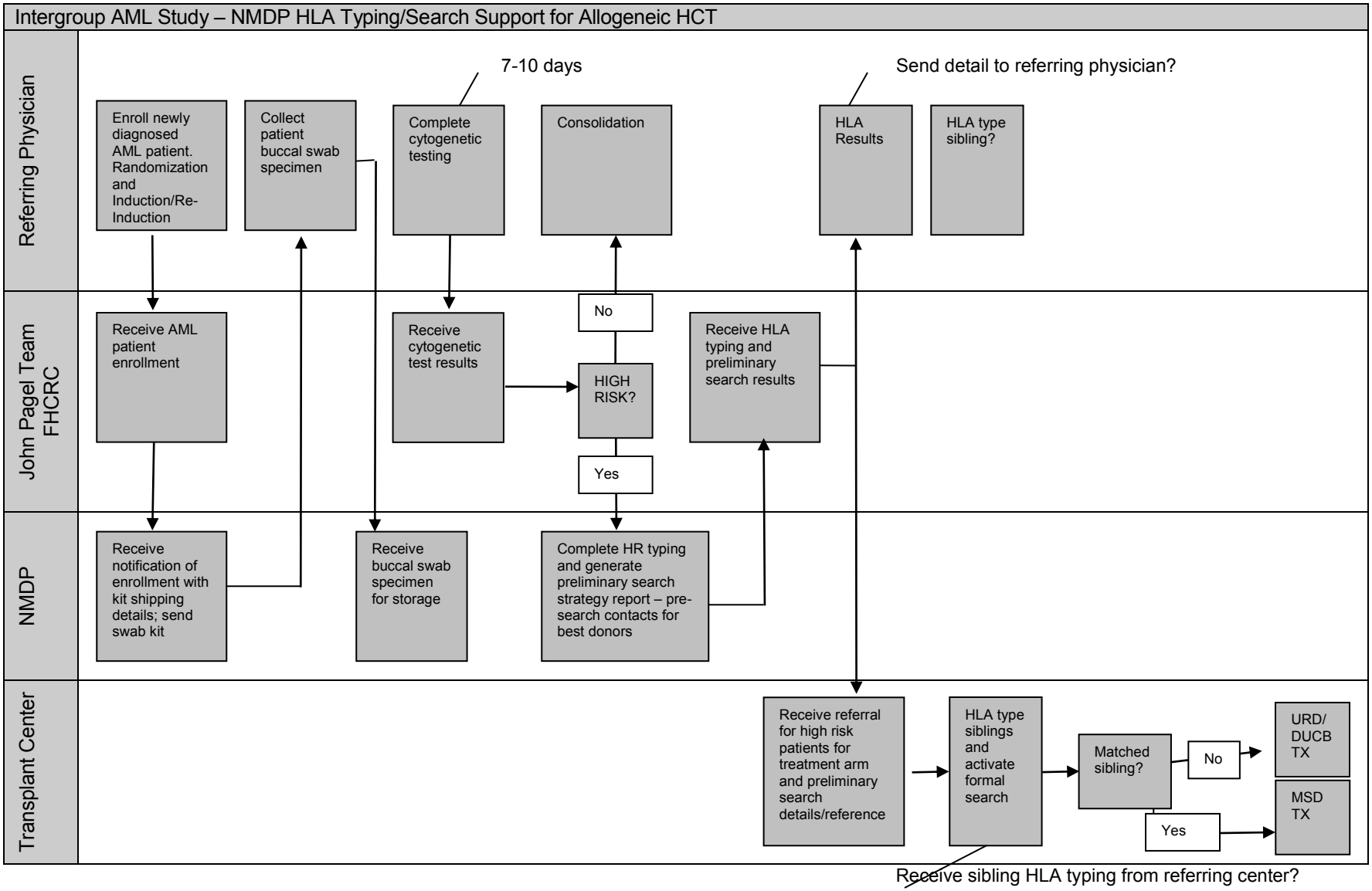
Patient Signature:_____

18.4 Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI)

Comorbidity	Definition/compartments	Yes	Score
1. Arrhythmia	-Atrial fibrillation* -Atrial flutter* -Sick sinus syndrome* -Ventricular arrhythmia	☐ ☐ ☐ ☐	1
2. Cardiovascular	-Coronary artery disease* -Congestive heart failure* -Myocardial infarction* -Ejection fraction ≤ 50% £	☐ ☐ ☐ ☐	1
3. Inflammatory bowel disease	-Crohn's disease* -Ulcerative colitis	☐ ☐	1
4. Diabetes	-Treated with insulin or hypoglycemic drugs*	→	1
5. Cerebro-vascular	-Transient ischemic attacks* -Cerebro-vascular ischemic or hemorrhagic stroke*	☐ ☐	1
6. Depression/anxiety	-Requiring psychological consult and/or specific treatment £	→	1
7. Hepatic – mild	-Chronic hepatitis £ -Bilirubin > ULN – 1.5 x ULN £ -AST/ALT > ULN – 2.5 x ULN £	☐ ☐ ☐	1
8. Obesity	-Body mass index > 35 (adults) £ -Body mass index – for age ≥ 95% percentile (children) £	☐ ☐	1
9. Infection	-Requiring anti-microbial treatment before, during and after the start of conditioning regimen £	→	1
10. Rheumatologic	-Required treatment*	→	2
11. Peptic ulcer	-Confirmed by endoscopy and required treatment*	→	2
12. Renal	-Serum creatinine > 2 mg/dl (or > 177 mcmol/L) £ -On dialysis -Prior renal transplantation	☐ ☐ ☐	2
13. Pulmonary – Moderate	-DLco corrected for hemoglobin 66-80 % of predicted £ -FEV_1 66-80% of predicted £ -Dyspnea on slight activity £	☐ ☐ ☐	2
14. Pulmonary – Severe	-DLco corrected for hemoglobin ≤ 65% of predicted £ -FEV_1 ≤ 65% of predicted £ -Dyspnea at rest or requiring oxygen therapy £	☐ ☐ ☐	3
15. Heart valve disease	-Exept asymptomatic mitral valve prolapse £	→	3
16. Prior solid malignancy	-Treated with surgery, chemotherapy, and/or radiotherapy excluding non-melanoma skin cancer*	→	3
17. Hepatic – moderate/severe	-Liver cirrhosis £ -Bilirubin > 1.5 x ULN £ -AST/ALT > 2.5 x ULN £	☐ ☐	3
		Total score	

*Diagnosed at any time in the patient's past history
£Detected at the time of pre-transplant assessment
ULN indicates upper limit of normal; DLco, diffusion capacity of carbon monoxide; FEV_1, forced expiratory volume in one second; AST, Aspartate aminotransferase; and ALT, alanine aminotransferase

18.5 AML Transplant Study Flowchart



18.6 Transplant Donor Search Process

A primary objective of this protocol is to facilitate the matching of unrelated donors to high-risk patients (by cytogenetics) for transplant at first complete remission. To achieve this, SWOG has teamed with the Center for Blood and Marrow Transplant and Research (CIBMTR), OneMatch stem cell and marrow network (OneMatch) and Héma-Québec and developed an unrelated donor search process that will be utilized for this study.

a. The SWOG Data Operations Office will notify the SWOG Transplant Investigator, Study Chair and CIBMTR of new enrollments weekly. The notification will include the physician name, e-mail address, telephone number (and alternate contact person with corresponding e-mail address if available), shipping address for the registering institution and the patient's SWOG ID. The Transplant Investigator will follow up with CIBMTR to ensure the registration notification was received.

b. Upon notification of enrollment, CIBMTR will send a buccal swab collection kit with specimen collection and shipping instructions to the contact person listed for the registering institution.

c. The physician/CRA will collect the patient buccal swab specimen, complete the patient unrelated donor search request form (capturing information required to optimize the search process including weight, sex, race/ethnicity and birth month/year) and return it to CIBMTR using the pre-printed shipping label, per the provided instructions within 14 days after of kit receipt.

d. Institutions are required to submit local cytogenetics and FISH reports and the **S1203** Cytogenetics Report Form via MediDataRAVE® within 28 days after initial registration. Upon receipt, the SWOG Data Operations Center will notify the SWOG Transplant Investigator of the patient's risk status.

e. Institutions are required to submit AML Disease Assessment Form documenting results from the each response assessment within 14 days of the assessment. Upon receipt of an assessment documenting complete response (CR), the SWOG Data Operations Center will notify the SWOG Transplant Investigator.

f. Upon notification of a patient's CR, the SWOG Transplant Investigator will compare to determine whether the patient was reported as high-risk. If the patient's risk status has not been reported, the Transplant Investigator will contact the site to request that the necessary documentation be submitted in an expeditious manner.

g. The SWOG Transplant Investigator will notify CIBMTR when a patient is designated as high-risk and CIBMTR will initiate patient HLA typing. Upon completion of HLA typing, CIBMTR will conduct an unrelated donor/cord blood search and produce a search strategy report. For Canadian sites participating via NCIC CTG, CIBMTR will forward the necessary search information to OneMatch (for non-Québec sites) or to Héma-Québec (for Québec sites) and OneMatch/Héma-Québec will perform the donor search and produce the search strategy report. The patient HLA typing and search strategy report will be submitted to the SWOG Transplant Investigator within two weeks of initiation of patient HLA typing.

h. When a patient that achieves CR is also high-risk, the Transplant Investigator will contact the site to determine if a sibling donor has already been identified and will provide a copy of the patient HLA typing and CIBMTR/OneMatch/Héma-Québec unrelated donor search strategy report. The subsequent transplant plan will be at the discretion of the treating site.

Note: The Study Chair will act as primary backup to the Transplant Investigator upon request during the donor search process.

18.7 ECOG-ACRIN Ancillary Study – NO SUBMISSIONS AFTER 1/29/14

As of January 29, 2014 ECOG-ACRIN patients under consideration for S1203 are NOT to be registered to E3903 and no specimens are to be submitted to the ECOG Leukemia Translational Studies Laboratory (LTSL) from patients participating in S1203. Instructions below are retained for archival information only.

The following instructions are specific to additional specimens submitted for ECOG-ACRIN patients.

All ECOG-ACRIN patients must be registered to **E3903**, *Ancillary Laboratory Protocol for the Collection of Diagnostic Material on Patients Considered for ECOG Treatment Trials for Leukemia or Related Hematologic Disorders.* Pretreatment specimens must be collected and submitted to the ECOG-ACRIN Leukemia Translational Studies Laboratory (LTSL) within 28 days prior to registration to SWOG **S1203**.

NOTE: Copies of the patient's signed **E3903** consent, **S1203** consent and signed authorization must be submitted to the Leukemia Translational Studies Laboratory (LTSL) prior to or with the pre-treatment sample submissions on the respective trial.

a. Mandatory Specimens

The following specimens must be submitted for all ECOG-ACRIN patients at pretreatment (within 28 days prior to registration):

1. Peripheral Blood (Heparinized)

2. Bone Marrow Aspirate (Heparinized and smear)

b. Optional Specimens

The following specimens must be submitted for patients answering YES to the question *My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.*

1. Buccal cells (mouthwash) at pretreatment (within 28 days prior to registration) via **E3903**

2. Peripheral blood (in red top tubes) at pre-treatment (within 28 days prior to registration) via **E3903**

3. Peripheral Blood (Heparinized) at

- Time of Outcome Following Induction (Prior to Consolidation)
- End of Consolidation, if applicable
- Relapse

4. Bone Marrow Aspirate (Heparinized and smear) at

- Time of Outcome Following Induction (Prior to Consolidation)
- End of Consolidation, if applicable
- Relapse

All specimens submitted to the ECOG LTSL must be logged into the ECOG Sample Tracking System (ECOG-STS) and a shipping manifest generated by this system is to accompany all submissions. See Appendix 18.7 for additional specimen preparation and shipping and ECOG-STS instructions.

c. Specimen Preparation

1. Bone marrow aspirate: Heparinized (10 units heparin/ml), two (2) 4-5mL tubes

Note: For patients with an inaspirable bone marrow ("dry tap") call Dr. Paietta's laboratory at (718) 920-9992 to discuss the case and the possibility for submitting peripheral blood only. Be prepared to report the WBC

2. Peripheral blood: Heparinized (green top tubes) 30-40 cc

3. One air dried bone marrow smear must be submitted

NOTE: Additionally, prior to treatment buccal cells (mouthwash) and peripheral blood collected in a red top tube are requested on **E3903** from consenting patients. Buccal cells submitted on **E3903** will NOT be used for HLA typing and do not replace the submission requirements outlined in Section 15.3

d. Shipping of specimens to LTSL

The bone marrow and peripheral blood must be sent fresh (on the day of collection) **on cool packs,** packaging so that samples DO NOT FREEZE by wrapping them at least in bubble wrap. 24 hours prior to arrival of the samples at the LTSL, the following must be done:

- If the ECOG – STS is unavailable, The Leukemia Translational Studies Laboratory **must** be notified by telephone. **Fax is not acceptable**.

Phone: (718) 920-9992 Beeper (off hours): (917) 729-7231

If you want to notify the laboratory of a sample submission during off hours, please leave a message on the laboratory's answering machine (718-920-9992). Page Dr. Paietta at the beeper number above only if there are questions regarding the sample submission.

- Ship by overnight courier (preferably Federal Express) to arrive within 24 hours to:

  Elisabeth Paietta, Ph.D.
  Montefiore Medical Center - North Campus
  600 East 233rd Street
  6th Floor, Immunology Laboratory
  Bronx, NY 10466-2697
  Tel: (718) 920-9992

  The laboratory is open to receive shipments Monday through Saturday. Shipments on Fridays for Saturday delivery must have "Saturday Delivery" marked on the overnight courier slip.

  If you have questions, contact the Leukemia Translational Studies Laboratory (718) 920-9992.

  The LSTL will forward specimens for the protocol-defined studies per protocol requirements.

e. ECOG Sample Tracking System (ECOG-STS)

It is required that all samples submitted on this trial be entered and tracked using the ECOG Sample Tracking System (ECOG-STS). The software will allow the use of either 1) an ECOG user-name and password previously assigned (for those already using ECOG-STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Any case reimbursements associated with specimen submissions will not be credited if specimens are not logged into ECOG-STS. Additionally, please note that the ECOG-STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link:
http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An ECOG-STS generated shipping manifest should be shipped with all specimen submissions.

Please direct questions or comments pertaining to the ECOG-STS to ecog.tst@jimmy.harvard.edu

ECOG Generic Specimen Submission Form (#2981v2) will be required only if STS is unavailable at time of sample submission. Notify the laboratory of the shipment as outlined above. Indicate the appropriate Lab ID# on the submission form:

- 0003 = Leukemia Translational Studies Laboratory (LTSL)

Retroactively enter all specimen collection and shipping information when ECOG-STS is available.

18.8 Alliance Ancillary Studies – NO SUBMISSIONS AFTER 2/28/14

As of February 28, 2014, CALGB 20202 and CALGB 9665 have been Temporarily Closed. Patients already enrolled on these studies should continue to submit specimens as outlined below. Instructions below are retained for archival information only.

As of 7/1/14, CALGB 8461 will no longer accrue patients from S1203. Patients already enrolled in this study should continue to submit specimens as outlined in Section 18.8f.

NOTE: Patients already enrolled on these ancillaries should continue to submit specimens as outlined in each study.

a. Registration to Ancillary Studies

In addition to the **CALGB 8461** cytogenetics correlative registration (see Section 15.2a), Alliance institutions participating in **S1203** are required to register patients to **CALGB 20202** (see Section 15.5b). All patients must also be offered participation in **CALGB 9665**, the Alliance specimen repository (see Section 15.5c); it is highly recommended that patients enroll on **CALGB 9665**.

Patient registration to **CALGB 9665** and **CALGB 20202**, should take place using OPEN, and will occur separately from registration to **S1203**.

b. Specimens for the assessment of novel molecular markers in AML (**CALGB 20202**) (Temporarily Closed 2/28/14):

As of February 28, 2014, CALGB 20202 has been Temporarily Closed, so Alliance patients under consideration for S1203 are NOT to be registered to CALGB 20202 and no specimens are to be submitted via this ancillary study. Patients already enrolled on CALGB 20202 should continue to submit specimens as outlined below.

Alliance institutions participating in **S1203** are required to consent and enroll patients on **CALGB 20202**. A marrow aspirate, peripheral blood sample, buccal cell sample, and bone marrow biopsy slides are required at the following intervals:

1. At diagnosis;

2. At complete remission (bone marrow aspirate and blood sample only);

3. At relapse (bone marrow aspirate and blood sample only).

Follow specimen collection and submission instructions as outlined in **CALGB 20202** and Appendix 18.8.

c. Specimens for banking (submitted to the Alliance Hematologic Malignancy Biorepository via **CALGB 9665**) (Temporarily Closed 2/28/14):

As of February 28, 2014, CALGB 9665 has been Temporarily Closed, so Alliance patients under consideration for S1203 are NOT to be registered to CALGB 9665 and no specimens are to be submitted via this ancillary study. Patients already enrolled on CALGB 9665 should continue to submit specimens as outlined below.

Alliance institutions participating in **S1203** must offer all patients the opportunity to take part in **CALGB 9665**; it is highly recommended that patients take part in **CALGB 9665**. For consenting patients, a marrow aspirate, whole blood sample, and buccal cell sample must be submitted at the following intervals:

1. At diagnosis;

2. At complete remission (bone marrow aspirate and blood sample only);

3. At relapse (bone marrow aspirate and blood sample only)

Follow specimen collection and submission instructions as outlined in **CALGB 9665** and Appendix 18.8.

NOTE: The buccal cell samples for Sections 15.5b and 15.5c should be obtained from each patient by rinsing with 10 mL of mouth wash for 30 to 60 seconds, and then spitting the mouth wash back into a 50 mL sterile tube. This buccal cell sample is in addition to the buccal swab that is

d. **CALGB 20202**

All specimens must be logged and shipped using the Biospecimen Management System (BioMS). All submitted specimens must be labeled with the protocol number (**CALGB 20202**), CALGB patient ID, patient's initials, date and time of specimen collection and type of specimen collected (e.g., whole blood, bone marrow aspirate, etc.).

All specimens must be shipped on the same day they are obtained. Please be sure to use a method of shipping that is secure and traceable. Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If sampling on Friday, check Saturday delivery on the Federal Express invoice.

Ship specimens along with the shipment manifest produced by BioMS to the following address:

Michael Caligiuri, M.D.
Attn.: CALGB 20202 Sample
Alliance Hematologic Malignancy Biorepository
The Arthur G. James Cancer Hospital and
Richard J. Solove Research Institute
300 W. 10th Avenue, Lobby
Columbus, OH 43210
Phone: 614/688-4754
Fax: 614/688-4755

If holiday schedule prevents same day shipment, please contact the Alliance Hematologic Malignancy Biorepository for instructions at 614/292-5888.

e. **CALGB 9665** (for consenting patients)

All specimens must be logged and shipped using the Biospecimen Management System (BioMS). All submitted specimens must be labeled with the protocol number (**CALGB 9665**), CALGB patient ID, patient's initials, date and time of specimen collection, and type of specimen collected (e.g., whole blood, bone marrow aspirate, etc.).

Samples must be shipped on the same day they are obtained. If holiday schedules prevent same day shipment, please contact the Alliance Hematologic Malignancy Biorepository Lab Supervisor at 614/292-5888 for sample shipment instructions. Send bone marrow, blood and buccal cell sample along with the shipment manifest produced by BioMS at ambient temperatures, any day of the week, via overnight carrier for next day **(check AM)** delivery to:

Michael A. Caligiuri, M.D.
Alliance Hematologic Malignancy Biorepository
The Arthur G. James Cancer Hospital and Research Institute
300 W. 10th Avenue, Lobby
Columbus, OH 43210
Phone: 614/688-4754
Fax: 614/688-4755

Note: If specimen is sent on Friday, CHECK SATURDAY DELIVERY on the FEDERAL EXPRESS INVOICE.

f. **CALGB 8461** (for patients enrolled prior to 7/1/14)

Alliance institutions participating in **S1203** are required to consent and enroll patients on **CALGB 8461** using OPEN (Oncology Patient Enrollment Network) in order to enroll on **S1203**. Specimens must be submitted to an Alliance-approved institutional cytogeneticist. Patient registration to **CALGB 8461** occurs separately from registration to **S1203**.

A bone marrow aspirate and/or peripheral blood sample are required at the following intervals:

1. At diagnosis;

2. At complete remission, if diagnostic specimen is abnormal (bone marrow aspirate sample only);

3. At relapse.

Follow specimen collection and submission instructions as outlined in **CALGB 8461** and below. Alliance institutions are required to submit both of the following forms along with the specimen to an Alliance-approved cytogeneticist.

1. **CALGB 8461** Form C-030 (see **CALGB 8461** protocol document).

2. **S1203** Cytogenetics Lab Report Form (see Sections 12.0 and 15.2.a).

The cytogenetics laboratory will then return the completed **S1203** Cytogenetics Lab Report Form and images to the Data Manager at the institution. The institution will then complete and submit the **S1203** Mutational Analysis and Cytogenetics Report Form via Medidata RAVE using the information and pdf/jpeg/gif files provided by the lab (see Section 15.2.a). The Alliance Cytogenetic Office will not facilitate any data submission in Medidata RAVE for the SWOG Leukemia Cytogenetics Committee; please direct all inquiries to the SWOG Protocol Coordinator

NOTE: Institutions must have either an Alliance-approved cytogeneticist or an agreement from a Alliance-approved main member cytogenetics laboratory to enroll a patient on **CALGB 8461**. See the list of Alliance-approved institutional cytogeneticists under the "Studies" tab of the CALGB website. Contact the Alliance Cytogenetic Office at 614/292-2088 for questions regarding Alliance-approved cytogeneticists.

Specimen Shipment

Each sample should be submitted to the institution's Alliance-approved Cytogeneticist with a completed CALGB Form C-030 (CALGB Cytogenetic Sample Referral Form). Submit a copy of the CALGB Form C-030 to the Alliance Statistical Center, Data Operations at Duke University along with copies of local cytogenetic reports.

To obtain a copy of the CALGB Cytogenetic Sample Referral Form, (C-030), contact the Administrative Secretary at the Alliance Statistical Center at 919/668-9350. You will need to provide the following information:

- Your name
- Your institution
- Fax number
- Number of forms needed

18.9 Specimen Submission Consent

* NOTES FOR LOCAL INVESTIGATORS:

- This template specimen submission consent is provided as a tool to be used when specimens must be submitted prior to the patient being consented to the clinical trial if a local specimen submission consent is not available. This consent is not mandatory. Sites may use local specimen consent forms, modify specimen collection consents to include specimen submission information, or consent the patient to the clinical trial for the purpose of specimen submission, so long as specimen submission consent is obtained in some written and IRB approved form prior to specimen shipment.
- This template has been reviewed by the DCTD/NCI. Local IRB changes to this document are allowed without prior approval from the SWOG Operations Office. It is suggested that sections of this document that are in bold type be used in their entirety.

* These notes for investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

NOTE: For patients submitting specimens prior to study registration, a SWOG patient ID must be obtained prior to submission. This patient ID will be used to label the specimen and log it into SpecTrack, and will be entered into the registration system if/when the patient is registered to the study. See Sections 13.1 and 15.1 for additional information.

Specimen Submission Consent

What is the purpose of this consent form?

You are going to have a bone marrow exam and blood tests to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

If you do have cancer, one of your treatment options might be a clinical trial. A clinical trial is a type of research study. If your doctor thinks a clinical trial would be a good option for you, he or she will discuss everything that would be involved in taking part in the study, like what type of treatment you would get and what tests you will need to take part.

Many clinical trials require that samples (specimens) of your bone marrow and blood be submitted before you start treatment. The specimens are used for testing that is needed as part of the clinical trial.

The purpose of this consent form is to ask your permission to draw extra blood and bone marrow at the same time they are being taken for your diagnosis to send to a central laboratory, so that if you decide to take part in a clinical trial you will not have to have another bone marrow and blood draw. If you agree, you will have an extra 2 teaspoons of bone marrow and 1-2 tablespoons of blood taken. The extra marrow and blood can usually be taken through the same needle stick and do not require extra procedures. By taking the extra marrow and blood at the time of diagnosis, we hope to prevent the need for an extra marrow/blood draw if the clinical trial requires them.

No tests will be done on any of your specimens without your permission. If you and your doctor do not feel that a clinical trial is your best option after getting your diagnosis, or if you decide not to take part in the clinical trial for any reason, your specimens will not be used for testing.

If you and your doctor decide a clinical trial is your best option, and the trial requires specimens before you start treatment, you will be told about any tests that will be done with your specimens as part of the clinical trial consent. Your specimens will not be used unless you agree to take part in the clinical trial.

By signing this consent form you are agreeing to allow extra bone marrow and blood to be drawn at the time specimens are being taken to get your diagnosis, and to allow these specimens to be sent to the central laboratory to be used as part of a clinical trial if you take part in one. You are not consenting to take part in a clinical trial or to have your specimens used for any other research.

What are the risks?

The bone marrow and blood draws are part of your regular cancer screening and care, so your doctor will discuss their risks with you. The risks that are part of collecting extra specimens are unlikely, but are:

- **Extra pain during the bone marrow draw**
- **A second needle stick might be needed to get enough bone marrow or blood**

Your name and identifying information will not be sent with your specimens, so there is little risk of anyone getting your identifying information. Instead, your specimens will be labeled with a number that is assigned by the clinical trials registration system. Your identifying information will be linked to the number in a secure database to help make sure it cannot be accessed.

Signature

I have been given a copy of all 2 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant (or legally authorized representative) _____

Date _____