# LEUKEMIA COMMITTEE

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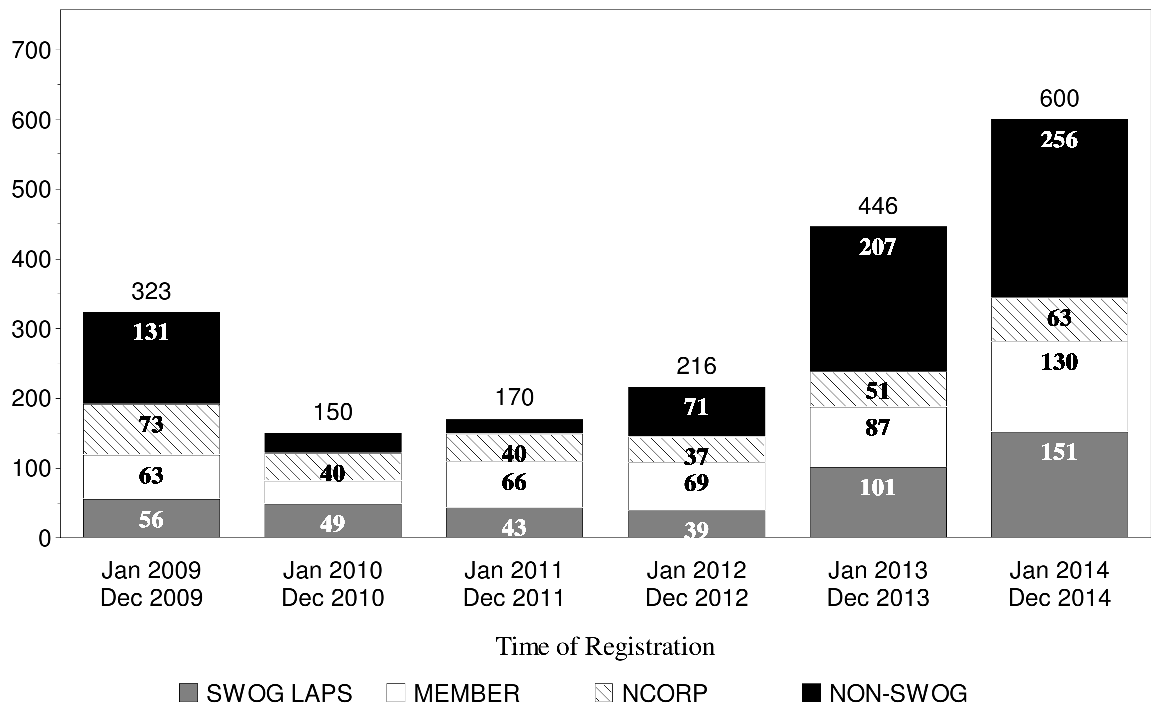
# Patient Registrations to Studies

By 12 Month Intervals
LEUKEMIA COMMITTEE




Screening registrations and registrations to Biologic only studies are excluded

# Patient Registrations by Study and Arm

## LEUKEMIA COMMITTEE

| | Jul 2014 Dec 2014 | Jan 2014 Jun 2014 | Jul 2013 Dec 2013 | All Patients |
|---|---|---|---|---|
| **S0535 APL,High Risk, ATRA/arsenic/GO** | | | | |
| **Consolidation** | | | | |
| Consolidation | 0 | 0 | 0 | 62 |
| **Maintenance** | | | | |
| ATRA + 6-MP + MTX | 0 | 0 | 6 | 47 |
| **S0805 Ph+ ALL, Dasatinib/CVAD +/- BMT** | | | | |
| **Induction/Consolidation** | | | | |
| Induction/Consolidation | 0 | 0 | 13 | 97 |
| **S0919 Rel AML: Pravastatin+Ida+Ara-C** | | | | |
| **Induction** | | | | |
| Pravastatin+Idarubicin+Ara-C | 14 | 13 | 21 | 94 |
| **S1117 MDS/CMML, Aza+Len/Aza/Aza+Vor** | | | | |
| **Randomization** | | | | |
| Azacitidine+Lenalidomide | 0 | 23 | 32 | 97 |
| Azacitidine | 0 | 21 | 30 | 92 |
| Azacitidine+Vorinostat | 0 | 19 | 33 | 93 |
| | 0 | 63 | 95 | 282 |
| **S1203 AML, Age 18-60, 7+3/IA/IA+V** | | | | |
| **Randomization** | | | | |
| AraC + Daunorubicin | 66 | 53 | 40 | 168 |
| AraC + Idarubicin | 69 | 53 | 42 | 173 |
| Vorinostat + AraC + Idarubicin | 72 | 54 | 39 | 176 |
| | 207 | 160 | 121 | 517 |
| **S1312 ALL,CD22+,REL/REF,Inotuzumab+CVP** | | | | |
| **Initial Registration** | | | | |
| CVP + Inotuzumab dose level 1 | 2 | 3 | 0 | 5 |
| CVP + Inotuzumab dose level 2 | 1 | 0 | 0 | 1 |
| | 3 | 3 | 0 | 6 |
| **A041202 CLL,65+,Ben+Rtx vs Ibrut±Rtx*** | | | | |
| Total Registrations | 29 | 6 | 0 | 35 |

| | Jul 2014 Dec 2014 | Jan 2014 Jun 2014 | Jul 2013 Dec 2013 | All Patients |
|---|---|---|---|---|
| **C10701 Ph+ ALL, age 50+, Dasatinib+HCT*** | | | | |
| Total Registrations | 9 | 1 | 3 | 13 |
| **E1910 BCR-ABL-neg B ALL, blinatumomab*** | | | | |
| Total Registrations | 13 | 2 | 0 | 15 |
| **E1912 CLL, age 18-70, Ibrutinib vs FCR*** | | | | |
| Total Registrations | 19 | 16 | 0 | 35 |
| **E2905 MDS, Len vs Len + Epo*** | | | | |
| Total Registrations | 9 | 8 | 6 | 60 |
| **E2906 AML,age 60+,Clo vs Dauno+Cy*** | | | | |
| Total Registrations | 16 | 9 | 24 | 75 |

* For non-SWOG coordinated studies only SWOG registrations are shown.

# S0805 Phase II

## Coordinating Group: SWOG

# Phase II Study of Combination of Hyper-CVAD and Dasatinib (NSC-732517) With or Without Allogeneic Stem Cell Transplant in Patients with Philadelphia (Ph) Chromosome Positive and/or BCR-ABL Positive Acute Lymphoblastic Leukemia (ALL) (A BMT Study)

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**Participants:**
SWOG, CTSU (supported by Alliance, BMT-CTN, and ECOG-ACRIN)

**Study Chairs:**
F Ravandi, S O'Brien, S Forman, C Ha, J Radich, J Wong, M Tallman (ECOG-ACRIN), M Wetzler (Alliance), M Horowitz (BMT-CTN)

**Statisticians:**
H Li, M Othus

**Data Coordinator:**
L Kingsbury

**Date Activated:**
09/01/2009

**Date Closed:**
10/01/2013

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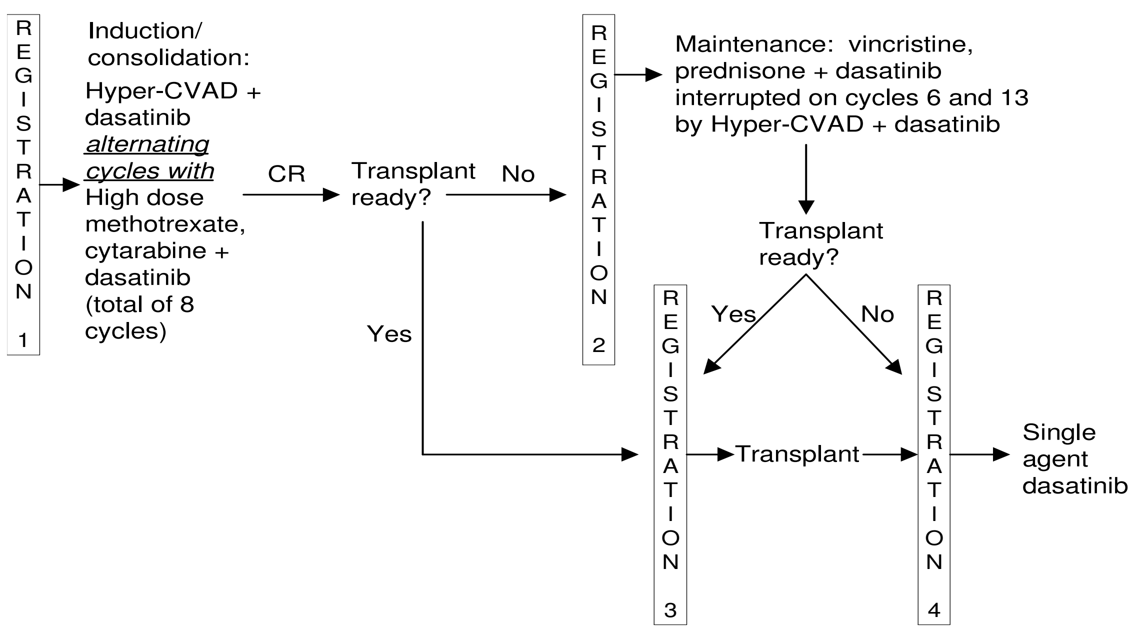
## SCHEMA



### Objectives

To test whether the relapse-free survival after allogeneic stem cell transplantation among Philadelphia chromosome positive and/or BCR/ABL positive acute lymphoblastic leukemia (ALL) patients given an intensive short-term chemotherapy regimen of Hyper-CVAD in combination with the tyrosine kinase inhibitor dasatinib is sufficiently high to warrant further investigation.

To test whether the continuous complete remission rate for previously untreated Philadelphia chromosome positive and/or BCR/ABL positive acute lymphoblastic leukemia (ALL) patients given an intensive short-term chemotherapy regimen of Hyper-CVAD given in combination with the tyrosine kinase inhibitor dasatinib is sufficiently high to warrant Phase III investigation.

To investigate in a preliminary manner the relative effectiveness of MRD detection using real-time quantitative PCR for BCR/ABL versus flow cytometry to predict the outcome of patients treated by the hyper-CVAD + dasatinib regimen and/or allogeneic stem cell transplant.

To estimate the frequency and severity of toxicities of the intensive short-term chemotherapy regimen in these patients.

To estimate the overall survival of all patients on this study.

### Patient Population

Patients must have a morphologic diagnosis of acute lymphoblastic leukemia (ALL), as defined in the protocol, with evidence of ALL involvement in bone marrow and/or blood. Patients with only extramedullary disease in the absence of bone marrow or blood involvement are not eligible. Patients with M0 AML, mixed lineage leukemia, or L3 (Burkitts) are not eligible for this study. For ALL in marrow or peripheral blood, immunophenotyping of the blood or marrow lymphoblasts must be performed to determine lineage. Patients must be Philadelphia (Ph) chromosome positive and/or BCR/ABL positive as confirmed by standard cytogenetics, FISH, and/or polymerase chain reaction (PCR) testing performed by a local laboratory.

Patients may have received no more than one course of remission induction therapy for ALL, providing this induction course was given prior to the results of the cytogenetics testing for Ph chromosome or BCR/ABL status being known. Patients who have received any post-remission therapy for ALL or who have relapsed from complete remission are not eligible. Any prior induction chemotherapy must have been completed within 28 days prior to registration. For patients who have received any prior therapy that was not remission induction therapy, one of the following must be true: at least six weeks must have elapsed since any monoclonal antibodies were given, at least seven days must have elapsed since any other treatment was given, and all toxicities of the remission induction therapy must have resolved to Grade $\leq 2$; or the patient must have rapidly progressive disease. For previously treated patients, the Study Coordinator must be contacted before registration, in order to determine the regimen to be given in the first course of induction/consolidation therapy, based on prior therapy.

Patients must be at least 18 but no more than 60 years of age and must have Zubrod performance status of 0, 1, or 2. Patients must not have active pericardial effusion, ascites, or pleural effusion of any grade, or prolonged QTc interval (QTc > 480 msec). Patients must not have prior history of known Type I hypersensitivity or anaphylactic reactions to doxorubicin and must have adequate renal and hepatic function.

### Stratification/Descriptive Factors

The patients will be stratified as follows: previously untreated vs previously treated and achieved remission (CR or CRi) vs refractory (previously treated but did not achieve CR or CRi) vs previously treated and remission status unknown.

### Accrual Goals

Accrual will continue until 34 eligible patients have received an allogeneic stem cell transplant. It is anticipated that 85 eligible patients will need to be registered to reach the accrual goal for the transplanted patients.

### Summary Statement

The study closed on October 1, 2013 as the accrual goal was met with 97 registered patients. Two patients were ineligible: one due to elevated liver enzymes and one with effusion not due to leukemia. One additional patient was denied by insurance coverage before starting protocol treatment and is not included in any analyses.

Three patients refused to continue protocol induction/consolidation therapy. Fourteen other patients were removed from protocol induction/consolidation therapy; three at physician's discretion, four to receive stem cell transplants, three were unable to find matched donors, three were unable to have remission determined within two courses of induction/consolidation therapy, one was denied by insurance, and another one was diagnosed with renal cell cancer.

Of the 92 patients evaluated for induction/consolidation toxicities, three fatal toxicities have been reported: one due to sepsis (coded as both Inf, Unk ANC: blood and Inf, 3-4 ANC: blood), one due to septic shock, and one due to respiratory arrest (coded as sudden death). Grade 4 non-hematologic toxicities have been reported for 17 additional patients, including respiratory failure (coded as DLCO) and pulmonary airspace disease (coded as Pulmonary-other).

One patient receiving maintenance therapy experienced Grade 4 psychosis. No additional Grade 4 or higher non-hematologic toxicities have been reported for patients receiving maintenance protocol therapy.

One patient was ineligible for induction/consolidation and thus ineligible for transplant. One patient did not receive transplant after registration to transplant due to insurance refusal. One patient who received allogeneic transplant experienced Grade 4 hypoxia as the only non-hematologic Grade 4 toxicity reported.

One patient was ineligible for induction/consolidation and thus ineligible for dasatinib. Another patient started post-transplant dasatinib treatment early and was ineligible for registration to dasatinib. Two patients receiving dasatinib treatment experienced Grade 4 non-hematologic toxicity: one with respiratory failure and one with hypoglycemia. No additional Grade 4 or higher non-hematologic toxicities have been reported for patients registered for post-remission maintenance protocol therapy.

Institutions are encouraged to submit data in a timely fashion to ensure rapid reporting of the study results as the data mature.

## Registration by Institution

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| ECOG-ACRIN | 34 | Davis, U of CA | 2 |
| Alliance | 18 | Stanford University | 2 |
| MD Anderson | 9 | Utah, U of | 2 |
| PCRC NCORP | 5 | Arizona MC, U of | 1 |
| Cleveland Clinic OH | 4 | BMT-CTN | 1 |
| Kansas, U of | 4 | City of Hope Med Ctr | 1 |
| Kentucky, U of | 4 | MUSC MU-NCORP | 1 |
| Loyola University | 3 | Wayne State Univ | 1 |
| Rochester, Univ of | 3 | **Total (18 Institutions)** | **97** |
| Baylor Univ Med Ctr | 2 | | |

## Registration, Eligibility, and Evaluability

Data as of March 5, 2015

| | Induction /Consolidation |
|---|---|
| NUMBER REGISTERED | 97 |
| INELIGIBLE | 2 |
| ELIGIBLE | 95 |
| Not Analyzable | 1 |
| ADVERSE EVENT ASSESSMENT | |
| Evaluable | 92 |
| Too Early | 2 |

## Patient Characteristics

Data as of March 5, 2015

| | Induction /Consolidation (n=94) | |
|---|---|---|
| AGE | | |
| Median | 44.0 | |
| Minimum | 20.5 | |
| Maximum | 60.7 | |
| SEX | | |
| Males | 42 | 45% |
| Females | 52 | 55% |
| HISPANIC | | |
| Yes | 7 | 7% |
| No | 74 | 79% |
| Unknown | 13 | 14% |
| RACE | | |
| White | 81 | 86% |
| Black | 9 | 10% |
| Asian | 1 | 1% |
| Unknown | 3 | 3% |
| PRIOR TREATMENT | | |
| Previously untreated | 60 | 64% |
| Previously treated and achieved remission (CR or CRi) | 16 | 17% |
| Refractory (previously treated but did not achieve CR or CRi) | 11 | 12% |
| Previously treated and remission status unknown | 7 | 7% |

## Treatment Summary

Data as of March 5, 2015

| | Induction /Consolidation |
|---|---|
| NUMBER ON PROTOCOL TREATMENT | 1 |
| NUMBER OFF PROTOCOL TREATMENT | 93 |
| REASON OFF TREATMENT | |
| Treatment completed as planned | 64 |
| Adverse Event or side effects | 6 |
| Refusal unrelated to adverse event | 3 |
| Progression/relapse | 0 |
| Death | 4 |
| Other - not protocol specified | 14 |
| Reason under review | 2 |
| MAJOR PROTOCOL DEVIATIONS | 0 |

## Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Non-Hematologic Adverse Events Only

Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed

Data as of March 5, 2015

| | Induction/Consolidation (n=92) | | | |
|---|---|---|---|---|
| | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** |
| ALT | 70 | 18 | 4 | 0 |
| ARDS | 91 | 0 | 1 | 0 |
| AST | 75 | 15 | 2 | 0 |
| Alkaline phosphatase | 91 | 1 | 0 | 0 |
| Anorexia | 91 | 1 | 0 | 0 |
| Bilirubin | 90 | 2 | 0 | 0 |
| Colitis | 90 | 2 | 0 | 0 |
| Colitis, infectious | 90 | 2 | 0 | 0 |
| Confusion | 91 | 1 | 0 | 0 |
| Creatinine | 90 | 2 | 0 | 0 |
| DLCO | 91 | 0 | 1 | 0 |
| Dehydration | 91 | 1 | 0 | 0 |
| Diarrhea | 89 | 3 | 0 | 0 |
| Dyspnea | 89 | 3 | 0 | 0 |
| Fatigue | 85 | 7 | 0 | 0 |
| Febrile neutropenia | 46 | 40 | 6 | 0 |
| Fever | 91 | 0 | 1 | 0 |
| Fibrinogen | 91 | 1 | 0 | 0 |
| GGT | 89 | 3 | 0 | 0 |
| GI Hemorrhage: lower GI | 91 | 1 | 0 | 0 |

| | Induction/Consolidation (n=92) | | | |
|---|---|---|---|---|
| | Grade | | | |
| ADVERSE EVENT | ≤ 2 | 3 | 4 | 5 |
| GI Inf, 0-2 ANC: colon | 91 | 1 | 0 | 0 |
| GI Inf, 3-4 ANC: gums | 91 | 1 | 0 | 0 |
| GI Pain: abdomen | 90 | 1 | 1 | 0 |
| GI Perforation: stomach | 91 | 0 | 1 | 0 |
| GU Inf, Unk ANC: UTI | 91 | 1 | 0 | 0 |
| Heartburn | 91 | 1 | 0 | 0 |
| Hematoma | 91 | 1 | 0 | 0 |
| Hemorrhage-other | 91 | 1 | 0 | 0 |
| Hyperglycemia | 75 | 16 | 1 | 0 |
| Hyperkalemia | 91 | 0 | 1 | 0 |
| Hypermagnesemia | 91 | 1 | 0 | 0 |
| Hypertension | 90 | 2 | 0 | 0 |
| Hypoalbuminemia | 89 | 3 | 0 | 0 |
| Hypocalcemia | 77 | 14 | 1 | 0 |
| Hypokalemia | 73 | 18 | 1 | 0 |
| Hyponatremia | 90 | 2 | 0 | 0 |
| Hypophosphatemia | 85 | 6 | 1 | 0 |
| Hypotension | 90 | 1 | 1 | 0 |
| Hypoxia | 91 | 1 | 0 | 0 |
| Inf, 0-2 ANC: cath.-related | 91 | 1 | 0 | 0 |
| Inf, 0-2 ANC: wound | 91 | 1 | 0 | 0 |
| Inf, 3-4 ANC: blood | 79 | 8 | 4 | 1 |
| Inf, 3-4 ANC: cath-related | 89 | 3 | 0 | 0 |
| Inf, Unk ANC: blood | 86 | 0 | 4 | 2 |
| Inf, Unk ANC: cath.-related | 90 | 2 | 0 | 0 |
| Infection-other | 87 | 5 | 0 | 0 |
| Lung Hemorrhage: nose | 90 | 2 | 0 | 0 |
| Lung Inf, 0-2 ANC: lung | 90 | 2 | 0 | 0 |
| Lung Inf, 3-4 ANC: lung | 86 | 5 | 1 | 0 |
| Lung Inf, 3-4 ANC: up. airway | 90 | 2 | 0 | 0 |
| Lung Inf, Unk ANC: bronchus | 91 | 1 | 0 | 0 |
| Lung Inf, Unk ANC: lung | 88 | 4 | 0 | 0 |
| Lung Inf, Unk ANC: sinus | 91 | 1 | 0 | 0 |
| Metabolic/Lab-other | 91 | 1 | 0 | 0 |
| Mood alteration: depression | 91 | 0 | 1 | 0 |
| Mucositis, clin: oral cavity | 90 | 2 | 0 | 0 |
| Mucositis, funct: esophagus | 91 | 1 | 0 | 0 |
| Mucositis, funct: oral cav. | 91 | 1 | 0 | 0 |
| Musc Inf, Unk ANC: soft tiss. | 91 | 1 | 0 | 0 |
| Muscle weakness: low. extrem. | 91 | 1 | 0 | 0 |
| Muscle weakness: whole body | 89 | 3 | 0 | 0 |
| Musculo. Pain: bone | 91 | 1 | 0 | 0 |
| Musculo. Pain: joint | 91 | 1 | 0 | 0 |
| Musculo. Pain: muscle | 90 | 2 | 0 | 0 |
| Nausea | 85 | 7 | 0 | 0 |
| Neuro Pain: head/headache | 86 | 5 | 1 | 0 |
| Neurology-other | 91 | 1 | 0 | 0 |
| Neuropathy-motor | 91 | 1 | 0 | 0 |
| Neuropathy-sensory | 91 | 1 | 0 | 0 |
| Pericardial effusion | 91 | 1 | 0 | 0 |
| Petechiae | 91 | 1 | 0 | 0 |

| | Induction/Consolidation (n=92) | | | |
|---|---|---|---|---|
| | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** |
| Pleural effusion | 91 | 1 | 0 | 0 |
| Pneumonitis | 91 | 1 | 0 | 0 |
| Pulmonary-other | 91 | 0 | 1 | 0 |
| Rash | 90 | 2 | 0 | 0 |
| Renal failure | 91 | 1 | 0 | 0 |
| Skin Inf, 3-4 ANC: skin | 89 | 3 | 0 | 0 |
| Skin Inf, Unk ANC: skin | 90 | 2 | 0 | 0 |
| Soft tiss. nec.: low. extrem. | 91 | 1 | 0 | 0 |
| Sudden death | 91 | 0 | 0 | 1 |
| Supra Arrhyth: Atrial Fib. | 91 | 1 | 0 | 0 |
| Thrombosis/embolism | 89 | 3 | 0 | 0 |
| Tumor lysis syndrome | 91 | 1 | 0 | 0 |
| Vomiting | 89 | 3 | 0 | 0 |
| Weight Loss | 91 | 1 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 18 | 54 | 17 | 3 |

# S0919 Phase II

# A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-risk Acute Myelogenous Leukemia (AML)

**Study Chairs:**
A Advani, L Michaelis

**Date Activated:**
08/15/2009

**Statisticians:**
H Li, M Othus

**Data Coordinator:**
L Highleyman

## Objectives

To test whether the complete remission (CR) rate (including CR with incomplete recovery [CRi]) in poor-risk patients with acute myeloid leukemia (AML) treated with a combination of chemotherapy and pravastatin is sufficiently high to warrant Phase III investigation. This will be tested independently in two groups of patients: (1) patients with MDS transformed to AML, and (2) refractory or relapsed patients with previous remission < 6 months.

To estimate relapse-free survival and overall survival rates in these two groups of patients.

To estimate the frequency and severity of toxicities of this regimen in these two groups of patients.

To evaluate in a preliminary manner whether prestudy cytogenetic features correlate with response in these two groups of patients.

## Patient Population

MDS transformed to AML cohort:

Patients must have a previous morphologically confirmed diagnosis of MDS/CMML. Patients may have received previous non-intensive therapy (e.g. azacitidine, decitabine, low-dose cytarabine (LDAC), lenalidomide) given for treatment of MDS. At the time of registration patients must have a morphologically confirmed diagnosis of acute myeloid leukemia (AML).

Relapsed/Refractory Cohort:

Patients must have a previous morphologically confirmed diagnosis of acute myeloid leukemia (AML). Relapse or refractory disease must be documented by a bone marrow examination demonstrating > 5% blasts in the bone marrow not attributable to another cause.

Patients must have received at least one prior chemotherapy regimen for their AML and they may have received any type of chemotherapy. Patients must not have received chemotherapy within 14 days prior to registration. Relapsed patients must have achieved CR or CRi, lasting less than six months with their last induction regimen. Primary refractory patients are eligible if, on Day 14 of their most recent chemotherapy regimen, they have significant residual disease. Refractory patients who received only hypomethylating agent or low dose therapy for induction are not eligible.

All patients:

Patients with acute promyelocytic leukemia (APL, FAB M3) or blastic transformation of chronic myelogenous leukemia are not eligible.

Patients who have received autologous or allogeneic stem cell transplantation are not eligible.

Patients must have adequate cardiac function as defined in the protocol. Patients must be at least 18 years of age, must have a Zubrod performance status of 0, 1, or 2, and must have adequate renal and hepatic function. Patients must not have clinical evidence of leptomeningeal disease and must not have a systemic fungal, bacterial, viral or other infection that is not controlled. Patients not known to be HIV+ must be tested for HIV infection. Patients who are HIV+ may be eligible providing they meet all of the criteria in the protocol.

**Stratification/Descriptive Factors**

Patients will be stratified according to disease status: patients with MDS transformed to AML vs refractory or relapsed patients with previous remission < 6 months.

**Accrual Goals**

Seventy-four eligible patients will be accrued, 37 in each cohort.

**Summary Statement**

On July 1, 2012, the study was temporarily closed to accrual to relapsed patients with previous remission of longer than three months. Final results for this cohort of 36 patients were reported in the Spring 2013 Report of Studies and are not included in this report. On April 1, 2013, the study was re-opened to two additional poor-risk cohorts: patients with MDS transformed to AML, and refractory or relapsed patients with previously remission less than six months. The following tables, other than 'Registration by Institution', show accrual only for these two poor-risk cohorts.

The study has closed to accrual to the relapsed/refractory AML patients on November 24, 2014, after meeting the accrual goal with 45 patients registered. Three patients are ineligible: one due to prior stem cell transplant and two due to previous remission longer than six months. One patient had a cardiac event prior to starting treatment causing a decline in performance status. This patient did not receive any protocol therapy and is not included in any analyses. Major protocol deviation is coded for one patient who received an extra dose of AraC.

Forty relapsed/refractory AML patients have been assessed for adverse events. Three treatment related deaths occurred: one due to sepsis (reported as Inf, Unk ANC: blood) and this patient also reported Grade 4 bronchopulmonary hemorrhage, another one due to hypotension and this patient also experienced Grade 4 renal failure, and the third death was due to beta strep Group B (reported as Inf, 3-4 ANC: blood) and this patient also experienced Grade 4 febrile neutropenia. An additional five patients experienced treatment-related Grade 4 non-hematologic toxicities.

As of December 31, 2014, 13 patients have been accrued to the MDS transformed to AML cohort. One patient who did not meet WHO criteria for acute erythroleukemia is ineligible. Among the ten patients assessed for adverse events, four reported treatment-related Grade 4 non-hematologic toxicities.

Two patients accrued to the relapsed/refractory cohort are ineligible for consolidation therapy because the patients are ineligible for induction step. An additional patient who relapsed prior to consolidation treatment began is not evaluable for toxicities.

## Registration by Institution

Registrations ending December 31, 2014

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| Stanford University | 24 | Birmingham, U of AL | 3 |
| Cleveland Clinic OH | 20 | PCRC NCORP | 2 |
| H Lee Moffitt CC | 11 | Wichita NCORP | 2 |
| Rochester, Univ of | 11 | LSU-Shreveport/Gulf South MU-NCORP | 1 |
| Baylor College | 5 | Mississippi, Univ of | 1 |
| Colorado, U of | 5 | Tulane Univ MBCCOP | 1 |
| Loyola University | 4 | **Total (14 Institutions)** | **94** |
| New Mexico MU-NCORP | 4 | | |

## Registration, Eligibility, and Evaluability

Classified by Disease status

Induction

Registrations from April 1, 2013 through December 31, 2014; Data as of March 17, 2015

| | TOTAL | MDS transformed to AML | Refractory or relapsed with previous remission < 6 months |
|---|---|---|---|
| NUMBER REGISTERED | 58 | 13 | 45 |
| INELIGIBLE | 4 | 1 | 3 |
| ELIGIBLE | 54 | 12 | 42 |
| Not Analyzable | 1 | 0 | 1 |
| RESPONSE ASSESSMENT | | | |
| Determinable | 46 | 10 | 36 |
| Not Determinable | 6 | 1 | 5 |
| Too Early | 1 | 1 | 0 |
| ADVERSE EVENT ASSESSMENT | | | |
| Evaluable | 50 | 10 | 40 |
| Too Early | 3 | 2 | 1 |

## Patient Characteristics

Classified by Disease status
Induction
Registrations from April 1, 2013 through December 31, 2014; Data as of March 17, 2015

| | MDS transformed to AML (n=12) | | Refractory or relapsed with previous remission < 6 months (n=41) | |
|---|---|---|---|---|
| AGE | | | | |
| Median | 66.7 | | 54.4 | |
| Minimum | 29.6 | | 23.1 | |
| Maximum | 71.9 | | 75.0 | |
| SEX | | | | |
| Males | 8 | 67% | 19 | 46% |
| Females | 4 | 33% | 22 | 54% |
| HISPANIC | | | | |
| Yes | 0 | 0% | 4 | 10% |
| No | 10 | 83% | 34 | 83% |
| Unknown | 2 | 17% | 3 | 7% |
| RACE | | | | |
| White | 11 | 92% | 30 | 73% |
| Black | 1 | 8% | 2 | 5% |
| Asian | 0 | 0% | 6 | 15% |
| Multi-Racial | 0 | 0% | 3 | 7% |

## Treatment Summary

Classified by Disease status
Induction
Registrations from April 1, 2013 through December 31, 2014; Data as of March 17, 2015

| | TOTAL | MDS transformed to AML | Refractory or relapsed with previous remission < 6 months |
|---|---|---|---|
| NUMBER ON PROTOCOL TREATMENT | 0 | 0 | 0 |
| NUMBER OFF PROTOCOL TREATMENT | 53 | 12 | 41 |
| REASON OFF TREATMENT | | | |
| Treatment completed as planned | 46 | 11 | 35 |
| Adverse Event or side effects | 1 | 0 | 1 |
| Refusal unrelated to adverse event | 1 | 1 | 0 |
| Progression/relapse | 0 | 0 | 0 |
| Death | 5 | 0 | 5 |
| Other - not protocol specified | 0 | 0 | 0 |
| Reason under review | 0 | 0 | 0 |
| MAJOR PROTOCOL DEVIATIONS | 1 | 0 | 1 |

## Number of Patients with a Given Type and Grade of Adverse Event

Classified by Disease status
Induction
Adverse Events Unlikely or Not Related to Treatment Excluded
Non-Hematologic Adverse Events Only
Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed
Registrations from April 1, 2013 through December 31, 2014; Data as of March 17, 2015

| | MDS transformed to AML (n=10) | | | | Refractory or relapsed with previous remission < 6 months (n=40) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** |
| ALT | 8 | 2 | 0 | 0 | 39 | 1 | 0 | 0 |
| AST | 9 | 1 | 0 | 0 | 39 | 1 | 0 | 0 |
| Colitis, infectious | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Creatinine | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Diarrhea | 9 | 1 | 0 | 0 | 37 | 3 | 0 | 0 |
| Dyspnea | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Fatigue | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Febrile neutropenia | 3 | 7 | 0 | 0 | 22 | 16 | 2 | 0 |
| GI Pain: abdomen | 9 | 1 | 0 | 0 | 40 | 0 | 0 | 0 |
| GU Inf, 3-4 ANC: kidney | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Hypoalbuminemia | 10 | 0 | 0 | 0 | 37 | 3 | 0 | 0 |
| Hypocalcemia | 10 | 0 | 0 | 0 | 39 | 0 | 1 | 0 |
| Hypokalemia | 10 | 0 | 0 | 0 | 37 | 3 | 0 | 0 |
| Hyponatremia | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Hypophosphatemia | 10 | 0 | 0 | 0 | 38 | 2 | 0 | 0 |
| Hypotension | 10 | 0 | 0 | 0 | 39 | 0 | 0 | 1 |
| Hypoxia | 10 | 0 | 0 | 0 | 37 | 3 | 0 | 0 |
| Inf, 3-4 ANC: blood | 7 | 0 | 3 | 0 | 35 | 1 | 3 | 1 |
| Inf, Unk ANC: blood | 8 | 0 | 2 | 0 | 37 | 0 | 2 | 1 |
| Lung Hemorrhage: bronchopulm. | 10 | 0 | 0 | 0 | 39 | 0 | 1 | 0 |
| Lung Inf, 3-4 ANC: lung | 9 | 1 | 0 | 0 | 36 | 3 | 1 | 0 |
| Mucositis, funct: oral cav. | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Musculo. Pain: bone | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Musculo. Pain: limb | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Nausea | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| Renal failure | 10 | 0 | 0 | 0 | 39 | 0 | 1 | 0 |
| Weight Loss | 10 | 0 | 0 | 0 | 39 | 1 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 0 | 6 | 4 | 0 | 14 | 18 | 5 | 3 |

# S1117 Phase II

## Coordinating Group: SWOG

# A Randomized Phase II Study of Azacitidine in Combination with Lenalidomide (NSC-703813) vs. Azacitidine Alone vs. Azacitidine in Combination with Vorinostat (NSC-701852) for Higher-Risk Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML)

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**Participants:**
SWOG, CTSU (supported by Alliance, ECOG-ACRIN, NRG, and NCIC-CTG)

**Study Chairs:**
M Sekeres, A List, S Gore (ECOG-ACRIN), O Odenike (Alliance)

**Statisticians:**
M Othus, H Li

**Data Coordinator:**
T Maher

**Date Activated:**
04/03/2012

**Date Closed:**
11/14/2014

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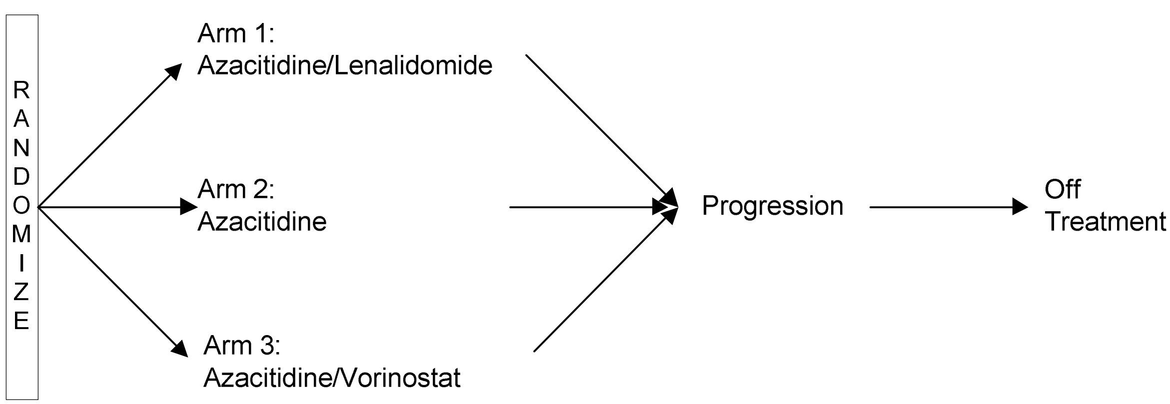
## SCHEMA




Patients will receive treatment until progression

**Objectives**

To test whether the response rate (complete remission, partial remission, or hematologic improvement) of patients with higher-risk myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) who receive either the combination of lenalidomide and azacitidine or the combination of vorinostat and azacitidine is improved compared to patients who receive single-agent azacitidine.

To estimate relapse-free survival, overall survival and cytogenetic response rate of patients treated on each regimen.

To estimate the frequency and severity of toxicities of the three regimens in this patient population.

To investigate in a preliminary manner the frequency of subgroups from prestudy cytogenetic studies and correlate these subgroups with clinical outcomes in this patient population.

To collect specimens for banking for use in future research studies.

**Patient Population**

Patients must have morphologically confirmed diagnosis of myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) based on French-American-British (FAB) or World Health Organization (WHO) classifications or by the International Prognosis Score (IPSS) as defined in the protocol.

Patients must not have received prior treatment with lenalidomide, azacitidine, vorinostat or decitabine. Any hematopoietic growth factors must be stopped for at least 14 days prior to registration. Patients may have received low dose cytarabine for MDS treatment previously, but they must have discontinued its use for at least 28 days prior to registration. Patients must not have received radiation therapy, chemotherapy, or cytotoxic therapy to treat conditions other than MDS within 12 months prior to registration, or prior stem cell or bone marrow transplantation at any time. Patients must not have received greater than physiologic doses of a corticosteroid agent (dose equivalent to > 10 mg/day of prednisone) within 28 days prior to registration. Patients must not have used or be using HDAC inhibitor agents for anticancer treatment. Patients may not have received agents such as valproic acid for epilepsy within 30 days prior to registration.

Patients must be at least 18 years of age and have Zubrod performance status of 0, 1 or 2. Patients must not have any pre-existing neurotoxicity/neuropathy of Grade 2 or higher according to the NCI Common Toxicity Criteria Version 4.0, or prior Grade 3 or higher allergic reaction/hypersensitivity or rash to thalidomide, that has not resolved to Grade 1 or lower. Patients must not have history of thromboembolic event or other condition requiring current use of anticoagulation with coumadin (warfarin) or low molecular-weight heparin. Patients must not have known or suspected hypersensitivity to mannitol. Patients must be tested for adequate cardiac, renal, and hepatic function. Females of childbearing potential (FCBP), as defined in the protocol, must have a negative serum or urine pregnancy test within 10-14 days prior to registration. Patients must agree to additional pregnancy testing, birth control use and counseling during the study as defined in the protocol.

**Stratification/Descriptive Factors**

Patients will be stratified by disease diagnosis: MDS vs CMML.

**Accrual Goals**

The accrual goal of this study is 240 eligible patients (80 eligible patients per arm).

**Summary Statement**

The SWOG Data Safety and Monitoring Committee (DSMC) reviewed a formal interim analysis of the study on October 24, 2014. Based on compelling null findings which ruled out the pre-specified treatment benefit with high confidence, the DSMC recommended the primary treatment comparison results be reported now and that the study will not proceed to Phase III.

The study was permanently closed to accrual on November 14, 2014 with a total registration of 282 patients. Five patients are ineligible due to the following reasons: diagnosis of AML (2), diagnosis of deep vein thrombosis, diagnosis of ALL, and coronary artery disease. Six eligible patients who did not receive any protocol treatment are not evaluable for adverse events: three due to patient's refusal, two patients required non-protocol treatment after randomization, and another patient expired prior to starting treatment. These patients are coded as major protocol deviations.

Two hundred sixty-eight patients were assessed for adverse events. There have been four treatment-related deaths reported on the azacitidine + lenalidomide arm: one due to pneumonia and this patient also experienced Grade 4 dyspnea, one due to ARDS and this patient also experienced Grade 4 cardiac arrest and sepsis, one due to sepsis and this patient also experienced Grade 4 febrile neutropenia, and another one due to intracranial hemorrhage. An additional six patients experienced Grade 4 non-hematologic toxicities including one with sepsis (coded as ‘Infections/infestations-Other’).

Two treatment-related deaths occurred on the azacitidine arm. One patient died of sepsis and the other died of hemorrhage (coded as ‘Sudden death NOS’). Four additional patients on the azacitidine arm experienced Grade 4 non-hematologic toxicities.

No treatment related death occured on the azacitidine + vorinostat arm. Six patients on the azacitidine + vorinostat arm reported Grade 4 non-hematologic toxicities, including one with pyoderma gangrenosum (coded as 'Skin infection' and 'Infections/infestations-Other').

## Registration by Institution

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| ECOG-ACRIN | 85 | So Calif, U of | 3 |
| Alliance | 62 | Upstate Carolina | 3 |
| NCIC-CTG | 34 | Kentucky, U of | 2 |
| Cleveland Clinic OH | 17 | New Mexico MU-NCORP | 2 |
| Heartland NCORP | 8 | Stormont-Vail Health/Kansas, U of | 2 |
| Kansas City NCORP | 7 | Arizona MC, U of | 1 |
| Greenville NCORP | 6 | Cincinnati MC, U of | 1 |
| Michigan CRC NCORP | 6 | Columbus NCORP | 1 |
| Colorado, U of | 5 | Good Samaritan Hosp/Oregon Hlth Sci Univ | 1 |
| City of Hope Med Ctr | 4 | Loyola University | 1 |
| Hawaii MU-NCORP | 4 | Montana NCORP | 1 |
| Kaiser Vallejo NCORP | 4 | Oklahoma, Univ of | 1 |
| Kansas, U of | 4 | Southeast CCC NCORP | 1 |
| Utah, U of | 4 | St Louis CCOP | 1 |
| West Michigan NCORP | 4 | Thompson Ca Surv Ctr/San Antonio, U of TX | 1 |
| Birmingham, U of AL | 3 | **Total (32 Institutions)** | **282** |
| Rochester, Univ of | 3 | | |

## Registration, Eligibility, and Evaluability

Data as of March 16, 2015

| | TOTAL | Azacitidine +Lenalidomide | Azacitidine | Azacitidine +Vorinostat |
|---|---|---|---|---|
| NUMBER REGISTERED | 282 | 97 | 92 | 93 |
| INELIGIBLE | 5 | 4 | 0 | 1 |
| ELIGIBLE | 277 | 93 | 92 | 92 |
| RESPONSE ASSESSMENT | | | | |
| Determinable | 201 | 62 | 71 | 68 |
| Not Determinable | 69 | 28 | 20 | 21 |
| Too Early | 7 | 3 | 1 | 3 |
| ADVERSE EVENT ASSESSMENT | | | | |
| Evaluable | 268 | 88 | 90 | 90 |
| Not Evaluable | 6 | 4 | 1 | 1 |
| Too Early | 3 | 1 | 1 | 1 |

## Patient Characteristics

Data as of March 16, 2015

| | Azacitidine +Lenalidomide (n=93) | | Azacitidine (n=92) | | Azacitidine +Vorinostat (n=92) | |
|---|---|---|---|---|---|---|
| AGE | | | | | | |
| Median | 70.8 | | 69.6 | | 70.3 | |
| Minimum | 51.3 | | 42.7 | | 28.7 | |
| Maximum | 86.7 | | 89.0 | | 93.0 | |
| SEX | | | | | | |
| Males | 61 | 66% | 61 | 66% | 70 | 76% |
| Females | 32 | 34% | 31 | 34% | 22 | 24% |
| HISPANIC | | | | | | |
| Yes | 3 | 3% | 3 | 3% | 3 | 3% |
| No | 89 | 96% | 86 | 93% | 87 | 95% |
| Unknown | 1 | 1% | 3 | 3% | 2 | 2% |
| RACE | | | | | | |
| White | 86 | 92% | 80 | 87% | 83 | 90% |
| Black | 2 | 2% | 3 | 3% | 4 | 4% |
| Asian | 1 | 1% | 4 | 4% | 2 | 2% |
| Pacific Islander | 0 | 0% | 0 | 0% | 1 | 1% |
| Native American | 1 | 1% | 0 | 0% | 1 | 1% |
| Unknown | 3 | 3% | 5 | 5% | 1 | 1% |
| DISEASE DIAGNOSIS | | | | | | |
| MDS | 75 | 81% | 74 | 80% | 75 | 82% |
| CMML | 18 | 19% | 18 | 20% | 17 | 18% |

## Treatment Summary

Data as of March 16, 2015

| | Total |
|---|---|
| NUMBER ON PROTOCOL TREATMENT | 45 |
| NUMBER OFF PROTOCOL TREATMENT | 232 |
| REASON OFF TREATMENT | |
| Treatment completed as planned | 0 |
| Adverse Event or side effects | 38 |
| Refusal unrelated to adverse event | 34 |
| Progression/relapse | 67 |
| Death | 14 |
| Other - not protocol specified | 63 |
| Reason under review | 16 |
| MAJOR PROTOCOL DEVIATIONS | 6 |

## Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded

Non-Hematologic Adverse Events Only

Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed

Data as of March 16, 2015

| | Azacitidine+Lenalidomide (n=88) | | | | Azacitidine (n=90) | | | | Azacitidine+Vorinostat (n=90) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** |
| ALT increased | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 85 | 5 | 0 | 0 |
| ARDS | 87 | 0 | 0 | 1 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| AST increased | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 87 | 3 | 0 | 0 |
| Abdominal infection | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Abdominal pain | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 87 | 3 | 0 | 0 |
| Acute kidney injury | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Anorectal infection | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Anorexia | 84 | 4 | 0 | 0 | 90 | 0 | 0 | 0 | 87 | 3 | 0 | 0 |
| Apnea | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Ascites | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Ataxia | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Back pain | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Blood bilirubin increased | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 87 | 3 | 0 | 0 |
| Cardiac arrest | 87 | 0 | 1 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Catheter related infection | 87 | 1 | 0 | 0 | 88 | 1 | 1 | 0 | 89 | 1 | 0 | 0 |
| Cecal infection | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Cholecystitis | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Confusion | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Constipation | 86 | 2 | 0 | 0 | 89 | 1 | 0 | 0 | 89 | 1 | 0 | 0 |
| Creatinine increased | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Dehydration | 83 | 5 | 0 | 0 | 89 | 1 | 0 | 0 | 87 | 3 | 0 | 0 |
| Delirium | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |

| | Azacitidine+Lenalidomide (n=88) | | | | Azacitidine (n=90) | | | | Azacitidine+Vorinostat (n=90) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** |
| Diarrhea | 83 | 5 | 0 | 0 | 90 | 0 | 0 | 0 | 87 | 3 | 0 | 0 |
| Dizziness | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Dyspnea | 84 | 3 | 1 | 0 | 88 | 2 | 0 | 0 | 87 | 3 | 0 | 0 |
| Epistaxis | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Esophageal pain | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Esophagitis | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Fall | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Fatigue | 79 | 9 | 0 | 0 | 85 | 5 | 0 | 0 | 77 | 13 | 0 | 0 |
| Febrile neutropenia | 74 | 11 | 3 | 0 | 80 | 9 | 1 | 0 | 77 | 12 | 1 | 0 |
| Fever | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Flushing | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Gastric hemorrhage | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Gastrointestinal pain | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Gen disorders/admin site cond | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Generalized muscle weakness | 85 | 3 | 0 | 0 | 89 | 1 | 0 | 0 | 87 | 3 | 0 | 0 |
| Hallucinations | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Headache | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Hematoma | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Hematuria | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 88 | 2 | 0 | 0 |
| Hyperglycemia | 87 | 1 | 0 | 0 | 89 | 0 | 1 | 0 | 88 | 2 | 0 | 0 |
| Hypernatremia | 88 | 0 | 0 | 0 | 89 | 1 | 0 | 0 | 90 | 0 | 0 | 0 |
| Hypertension | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 88 | 2 | 0 | 0 |
| Hyperuricemia | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 0 | 1 | 0 |
| Hypoalbuminemia | 85 | 3 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Hypokalemia | 84 | 4 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Hypomagnesemia | 87 | 0 | 1 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Hyponatremia | 83 | 5 | 0 | 0 | 89 | 1 | 0 | 0 | 87 | 3 | 0 | 0 |
| Hypophosphatemia | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 88 | 2 | 0 | 0 |
| Hypotension | 84 | 4 | 0 | 0 | 90 | 0 | 0 | 0 | 87 | 3 | 0 | 0 |
| Hypoxia | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 0 | 1 | 0 |
| Infections/infestations-Other | 84 | 3 | 1 | 0 | 88 | 2 | 0 | 0 | 85 | 4 | 1 | 0 |
| Intracranial hemorrhage | 87 | 0 | 0 | 1 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Investigations-Other, specify | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Lower GI hemorrhage | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 88 | 2 | 0 | 0 |
| Lung infection | 85 | 2 | 0 | 1 | 89 | 1 | 0 | 0 | 88 | 1 | 1 | 0 |
| Mucosal infection | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Mucositis oral | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Nausea | 87 | 1 | 0 | 0 | 88 | 2 | 0 | 0 | 88 | 2 | 0 | 0 |
| Pain | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Papulopustular rash | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Pericardial effusion | 87 | 0 | 1 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Pneumonitis | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Pruritus | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Purpura | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Rash maculo-papular | 75 | 13 | 0 | 0 | 88 | 2 | 0 | 0 | 89 | 1 | 0 | 0 |
| Renal/urinary disorders-Other | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Respiratory failure | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 0 | 1 | 0 |
| Sepsis | 84 | 0 | 3 | 1 | 88 | 0 | 1 | 1 | 87 | 0 | 3 | 0 |
| Sinus bradycardia | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| Skin infection | 85 | 2 | 1 | 0 | 89 | 1 | 0 | 0 | 88 | 1 | 1 | 0 |
| Soft tissue infection | 87 | 1 | 0 | 0 | 89 | 1 | 0 | 0 | 90 | 0 | 0 | 0 |

| | Azacitidine+Lenalidomide (n=88) | | | | Azacitidine (n=90) | | | | Azacitidine+Vorinostat (n=90) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** |
| Sudden death NOS | 88 | 0 | 0 | 0 | 89 | 0 | 0 | 1 | 90 | 0 | 0 | 0 |
| Syncope | 86 | 2 | 0 | 0 | 90 | 0 | 0 | 0 | 87 | 3 | 0 | 0 |
| Thromboembolic event | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Tooth infection | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Upper GI hemorrhage | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Upper respiratory infection | 88 | 0 | 0 | 0 | 89 | 1 | 0 | 0 | 90 | 0 | 0 | 0 |
| Urinary tract infection | 87 | 1 | 0 | 0 | 89 | 0 | 1 | 0 | 89 | 1 | 0 | 0 |
| Vasc disorders-Other, spec | 88 | 0 | 0 | 0 | 90 | 0 | 0 | 0 | 89 | 1 | 0 | 0 |
| Vomiting | 87 | 1 | 0 | 0 | 89 | 1 | 0 | 0 | 89 | 1 | 0 | 0 |
| Weight loss | 87 | 1 | 0 | 0 | 90 | 0 | 0 | 0 | 90 | 0 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 33 | 45 | 6 | 4 | 62 | 22 | 4 | 2 | 40 | 44 | 6 | 0 |

# S1203 Phase III

## Coordinating Group: 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)

**Participants:**
SWOG, CTSU (supported by Alliance, ECOG-ACRIN, NRG, and NCIC-CTG)

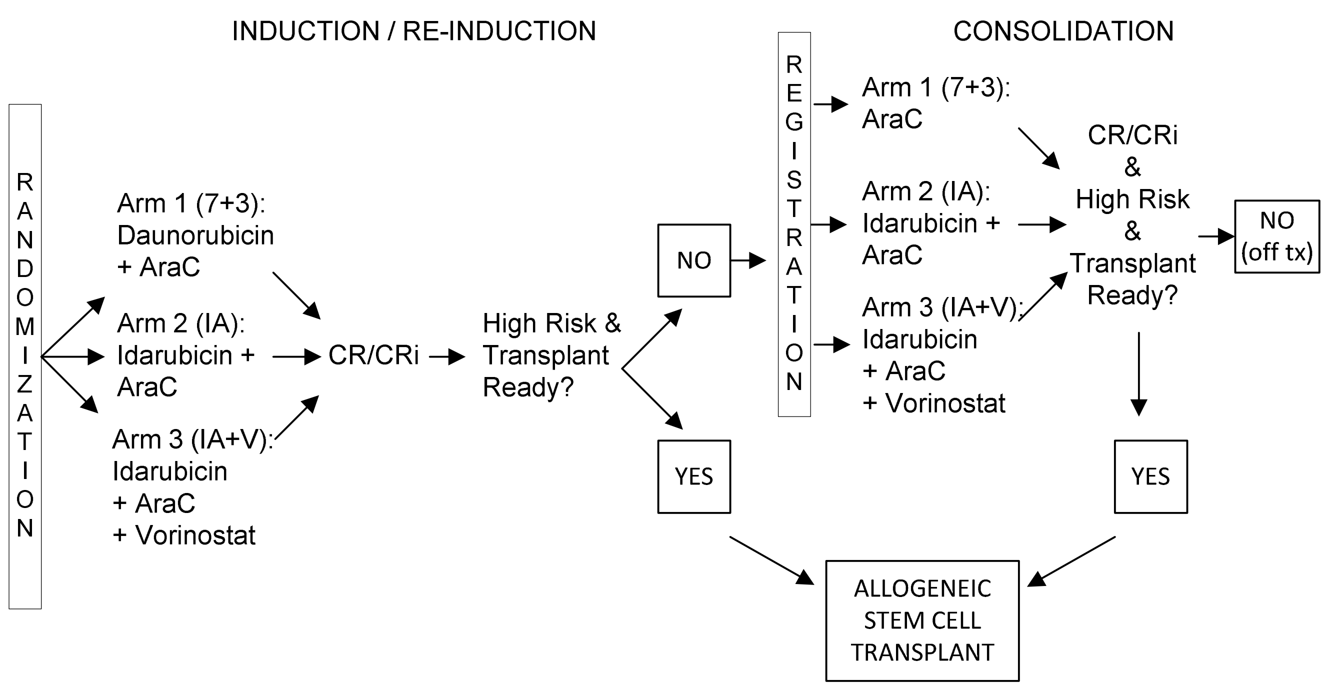
**Date Activated:**
02/08/2013

**Study Chairs:**
G Garcia-Manero, J Pagel, M Fang, J Radich,
D Rizzieri (Alliance), M Savoie (NCIC-CTG),
S Strickland (ECOG-ACRIN)

**Statisticians:**
M Othus, H Li

**Data Coordinators:**
T Maher, L Kingsbury

## SCHEMA



## Objectives

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.

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

To estimate the frequency and severity of toxicities of the three regimens in this patient population.

To estimate disease-free survival among patients who receive transplant.

To compare EFS between patients who receive standard 7+3 to patients who receive IA.

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.

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.

Future planned studies will include testing of histone H3 acetylation, induction of gammaH2AX, analysis of ROS resistance and DNA methylation profiles.

## Patient Population

Patients must have morphologically confirmed newly diagnosed acute myelogenous leukemia (AML), as defined in the protocol.

Patients must 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. Patients with prior history of MDS must not have received azacitidine, decitabine, lenalidomide or vorinostat.

Patients must be between 18 and 60 (inclusive) years of age. Patients must have Zubrod performance status of 3 or lower. Patients must have an adequate cardiac function. Patients must not have prolonged QTc interval or cardiac disease. Patients with a prior malignancy are eligible providing they do not require concurrent therapy. Patients must not be receiving valproic acid. Patients who are known to be HIV+ are eligible providing they meet additional criteria in the protocol. Patients with known Hepatitis B or Hepatitis C infection may be eligible providing they have viral load below 800,000 IU/L.

## Stratification/Descriptive Factors

At randomization, patients will be stratified as follows: (1) age at registration: $< 40$ years vs $\geq 40$ years; (2) onset of leukemia: de novo vs treatment related and/or AML arising from antecedent hematologic disease.

## Accrual Goals

The accrual goal of this study is 705 eligible patients (235 eligible patients per arm). Up to five interim analyses will be completed. The first analysis will check for harm and the second analysis will test for futility. The third, fourth, and fifth interim analyses will include both futility and efficacy analyses.

## Summary Statement

As of December 31, 2014, 517 patients have enrolled. Twelve patients were ineligible due to the following reasons: insufficient blasts (6), no evidence of AML (2), having APL, receiving valproic acid at the time of registration, being intubated prior to registration, and inadequate heart function (one patient each). Six eligible patients did not receive any protocol treatment, coded as major protocol deviations, are not evaluable for adverse events. Two additional patients were also coded as having major protocol deviations. One was given AraC at the wrong dose and the other was given an incorrect treatment at re-induction.

Four hundred sixty-five patients were assessed for adverse events on protocol induction treatment. There have been five treatment-related deaths on the 7+3 arm (AraC + Daunorubicin ): one due to multi-organ failure and this patient also experienced Grade 4 sepsis, febrile neutropenia, hepatic failure, and acute kidney injury; one due to cardiac arrest and this patient also experienced Grade 4 acute kidney injury; one due to venous occlusive disease (coded as 'Hepatobil disorders-Other'); one due to respiratory failure and the patient also experienced Grade 4 hypoxia and sepsis; and another one due to platelet decreased (coded as 'Death NOS'). Seventeen additional patients on the 7+3 arm experienced treatment-related Grade 4 non-hematologic toxicities.

Twelve treatment-related deaths occurred on the IA arm (AraC + Idarubicin) due to the following reasons: sepsis (5), cardiac arrest (3), ARDS (1), multi-organ failure (1), and gastric hemorrhage (1). One patient who died of sepsis also died of septic shock and septic emboli (coded as 'Infections/ infestations-Other') and uncal herniation, tonsillar herniation, and edema herniation (coded as 'Nervours system disorders-Other'), and this patient also experienced Grade 4 hypotension. Another patient who died of sepsis also experienced Grade 4 febrile neutropenia, enterocolitis, and ischemic bowel (coded as 'GI disorders-Other'). Another three patients who died of sepsis experienced Grade 4 respiratory failure, hypotension, and enterocolitis (one each). One patient who died of cardiac arrest also died of bronchopulmonary hemorrhage. The patient who died of ARDS experienced Grade 4 atrial fibrillation. Sixteen additional patients experienced Grade 4 toxicities, including acute respiratory distress (coded as 'Respiratory, thoracic and mediastinal disorders-Other').

Thirteen treatment-related deaths occurred on the IA+V arm (AraC + Idarubicin + Vorinostat) due to the following reasons: sepsis (8), respiratory failure (3), multi-organ failure (1), intracranial hemorrhage (1), cardiac arrest (1), and bronchopulmonary hemorrhage (1). Two patients who died of sepsis also died of respiratory failure. The patient who died of multi-organ failure also experienced Grade 4 fever, dyspnea, respiratory failure, increased blood bilirubin, bradycardia/supraventricular tachycardia (SVT) (coded as 'Cardiac disorder-Other'), creatinine increased, and hyperglycemia. Other patients also experienced Grade 4 non-hematologic toxicities: respiratory failure (4), sepsis (4), hypotension (2), hypoxia (2), ARDS (2), heart failure, atrial fibrillation, gastric hemorrhage, febrile neutropenia, lung infection, edema cerebral, multi-organ failure, stroke, hypernatremia, acute kidney injury, dyspnea, blood bilirubin increased, creatinine increased, and diffuse alveolar hemorrhage (coded as 'Respiratory, thoracic and mediastinal disorders-Other'). Twenty-five additional patients experienced Grade 4 toxicities, including cellulitis on both arms (coded as 'Infections/infestations-Other').

Eleven patients were ineligible for consolidation due to the following reasons: not meeting protocol defined remission (5), persistent leukemia cutis (1), evidence of residual extramedullary disease (1), being ineligible for step 1 (4). One patient on the IA arm did not receive any consolidation treatment, coded as a major protocol deviation, is not evaluable for adverse events.

One possibly treatment related death occurred on the 7+3 consolidation arm and is reported as both 'Respiratory, thoracic and mediastinal disorders-Other' and 'Death NOS'. Thirteen additional patients on the 7+3 consolidation arm experienced treatment-related Grade 4 non-hematologic toxicities, including cardiomyopathy (coded as 'Cardiac disorders-Other'), acute hepatic failure (coded as 'GI disorders-Other'), and klebsiella pneumonia (coded as Infections/ infestations-Other').

One treatment related death occurred on the IA consolidation arm. The patient died of sepsis and also experienced Grade 4 restrictive cardiomyopathy, acute coronary syndrome, multi-organ failure, acute kidney injury, and febrile neutropenia. Fourteen additional patients experienced Grade 4 non-hematologic toxicities during consolidation.

Four treatment-related deaths occurred on the IA+V arm due to the following reasons: respiratory failure (2), sepsis, and intracranial hemorrhage (one patient each). One patient who died of respiratory failure also experienced Grade 4 febrile neutropenia and sepsis. The patient who died of sepsis also experienced Grade 4 respiratory failure and increased blood bilirubin. Fifteen additional patients on the IA+V arm reported Grade 4 non-hematologic adverse events during consolidation.

## Registration by Institution

Registrations ending December 31, 2014

| Institutions | Total Reg |
|---|---|
| Alliance | 151 |
| ECOG-ACRIN | 107 |
| Stanford University | 41 |
| Birmingham, U of AL | 25 |
| NCIC-CTG | 21 |
| Cleveland Clinic OH | 18 |
| Kansas, U of | 17 |
| Rochester, Univ of | 17 |
| Davis, U of CA | 10 |
| Kentucky, U of | 9 |
| Loyola University | 8 |
| Yale University | 8 |
| Mississippi, Univ of | 7 |
| Oregon Hlth Sci Univ | 7 |
| NRG | 6 |
| Oklahoma, Univ of | 6 |
| West Michigan NCORP | 6 |
| Arizona MC, U of | 5 |
| Dayton NCORP | 5 |
| H Lee Moffitt CC | 5 |
| MUSC MU-NCORP | 5 |
| MD Anderson | 4 |
| Prov Portland MC/PCRC NCORP | 4 |
| City of Hope Med Ctr | 3 |
| Irvine, U of CA | 3 |
| Providence Hosp | 3 |
| Upstate Carolina | 3 |
| Florida, Univ of/Yale University | 2 |
| Michigan, U of | 2 |
| Montana NCORP | 2 |
| Wayne State Univ | 2 |
| Heartland NCORP | 1 |
| Kansas City NCORP | 1 |
| Michigan CRC NCORP | 1 |
| Southeast CCC NCORP | 1 |
| St Luke's Mt State/PCRC NCORP | 1 |
| **Total (36 Institutions)** | **517** |

## Registration, Eligibility, and Evaluability

Induction/Re-induction

Registrations ending December 31, 2014; Data as of March 5, 2015

| | TOTAL | AraC + Daunorubicin | AraC + Idarubicin | Vorinostat + AraC + Idarubicin |
|---|---|---|---|---|
| NUMBER REGISTERED | 517 | 168 | 173 | 176 |
| INELIGIBLE | 12 | 1 | 5 | 6 |
| ELIGIBLE | 505 | 167 | 168 | 170 |
| RESPONSE ASSESSMENT | | | | |
| Determinable | 420 | 144 | 139 | 137 |
| Not Determinable | 29 | 4 | 13 | 12 |
| Too Early | 56 | 19 | 16 | 21 |
| ADVERSE EVENT ASSESSMENT | | | | |
| Evaluable | 465 | 153 | 154 | 158 |
| Not Evaluable | 6 | 0 | 2 | 4 |
| Too Early | 34 | 14 | 12 | 8 |

## Patient Characteristics

Induction/Re-induction

Registrations ending December 31, 2014; Data as of March 5, 2015

| | AraC + Daunorubicin (n=167) | | AraC + Idarubicin (n=168) | | Vorinostat + AraC + Idarubicin (n=170) | |
|---|---|---|---|---|---|---|
| AGE | | | | | | |
| Median | 50.2 | | 51.3 | | 48.6 | |
| Minimum | 19.2 | | 18.8 | | 20.1 | |
| Maximum | 60.6 | | 60.9 | | 61.0 | |
| SEX | | | | | | |
| Males | 92 | 55% | 87 | 52% | 88 | 52% |
| Females | 75 | 45% | 81 | 48% | 82 | 48% |
| HISPANIC | | | | | | |
| Yes | 13 | 8% | 13 | 8% | 14 | 8% |
| No | 143 | 86% | 138 | 82% | 148 | 87% |
| Unknown | 11 | 7% | 17 | 10% | 8 | 5% |
| RACE | | | | | | |
| White | 143 | 86% | 140 | 83% | 141 | 83% |
| Black | 12 | 7% | 12 | 7% | 10 | 6% |
| Asian | 3 | 2% | 3 | 2% | 7 | 4% |
| Pacific Islander | 1 | 1% | 1 | 1% | 0 | 0% |
| Native American | 0 | 0% | 0 | 0% | 3 | 2% |
| Multi-Racial | 0 | 0% | 1 | 1% | 0 | 0% |
| Unknown | 8 | 5% | 11 | 7% | 9 | 5% |
| AGE | | | | | | |
| < 40 years | 44.0 | 26% | 46.0 | 27% | 46.0 | 27% |
| ≥ 40 years | 123.0 | 74% | 122.0 | 73% | 124.0 | 73% |
| ONSET | | | | | | |
| De novo | 151 | 90% | 152 | 90% | 154 | 91% |
| Treatment related and/or AML arising from antecedent hematologic disease | 16 | 10% | 16 | 10% | 16 | 9% |

## Treatment Summary

Induction/Re-induction

Registrations ending December 31, 2014; Data as of March 5, 2015

| | Total |
|---|---|
| NUMBER ON PROTOCOL TREATMENT | 40 |
| NUMBER OFF PROTOCOL TREATMENT | 465 |
| REASON OFF TREATMENT | |
| Treatment completed as planned | 355 |
| Adverse Event or side effects | 11 |
| Refusal unrelated to adverse event | 11 |
| Progression/relapse | 3 |
| Death | 23 |
| Other - not protocol specified | 54 |
| Reason under review | 8 |
| MAJOR PROTOCOL DEVIATIONS | 8 |

## Number of Patients with a Given Type and Grade of Adverse Event

Induction/Re-induction

Adverse Events Unlikely or Not Related to Treatment Excluded

Non-Hematologic Adverse Events Only

Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed

Registrations ending December 31, 2014; Data as of March 5, 2015

| | AraC + Daunorubicin (n=153) Grade | | | | AraC + Idarubicin (n=154) Grade | | | | Vorinostat + AraC + Idarubicin (n=158) Grade | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADVERSE EVENT | ≤ 2 | 3 | 4 | 5 | ≤ 2 | 3 | 4 | 5 | ≤ 2 | 3 | 4 | 5 |
| ALT increased | 144 | 9 | 0 | 0 | 144 | 10 | 0 | 0 | 145 | 13 | 0 | 0 |
| ARDS | 152 | 0 | 1 | 0 | 151 | 1 | 1 | 1 | 155 | 0 | 3 | 0 |
| AST increased | 146 | 6 | 1 | 0 | 146 | 8 | 0 | 0 | 150 | 8 | 0 | 0 |
| Abdominal infection | 152 | 1 | 0 | 0 | 153 | 0 | 1 | 0 | 157 | 1 | 0 | 0 |
| Abdominal pain | 151 | 2 | 0 | 0 | 150 | 4 | 0 | 0 | 153 | 5 | 0 | 0 |
| Acidosis | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Acute kidney injury | 151 | 0 | 2 | 0 | 152 | 1 | 1 | 0 | 155 | 1 | 2 | 0 |
| Alkaline phosphatase increased | 151 | 2 | 0 | 0 | 152 | 2 | 0 | 0 | 157 | 1 | 0 | 0 |
| Alkalosis | 152 | 1 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Allergic reaction | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Anal hemorrhage | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Anal pain | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Anal ulcer | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Anorectal infection | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 155 | 3 | 0 | 0 |
| Anorexia | 150 | 2 | 1 | 0 | 148 | 6 | 0 | 0 | 150 | 8 | 0 | 0 |

| ADVERSE EVENT | AraC + Daunorubicin (n=153) Grade ≤ 2 | 3 | 4 | 5 | AraC + Idarubicin (n=154) Grade ≤ 2 | 3 | 4 | 5 | Vorinostat + AraC + Idarubicin (n=158) Grade ≤ 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atrial fibrillation | 153 | 0 | 0 | 0 | 153 | 0 | 1 | 0 | 157 | 0 | 1 | 0 |
| Atrial flutter | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Blood bilirubin increased | 150 | 3 | 0 | 0 | 148 | 4 | 2 | 0 | 145 | 10 | 3 | 0 |
| Bone infection | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Bronchopulmonary hemorrhage | 153 | 0 | 0 | 0 | 153 | 0 | 0 | 1 | 157 | 0 | 0 | 1 |
| Bullous dermatitis | 153 | 0 | 0 | 0 | 152 | 2 | 0 | 0 | 158 | 0 | 0 | 0 |
| Cardiac arrest | 152 | 0 | 0 | 1 | 151 | 0 | 0 | 3 | 156 | 0 | 1 | 1 |
| Cardiac disorder-Other, spec | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 0 | 1 | 0 |
| Catheter related infection | 153 | 0 | 0 | 0 | 150 | 4 | 0 | 0 | 155 | 3 | 0 | 0 |
| Chills | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Chronic kidney disease | 153 | 0 | 0 | 0 | 153 | 0 | 1 | 0 | 158 | 0 | 0 | 0 |
| Colitis | 152 | 1 | 0 | 0 | 151 | 3 | 0 | 0 | 155 | 1 | 2 | 0 |
| Colonic hemorrhage | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Conjunctivitis | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Constipation | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Constrictive pericarditis | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Creatinine increased | 152 | 1 | 0 | 0 | 152 | 2 | 0 | 0 | 154 | 3 | 1 | 0 |
| DIC | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Death NOS | 152 | 0 | 0 | 1 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Dehydration | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 156 | 2 | 0 | 0 |
| Dental caries | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Device related infection | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Diarrhea | 145 | 8 | 0 | 0 | 145 | 9 | 0 | 0 | 132 | 26 | 0 | 0 |
| Duodenal hemorrhage | 152 | 0 | 1 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Dyspepsia | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Dyspnea | 151 | 1 | 1 | 0 | 154 | 0 | 0 | 0 | 153 | 3 | 2 | 0 |
| ECG QT corrected int prolong | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 156 | 2 | 0 | 0 |
| Edema cerebral | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 0 | 1 | 0 |
| Edema limbs | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 157 | 1 | 0 | 0 |
| Ejection fraction decreased | 152 | 1 | 0 | 0 | 151 | 3 | 0 | 0 | 157 | 1 | 0 | 0 |
| Enterocolitis | 153 | 0 | 0 | 0 | 150 | 2 | 2 | 0 | 157 | 1 | 0 | 0 |
| Enterocolitis infectious | 153 | 0 | 0 | 0 | 150 | 4 | 0 | 0 | 155 | 3 | 0 | 0 |
| Epistaxis | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 157 | 1 | 0 | 0 |
| Esophageal hemorrhage | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Esophageal pain | 152 | 1 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Esophagitis | 151 | 2 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Eye infection | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Fatigue | 146 | 7 | 0 | 0 | 145 | 9 | 0 | 0 | 149 | 9 | 0 | 0 |
| Febrile neutropenia | 65 | 84 | 4 | 0 | 64 | 86 | 4 | 0 | 77 | 77 | 4 | 0 |
| Fever | 151 | 1 | 1 | 0 | 151 | 3 | 0 | 0 | 152 | 5 | 1 | 0 |
| GERD | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| GGT increased | 151 | 2 | 0 | 0 | 153 | 1 | 0 | 0 | 155 | 3 | 0 | 0 |
| GI disorders-Other, specify | 152 | 1 | 0 | 0 | 152 | 0 | 2 | 0 | 157 | 1 | 0 | 0 |
| Gastric hemorrhage | 153 | 0 | 0 | 0 | 153 | 0 | 0 | 1 | 156 | 1 | 1 | 0 |
| Generalized muscle weakness | 151 | 2 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Genital edema | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Gum infection | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Hand-Foot syndrome | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Headache | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 154 | 4 | 0 | 0 |

| ADVERSE EVENT | AraC + Daunorubicin (n=153) Grade ≤ 2 | 3 | 4 | 5 | AraC + Idarubicin (n=154) Grade ≤ 2 | 3 | 4 | 5 | Vorinostat + AraC + Idarubicin (n=158) Grade ≤ 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heart failure | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 156 | 1 | 1 | 0 |
| Hematuria | 153 | 0 | 0 | 0 | 152 | 2 | 0 | 0 | 158 | 0 | 0 | 0 |
| Hepatic failure | 152 | 0 | 1 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Hepatic infection | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Hepatobil disorders-Other | 152 | 0 | 0 | 1 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Hyperglycemia | 152 | 1 | 0 | 0 | 149 | 5 | 0 | 0 | 146 | 11 | 1 | 0 |
| Hyperhidrosis | 152 | 1 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Hyperkalemia | 153 | 0 | 0 | 0 | 153 | 0 | 1 | 0 | 158 | 0 | 0 | 0 |
| Hypermagnesemia | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Hypernatremia | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 0 | 1 | 0 |
| Hypertension | 149 | 4 | 0 | 0 | 153 | 1 | 0 | 0 | 155 | 2 | 1 | 0 |
| Hypoalbuminemia | 151 | 2 | 0 | 0 | 150 | 4 | 0 | 0 | 152 | 6 | 0 | 0 |
| Hypocalcemia | 148 | 4 | 1 | 0 | 147 | 7 | 0 | 0 | 138 | 17 | 3 | 0 |
| Hypoglycemia | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Hypokalemia | 144 | 7 | 2 | 0 | 143 | 11 | 0 | 0 | 140 | 16 | 2 | 0 |
| Hypomagnesemia | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Hyponatremia | 144 | 9 | 0 | 0 | 147 | 7 | 0 | 0 | 154 | 4 | 0 | 0 |
| Hypophosphatemia | 140 | 12 | 1 | 0 | 137 | 14 | 3 | 0 | 137 | 19 | 2 | 0 |
| Hypotension | 152 | 1 | 0 | 0 | 151 | 1 | 2 | 0 | 152 | 3 | 3 | 0 |
| Hypoxia | 152 | 0 | 1 | 0 | 154 | 0 | 0 | 0 | 152 | 3 | 3 | 0 |
| Infections/infestations-Other | 147 | 6 | 0 | 0 | 144 | 9 | 0 | 1 | 148 | 9 | 1 | 0 |
| Infective myositis | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Intracranial hemorrhage | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 0 | 0 | 1 |
| Investigations-Other, specify | 152 | 1 | 0 | 0 | 150 | 1 | 3 | 0 | 157 | 1 | 0 | 0 |
| Jejunal obstruction | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Kidney infection | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| LV systolic dysfunction | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Laryngeal mucositis | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Lipase increased | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Lower GI hemorrhage | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 156 | 2 | 0 | 0 |
| Lung infection | 140 | 13 | 0 | 0 | 149 | 4 | 1 | 0 | 146 | 10 | 2 | 0 |
| Metab/nutrition disorders-Oth | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Middle ear inflammation | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Mucosal infection | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Mucositis oral | 147 | 6 | 0 | 0 | 146 | 8 | 0 | 0 | 152 | 6 | 0 | 0 |
| Multi-organ failure | 152 | 0 | 0 | 1 | 153 | 0 | 0 | 1 | 154 | 1 | 2 | 1 |
| Nausea | 149 | 4 | 0 | 0 | 144 | 10 | 0 | 0 | 153 | 5 | 0 | 0 |
| Nervous sys disorders-Other | 153 | 0 | 0 | 0 | 153 | 0 | 0 | 1 | 158 | 0 | 0 | 0 |
| Non-cardiac chest pain | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Oral pain | 151 | 2 | 0 | 0 | 151 | 3 | 0 | 0 | 158 | 0 | 0 | 0 |
| Pain in extremity | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Papulopustular rash | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Pericardial effusion | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Pharyngeal mucositis | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Pleural effusion | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Pneumonitis | 152 | 1 | 0 | 0 | 152 | 2 | 0 | 0 | 157 | 1 | 0 | 0 |
| Pruritus | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Pulmonary edema | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 154 | 3 | 1 | 0 |
| Rash acneiform | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |

| | AraC + Daunorubicin (n=153) | | | | AraC + Idarubicin (n=154) | | | | Vorinostat + AraC + Idarubicin (n=158) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** |
| Rash maculo-papular | 149 | 4 | 0 | 0 | 138 | 16 | 0 | 0 | 153 | 5 | 0 | 0 |
| Rectal hemorrhage | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Rectal pain | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Resp/thoracic/mediastinal ds | 153 | 0 | 0 | 0 | 153 | 0 | 1 | 0 | 156 | 1 | 1 | 0 |
| Respiratory failure | 151 | 0 | 1 | 1 | 152 | 0 | 1 | 1 | 149 | 0 | 6 | 3 |
| Scrotal infection | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 0 | 1 | 0 |
| Sepsis | 143 | 0 | 10 | 0 | 141 | 0 | 8 | 5 | 135 | 0 | 15 | 8 |
| Sinus bradycardia | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Sinus tachycardia | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 157 | 1 | 0 | 0 |
| Sinusitis | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Skin infection | 151 | 2 | 0 | 0 | 154 | 0 | 0 | 0 | 156 | 2 | 0 | 0 |
| Skin ulceration | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Skin/subq tissue ds-Other | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 157 | 1 | 0 | 0 |
| Soft tissue infection | 152 | 0 | 1 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Sore throat | 152 | 1 | 0 | 0 | 152 | 2 | 0 | 0 | 156 | 2 | 0 | 0 |
| Stomach pain | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Stroke | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 157 | 0 | 1 | 0 |
| Supraventricular tachycardia | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Syncope | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 156 | 2 | 0 | 0 |
| TTP | 151 | 0 | 2 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Testicular disorder | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Thromboembolic event | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 158 | 0 | 0 | 0 |
| Tumor lysis syndrome | 153 | 0 | 0 | 0 | 151 | 3 | 0 | 0 | 154 | 4 | 0 | 0 |
| Typhlitis | 150 | 3 | 0 | 0 | 147 | 7 | 0 | 0 | 142 | 16 | 0 | 0 |
| Upper respiratory infection | 152 | 1 | 0 | 0 | 154 | 0 | 0 | 0 | 156 | 2 | 0 | 0 |
| Urinary tract infection | 152 | 1 | 0 | 0 | 153 | 1 | 0 | 0 | 153 | 5 | 0 | 0 |
| Urine output decreased | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Vaginal hemorrhage | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| Vascular access complication | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 157 | 0 | 1 | 0 |
| Vasovagal reaction | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 0 | 1 | 0 |
| Ventricular tachycardia | 153 | 0 | 0 | 0 | 153 | 1 | 0 | 0 | 158 | 0 | 0 | 0 |
| Vomiting | 152 | 1 | 0 | 0 | 150 | 4 | 0 | 0 | 154 | 4 | 0 | 0 |
| Weight loss | 153 | 0 | 0 | 0 | 154 | 0 | 0 | 0 | 157 | 1 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 45 | 86 | 17 | 5 | 32 | 94 | 16 | 12 | 30 | 90 | 25 | 13 |

# S1204 Surveillance

## A Sero-Epidemiologic Survey and Cost-Effectiveness Study of Screening for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Among Newly Diagnosed Cancer Patients

**Study Chairs:**
S Ramsey, R Loomba, R Chugh, D Hershman, J Hwang

**Statisticians:**
J Unger, K Arnold

**Data Coordinator:**
M Yee

**Date Activated:**
08/29/2013

**Date Closed*:**
12/15/2014

*Temporary Closure

**Objectives**

Among newly diagnosed cancer patients presenting to SWOG-affiliated community and academic oncology clinics, estimate the prevalence of human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV) infection.

Evaluate known sociodemographic, clinical, and behavioral factors that are significantly associated with previously undiagnosed HIV, HBV, and/or HCV infection in a population of people with newly diagnosed cancer.

Among patients who are identified as having HIV, HBV, and/or HCV, evaluate the timing and type of treatments received, both for the viral infections and the cancers.

Evaluate type and rate of cancer treatment-related adverse events in patients with HIV, HBV, and/or HCV infection.

Determine the cost-effectiveness of (1) routine, universal screening and (2) risk factor-directed screening of newly diagnosed cancer patients for HIV, HBV and/or HCV versus current care.

Create a biorepository of stored serum for future translational medicine studies that may include identifying genomic and viral factors that increase the risk of serious adverse effects among participants infected with HIV, HBV, and/or HCV being treated for invasive cancers.

**Patient Population**

Patients must be presenting for evaluation or treatment for the first diagnosis of a new cancer malignancy (including hematologic). Confirmed pathologic diagnosis must be within 120 days of registration. Patients presenting for "second opinions" of confirmed malignancies are eligible, including those who have started cancer treatment at other facilities. Individuals are ineligible if they have been diagnosed with a malignancy other than the current malignancy within the past five years, with the exception of basal cell or squamous cell skin cancer, in situ cervical cancer, or in situ breast cancer. Individuals are eligible if they have had no evidence of disease for a prior malignancy, except as noted above, for at least five years prior to randomization.

Patients must be 18 years of age or older. Patients must have had their blood drawn for testing for HIV, HBV and HCV prior to registration. Patients who have had HIV, HBV and/or HCV testing within 60 days prior to registration and who do not wish to be retested are eligible, provided supporting documents can be obtained confirming viral test results for all three viruses. Patients who are viral positive for either HIV, HBV, and/or HCV and who do not wish to be retested are eligible, provided documentation of viral load within 120 days prior to registration can be obtained. Note that these patients must be tested for or provide current viral load for all three viruses to be eligible. All documentation must be obtained prior to registration. Patients are allowed to participate in other clinical trials.

**Cancer Control Credits**
No cancer control credits are awarded for this study.

**Accrual Goals**
A total of 3,000 eligible patients will be accrued.

**Summary Statement**
For the current status of this study, please refer to the Cancer Care Delivery chapter.

# S1312 Phase I

## A Phase I Study of Inotuzumab (NSC-772518) in Combination with CVP (Cyclophosphamide, Vincristine, Prednisone) for Patients with Relapsed/Refractory CD22-Positive Acute Leukemia (including B-ALL, Mixed Phenotypic Leukemia, and Burkitt's Leukemia)


**Study Chairs:**
A Advani, M Liedtke

**Date Activated:**
04/01/2014

**Statisticians:**
H Li, M Othus

**Data Coordinator:**
L Highleyman


**Objectives**

To assess the safety of inotuzumab in combination with cyclophosphamide, vincristine and prednisone (CVP) and to determine the maximum tolerated dose (MTD) of inotuzumab in this regimen for patients with relapsed or refractory CD22-positive acute leukemia (B-ALL, mixed phenotype, and Burkitt's).

To estimate the preliminary activity [response rate: complete remission (CR) + complete remission with incomplete count recovery (CRi)] of this combination in the expansion cohort.

To estimate the frequency and severity of toxicities of this combination in this patient population.

**Patient Population**

Patients must have a diagnosis of relapsed or refractory CD22-positive acute leukemia including B-ALL, mixed phenotype leukemia (bilineal and biphenotypic), or Burkitt's leukemia based on WHO classification. Patients must have evidence of acute leukemia in their peripheral blood or bone marrow. Patients must have $\geq$ 5% blasts in the peripheral blood or bone marrow. At least $\geq$ 20% of those blasts must be CD22-positive (surface) based on local immunophenotyping and histopathology. Patients must be refractory or have relapsed following prior induction therapy.

Patients may have received prior allogeneic transplant or autologous transplant. Patients with prior allogeneic bone marrow transplant will be eligible only if the conditions stated in the protocol are met. Patients known to have Ph+ ALL must have either failed treatment or been intolerant to treatment with at least one tyrosine kinase inhibitor. Patients must not have received prior treatment with inotuzumab. Previous treatment with other anti-CD22 antibodies must have been completed at least 90 days prior to registration. Patients must not have received any chemotherapy, investigational agents, or undergone major surgery within 14 days prior to registration with the following exceptions: (1) Monoclonal antibodies must not have been received for 42 days prior to registration; (2) Steroids, vincristine, 6-mercaptopurine, methotrexate, thioguanine and intrathecal chemotherapy are permitted within any time frame prior to registration.

Patients must be at least 18 years of age and have Zubrod performance status of 0-2. Patients must not have a systemic bacterial, fungal, or viral infection that is not controlled. Patients must not have active CNS involvement. Patients must not have Grade 2 or higher neuropathy (sensory/motor). Patients must not have a history of chronic or active hepatitis B or C infection. Patients must not have evidence or history of veno-occlusive disease or sinusoidal obstruction syndrome. Patients who are known to be HIV+ are eligible providing they meet all of the criteria in the protocol. Patients must have adequate hematologic, renal, hepatic and cardiac function.

**Accrual Goals**
Patient enrollment will follow the traditional "3+3" algorithm until the MTD for inotuzumab ozogamicin is reached or the highest dose tested is judged tolerable. This study will accrue 3 to 30 eligible and evaluable patients in the Phase I portion and six additional eligible patients in the expansion cohort.

**Summary Statement**
The study will evaluate up to five dose levels of inotuzumab ozogamicin in five separate cohorts. The initial dose level of 0.4 mg/m$^2$ inotuzumab ozogamicin has completed accrual. Five patients were registered. Two patients were not evaluable for dose limiting toxicities (DLT) and were replaced due to off-protocol treatment after the last dose of inotuzumab due to persistent disease. Of the three evaluable patients in the 0.4 mg/m$^2$ cohort, no DLTs were reported.

Among five patients on the dose 0.4 mg/m$^2$ cohort assessed for toxicity, no Grade 4 or higher non-hematologic toxicities reported.

As of February 4, 2015, four patients have been registered to the second cohort evaluating inotuzumab at 0.6 mg/m$^2$ at day 1 and 0.4 mg/m$^2$ at day 15 dose level. One patient was ineligible due to inadequate liver function. An additional patient was removed from study on Day 35 due to prolonged myelosuppression, this patient was not evaluable for DLTs and will be replaced. As of March 1, 2015, there have been no DLTs reported for the two evaluable patients on the dose 0.6 mg/m$^2$ cohort.

## Registration by Institution

Registrations ending February 4, 2015

| Institutions | Total Reg |
|---|---|
| Cleveland Clinic OH | 5 |
| Stanford University | 2 |
| Baylor College | 1 |
| Rochester, Univ of | 1 |
| **Total (4 Institutions)** | **9** |

## Registration, Eligibility, and Evaluability

Registrations ending February 4, 2015; Data as of March 1, 2015

| | TOTAL | CVP + Inotuzumab dose level 1 | CVP + Inotuzumab dose level 2 |
|---|---|---|---|
| NUMBER REGISTERED | 9 | 5 | 4 |
| INELIGIBLE | 1 | 0 | 1 |
| ELIGIBLE | 8 | 5 | 3 |
| RESPONSE ASSESSMENT | | | |
| Determinable | 6 | 5 | 1 |
| Too Early | 2 | 0 | 2 |
| ADVERSE EVENT ASSESSMENT | | | |
| Evaluable | 8 | 5 | 3 |

## Patient Characteristics

Initial Registration

Registrations ending February 4, 2015; Data as of March 1, 2015

| | CVP + Inotuzumab dose level 1 (n=5) | | CVP + Inotuzumab dose level 2 (n=3) | |
|---|---|---|---|---|
| AGE | | | | |
| Median | 48.9 | | 33.4 | |
| Minimum | 22.4 | | 20.7 | |
| Maximum | 73.7 | | 51.2 | |
| SEX | | | | |
| Males | 4 | 80% | 0 | 0% |
| Females | 1 | 20% | 3 | 100% |
| HISPANIC | | | | |
| Yes | 2 | 40% | 1 | 33% |
| No | 3 | 60% | 2 | 67% |
| RACE | | | | |
| White | 4 | 80% | 2 | 67% |
| Black | 1 | 20% | 1 | 33% |

## Treatment Summary

Initial Registration

Registrations ending February 4, 2015; Data as of March 1, 2015

| | TOTAL | CVP + Inotuzumab dose level 1 | CVP + Inotuzumab dose level 2 |
|---|---|---|---|
| NUMBER ON PROTOCOL TREATMENT | 2 | 0 | 2 |
| NUMBER OFF PROTOCOL TREATMENT | 6 | 5 | 1 |
| REASON OFF TREATMENT | | | |
| Treatment completed as planned | 1 | 1 | 0 |
| Adverse Event or side effects | 0 | 0 | 0 |
| Refusal unrelated to adverse event | 0 | 0 | 0 |
| Progression/relapse | 1 | 1 | 0 |
| Death | 0 | 0 | 0 |
| Other - not protocol specified | 4 | 3 | 1 |
| Reason under review | 0 | 0 | 0 |
| MAJOR PROTOCOL DEVIATIONS | 0 | 0 | 0 |

## Number of Patients with a Given Type and Grade of Adverse Event

Adverse Events Unlikely or Not Related to Treatment Excluded
Hematologic Adverse Events Only
Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed
Registrations ending February 4, 2015; Data as of March 1, 2015

| | CVP + Inotuzumab dose level 1 (n=5) | | | | CVP + Inotuzumab dose level 2 (n=3) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** |
| Anemia | 4 | 0 | 1 | 0 | 3 | 0 | 0 | 0 |
| Lymphocyte count decreased | 4 | 0 | 1 | 0 | 3 | 0 | 0 | 0 |
| Neutrophil count decreased | 3 | 0 | 2 | 0 | 2 | 0 | 1 | 0 |
| Platelet count decreased | 3 | 0 | 2 | 0 | 2 | 0 | 1 | 0 |
| White blood cell decreased | 2 | 0 | 3 | 0 | 0 | 1 | 2 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 2 | 0 | 3 | 0 | 0 | 1 | 2 | 0 |

## Number of Patients with a Given Type and Grade of Adverse Event

Initial Registration
Adverse Events Unlikely or Not Related to Treatment Excluded
Non-Hematologic Adverse Events Only
Adverse Events with No Entries for Grades 3 to 5 Have Been Suppressed
Registrations ending February 4, 2015; Data as of March 1, 2015

| | CVP + Inotuzumab dose level 1 (n=5) | | | | CVP + Inotuzumab dose level 2 (n=3) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade | | | | Grade | | | |
| **ADVERSE EVENT** | **≤ 2** | **3** | **4** | **5** | **≤ 2** | **3** | **4** | **5** |
| Febrile neutropenia | 5 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| GI disorders-Other, specify | 5 | 0 | 0 | 0 | 2 | 1 | 0 | 0 |
| Gastric hemorrhage | 4 | 1 | 0 | 0 | 3 | 0 | 0 | 0 |
| Intracranial hemorrhage | 4 | 1 | 0 | 0 | 3 | 0 | 0 | 0 |
| **MAX. GRADE ANY ADVERSE EVENT** | 3 | 2 | 0 | 0 | 2 | 1 | 0 | 0 |

# S1318 Phase II

## Coordinating Group: SWOG

# A Phase II Study of Blinatumomab and POMP (Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine) for Elderly Patients (≥ 65 Years of Age) with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)

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**Participants:**
SWOG, CTSU (supported by Alliance, NRG, and ECOG-ACRIN)

**Date Activated:**
01/12/2015

**Study Chairs:**
A Advani, K O'Dwyer, M Wiedewult (Alliance), J Park (ECOG-ACRIN)

**Statisticians:**
H Li, M Othus

**Data Coordinator:**
T Maher

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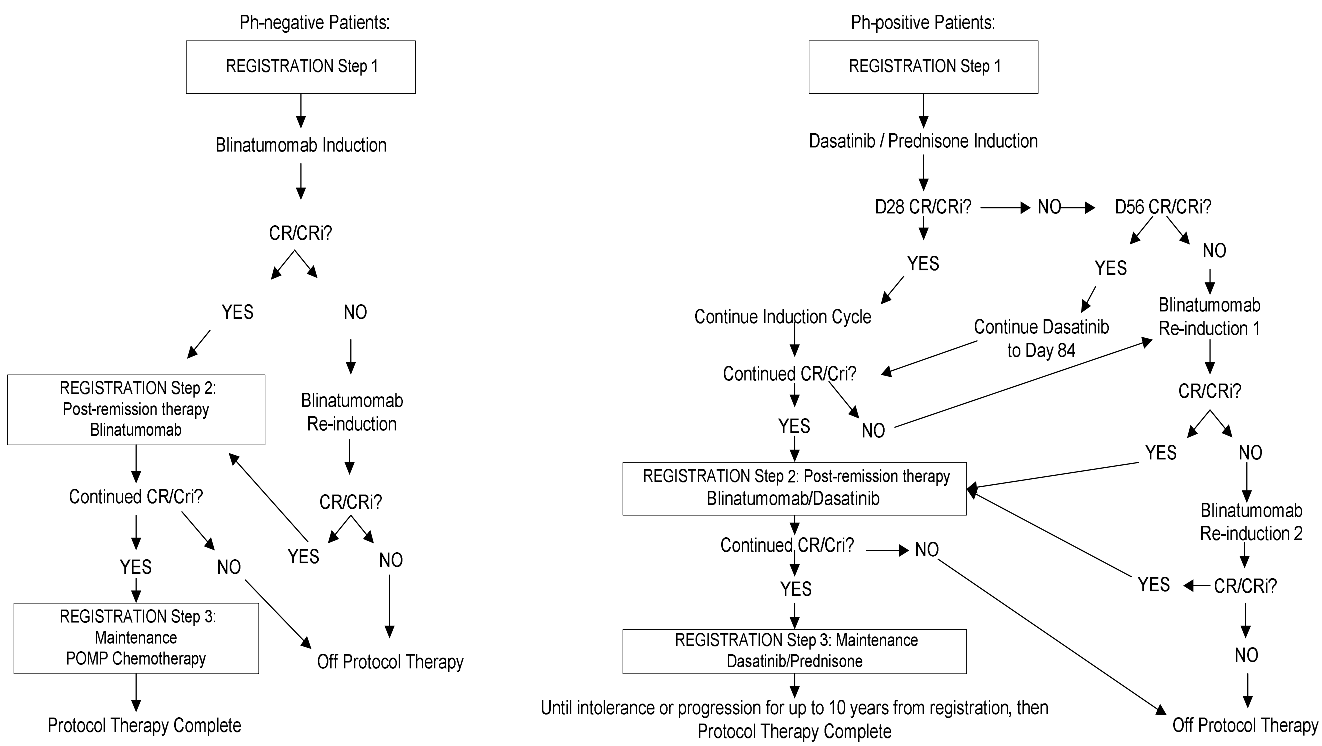
## SCHEMA



## Objectives

To evaluate the three-year survival rate in elderly patients with newly diagnosed Philadelphia chromosome (Ph) negative ALL treated with blinatumomab followed by POMP maintenance.

To evaluate in a preliminary manner (feasibility study) the safety of dasatinib-steroid based induction followed by blinatumomab treatment in combination with dasatinib followed by dasatinib-based maintenance in elderly patients with newly diagnosed Ph-positive ALL.

To evaluate toxicities in these patient populations treated with these regimens.

To estimate the rates of complete response (CR), complete response with incomplete count recovery (CRi), and disease-free survival in Ph-negative patients.

To estimate disease-free and overall survival in elderly Ph-positive patients.

To estimate in each cohort the rate of minimal residual disease (MRD) negativity, and the time to achieve MRD negativity (exploratory analysis).

To determine whether anti-idiotype antibodies directed against blinatumomab develop with blinatumomab treatment in this study.

## Patient Population

Patients must have a new morphologic diagnosis of precursor B cell acute lymphoblastic leukemia (ALL) (non-T cell) based on WHO criteria as defined in protocol. Patients with Burkitts (L3) are not eligible for this study. Patients must have a diagnosis of Ph-negative ALL or Ph-positive ALL by cytogenetics, FISH or polymerase chain reaction (PCR). If not already known, BCR-ABL status (p190 or p210) must be evaluated in Ph-positive patients by PCR. Patients must have evidence of ALL in their marrow or peripheral blood with at least 20% lymphoblasts present within 14 days prior to registration. Immunophenotyping of the blood or marrow lymphoblasts must be performed to determine lineage within 14 days prior to registration. Patients must not have testicular involvement.

Patients must not have received any prior chemotherapy, radiation therapy, or other therapy for the treatment of ALL (other than those noted below) and must not be receiving any immunosuppressive therapy. Patients must not have received any prior investigational therapy within 28 days prior to registration. Patients may have received the following within any time prior to registration: low dose chemotherapy, TKI therapy, steroids, hydroxyurea, leukapheresis, intrathecal chemotherapy, or vincristine. Patients must not have received any monoclonal antibody therapy within 42 days of registration.

Patients must be at least 65 years of age and have a Zubrod performance status of 0-2. Patients must have adequate hepatic, cardiac and renal function. Patients must not have a history or presence of clinically relevant CNS pathology and must have a lumbar puncture to determine CNS involvement of ALL within 14 days prior to registration. Patients must not have systemic fungal, bacterial, viral or other infection that is not controlled. Patients must not have Grade 2 or higher neuropathy (cranial, motor or sensory) within 14 days prior to registration. Patients known to be positive for HIV may be eligible, providing they meet the criteria in the protocol. Patients must not be candidates for allogeneic hematopoietic stem cell transplant. Patients must not have any known autoimmune disease. Ph-negative patients must have PT/PTT/INR/fibrinogen and neurologic assessment tests within 28 days prior to registration. Ph-positive patients must not have active pericardial effusion, ascites or pleural effusion of any grade.

## Accrual Goals

This study will accrue 26 eligible Ph-negative patients. An interim analysis will be performed among the first 11 of these patients. If at least five complete remissions (CR or CRi) are observed, then the study will continue to full accrual. The study will continue accruing while the remission data is being reviewed.

This study will initially accrue six eligible and evaluable Ph-positive patients. If the regimen is considered safe, then the study will accrue six additional eligible Ph-positive patients.

## Summary Statement

The study was activated on January 12, 2015.

# A041202 Phase III SWOG Supported CTSU Study

**Coordinating Group: Alliance**

# A Randomized Phase III Study of Bendamustine plus Rituximab Versus Ibrutinib plus Rituximab Versus Ibrutinib Alone In Untreated Older Patients (≥ 65 Years of Age) With Chronic Lymphocytic Leukemia (CLL)

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**Participants:**
Alliance, CTSU

**Date Activated:**
12/10/2013

**Study Chairs:**
J Woyach (Alliance), S Coutre (SWOG)

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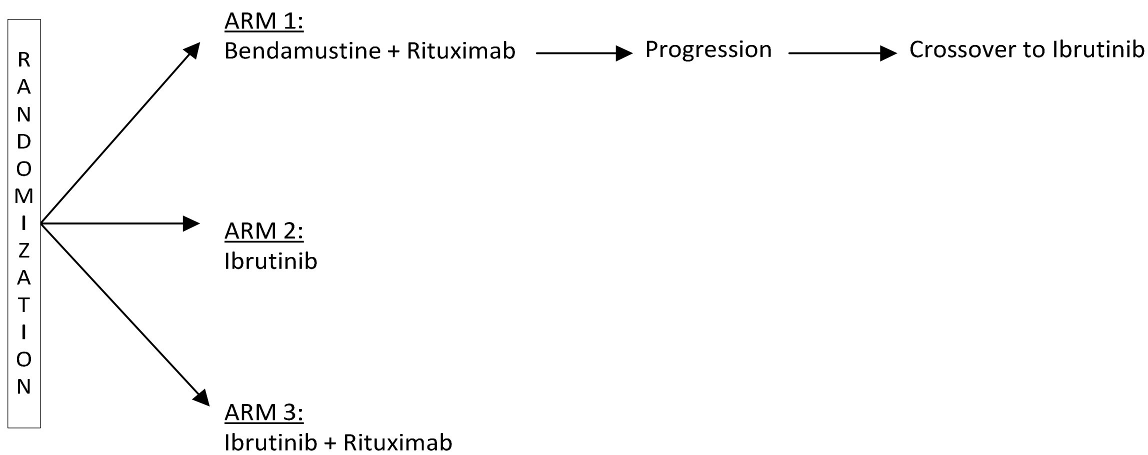
## SCHEMA




**Objectives**

To determine whether progression free survival (PFS) is superior after therapy with bendamustine in combination with rituximab, ibrutinib alone, or ibrutinib in combination with rituximab in patients age 65 or older with previously untreated CLL.

To determine 2-year PFS in each of the three treatment arms.

To determine which treatment arm produces superior overall survival (OS).

To determine the complete response (CR) rate, complete and nodular partial response (CR/nPR) rate, and overall response (PR+nPR+CR) rate (ORR) among the three treatment arms and compare these arms.

To determine the impact of MRD-negative disease at time of CR documentation and at 2 years on PFS and OS in each of the treatment arms.

To determine duration of response after each of the three treatments and compare these treatment arms.

To determine toxicity and tolerability of the three treatment regimens.

To determine response and PFS of patients initially on the bendamustine in combination with rituximab arm who cross over to ibrutinib.

To determine whether baseline cytogenetic markers, Zap-70 methylation, IgVH mutational status, or select DNA mutations predict outcomes or time to response in these three arms.

To determine whether local FISH results for del(11q22.3) and del(17p13.1) are consistent with central analysis.

To determine whether baseline microRNA and gene expression markers are correlated with clinical outcomes of interest (e.g. progression-free and alive at 2 years versus not), as well as to explore changes in microRNA expression from baseline to post-treatment time points, with a focus on those with persistent lymphocytosis and relapse.

To determine whether eradication of MRD predicts longer duration of response with standard therapy and ibrutinib-based regimens.

To describe the baseline functional status, comorbid medical conditions, and number of medications of older CLL patients who meet criteria for therapy.

To determine how functionalstatus changes with therapy using baseline to 3-month evaluation and end-of-study/2-year evaluation; to determine whether this change is different among the treatment groups.

To determine whether geriatric assessment variables known to be associated with chemotherapy toxicity in other disease groups can also predict therapy-associated toxicity in the CLL population.

To assess whether the FCGR3A polymorphism (rs396991) is correlated with depth of response (MRD status) to ibrutinib plus rituximab after six cycles, with secondary endpoints CR rate, rapidity of response, and progression-free survival (PFS).

To assess whether C1QA polymorphism (rs172378) is correlated with MRD status, CR rate, rapidity of response, and PFS.

**Patient Population**

Patients must be diagnosed with CLL in accordance with IWCLL 2008 criteria as defined in the protocol. Patients must have intermediate or high-risk Rai stage CLL.

Patients must not have had prior therapy for CLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab or steroids). Treatment with rituximab and/or high dose corticosteroids for autoimmune complications of CLL must be completed at least four weeks prior to enrollment. Palliative steroids must be at a dose not higher than 20 mg/day of prednisone or equivalent corticosteroid at the time of registration.

Patients must be at least 65 years of age and have ECOG performance status of 0-2. Patients with active hepatitis B are not eligible. Patients with a positive hepatitis B core antibody but with negative hepatitis B DNA may participate, but must have hepatitis serologies and hepatitis B DNA monitored periodically. Patients must not have uncontrolled active systemic infection requiring intravenous antibiotics. Patients must have adequate hematologic, renal, cardiac and hepatic function. Patients with HIV are eligible if their CD4 count is $\geq 350$ cells/mm^3 and if they are not taking prohibited CYP-interacting medications. Patients must not have a known allergy to mannitol or prior significant hypersensitivity to rituximab. Patients must not be receiving active systemic anticoagulation with heparin or warfarin.

**Stratification/Descriptive Factors**

Patients are stratified by (1) Rai stage: intermediate vs high; (2) presence or absence of del(11q22.3) or del(17p13.1) on FISH; and (3) methylation of CpG 3 on Zap-70: $< 20\%$ vs $\geq 20\%$.

**Cancer Control Credits**

The NCI Division of Cancer Prevention has not assigned cancer control credits for registration to this study. There are potential cancer control credits for geriatric assessment.

**Accrual Goals**

A total of 498 evaluable patients will be accrued to this study. The study will conduct three interim analyses taking place after approximately 33%, 50% and 75% of events have occurred.

**Summary Statement**

Alliance reported a total accrual of 209 patients as of December 31, 2015, including 34 CTSU registrations from SWOG institutions. The complete November 2014 summary of this study from Alliance is available on the SWOG web site.

## Registration by Institution

Registrations ending December 31, 2014

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| Kaiser NCORP | 7 | Fowler Family Center/Baptist MU-NCORP | 1 |
| City of Hope Med Ctr | 6 | KaiserPermanenteCOL/Kaiser NCORP | 1 |
| KaiserPermanenteSCAL/Kaiser NCORP | 4 | Kansas, U of | 1 |
| Stanford University | 4 | Sacred Heart Med Onc/Arkansas, U of | 1 |
| Rochester, Univ of | 3 | St Luke's Mt State | 1 |
| Arizona MC, U of | 1 | Wayne State Univ | 1 |
| Cleveland Clinic OH | 1 | Yale University | 1 |
| Columbus NCORP | 1 | **Total (15 Institutions)** | **34** |

# C10701 Phase II SWOG Supported CTSU Study

## Coordinating Group: Alliance

# A Phase II Study of Dasatinib (Sprycel®)(IND #73969, NSC #732517) as Primary Therapy Followed by Transplantation for Adults ≥ 50 Years with Newly Diagnosed Ph+ Acute Lymphoblastic Leukemia by CALGB, ECOG, and SWOG

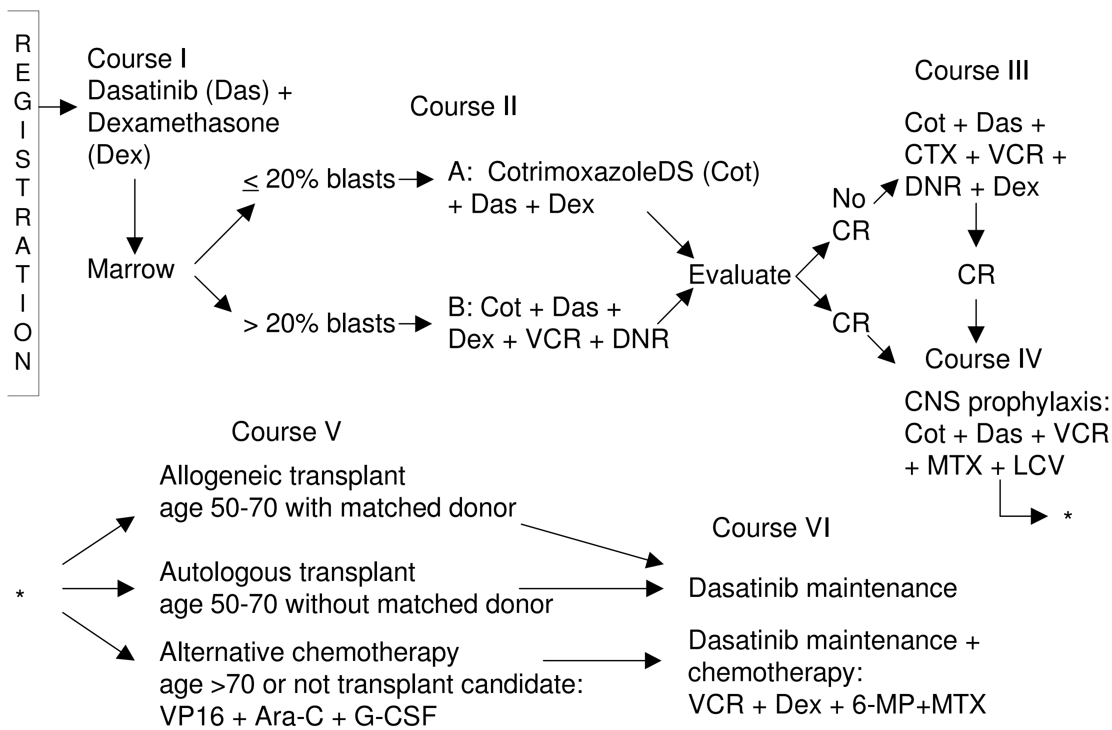
**Participants:**
Alliance, CTSU

**Date Activated:**
05/22/2012

**Study Chairs:**
M Wetzler (Alliance), M Liedtke (SWOG)

**Date Closed:**
11/14/2014

## SCHEMA




**<u>Objectives</u>**

To estimate the disease-free survival (DFS) and overall survival (OS) profiles in newly diagnosed patients 18 years or older who have Ph+ (BCR/ABL+) ALL receiving sequential dasatinib, followed by allogeneic or autologous HCT or chemotherapy followed by dasatinib maintenance.

To compare the OS and DFS profiles for each of the three cohorts to those from similar populations from other studies.

To determine the ability of dasatinib to produce or maintain a BCR/ABL-negative status, as judged by Q-PCR following sequential dasatinib, chemotherapy, and hematopoietic cell transplantation (HCT).

To determine the feasibility of collecting adequate peripheral blood stem cells for autologous HCT following dasatinib therapy, and assess for residual Ph+ (BCR/ABL+) cells by Q-PCR.

To study the safety and efficacy of autologous HCT following therapy with dasatinib.

To study the safety and efficacy of reduced-intensity preparatory regimen followed by an allogeneic HCT following induction therapy with dasatinib.

To study the safety and efficacy of dasatinib maintenance administered after allogeneic or autologous HCT or chemotherapy.

To correlate plasma and CSF levels of dasatinib when given orally during induction.

**Patient Population**

Patients must have an unequivocal histologic diagnosis of ALL and must have the detection of the t(9;22)(q34;q11) or 3-way variant by metaphase cytogenetics or BCR-ABL positive status by molecular analysis (Q-PCR or FISH) in a CLIA-approved laboratory.

Patients must have no prior therapy except up to one week of corticosteroids and/or hydroxyurea to enable time for the detection of t(9;22)(q34;q11) or BCR/ABL.

Patients must be 50 years of age or older. Patients must have adequate cardiac function and no major conduction abnormality. Patients must not have had a myocardial infarction or ventricular tachyarrhythmia within six months.

**Accrual Goals**

The accrual goal for this study is 60 evaluable patients.

**Summary Statement**

Alliance reported a total accrual of 66 patients as of December 31, 2014, including 13 CTSU registrations from SWOG institutions. A complete November 2014 summary of this study from Alliance is available on the SWOG web site.

## Registration by Institution

| Institutions | Total Reg |
|---|---|
| Stanford University | 7 |
| Rochester, Univ of | 4 |
| Kansas, U of | 1 |
| Wichita NCORP | 1 |
| **Total (4 Institutions)** | **13** |

# E1910 Phase III SWOG Supported CTSU Study

### Coordinating Group: ECOG-ACRIN

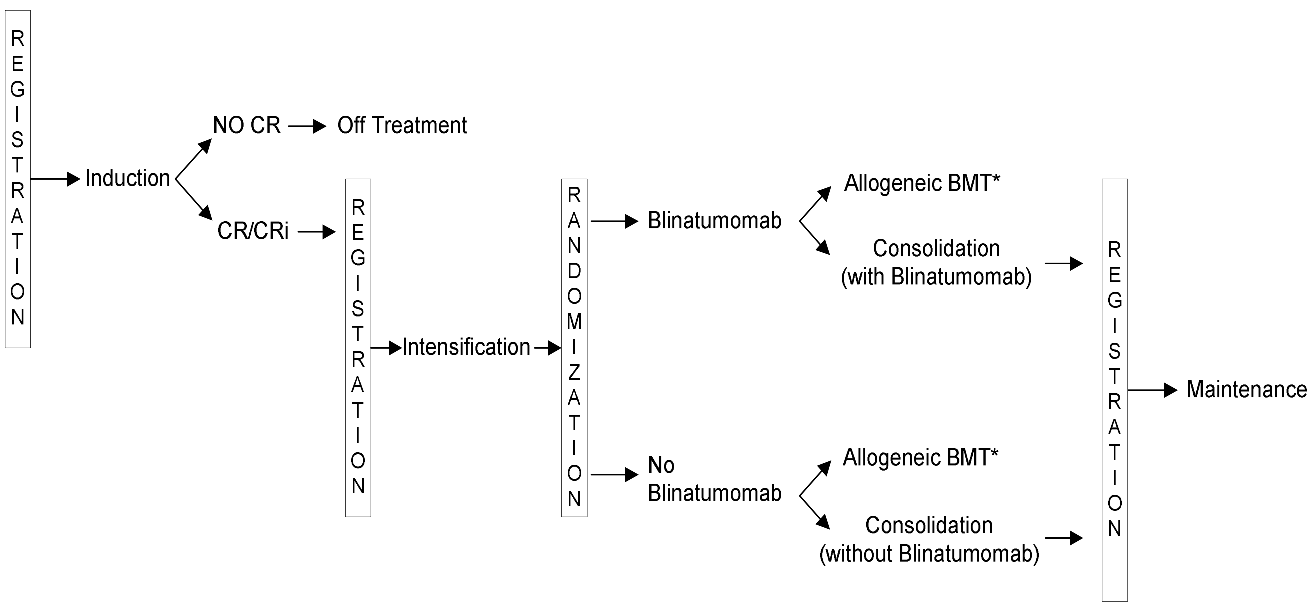
## A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL-negative B Lineage Acute Lymphoblastic Leukemia in Adults

**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
12/23/2013

**Study Chairs:**
M Litzow (ECOG-ACRIN), M Liedtke (SWOG)

### SCHEMA




*For those patients with a suitable donor who elect to proceed to BMT, patients may receive up to 2 cycles of consolidation chemotherapy prior to transplant.

**Objectives**

To compare the overall survival (OS) of blinatumomab in conjunction with chemotherapy to chemotherapy alone in patients with BCR-ABL-negative B cell precursor ALL who are MRD positive after induction and intensification chemotherapy, based on multiparameter flow cytometric (MFC) assessment of residual blasts.

If superiority of blinatumomab in the MRD positive group is shown, to compare the OS of blinatumomab in conjuction with chemotherapy to chemotherapy alone in patients with BCR-ABL-negative B cell precursor ALL who are MRD negative after induction and intensification chemotherapy, based on MFC assessment of residual blasts.

If superiority of blinatumomab in the MRD positive group is not shown, to compare the OS of blinatumomab in conjunction with chemotherapy to chemotherapy alone in the overall population of patients with BCR-ABL-negative B cell precursor ALL.

To determine if blinatumomab can convert patients who are MRD positive by MFC assessment of residual blasts after induction and intensification chemotherapy to MRD negativity.

To assess the toxicities of blinatumomab in this patient population.

To assess the toxicities of the modified E2993 chemotherapy regimen in this patient population.

To describe the outcome of patients who proceed to allogeneic blood or marrow transplant after treatment with or without blinatumomab.

To determine differences in MRD kinetics among patient with the BCR/ABL 1-like B-lineage ALL, and assess the efficacy of blinatumomab in each molecular subgroup.

To evaluate the incidence of anti-blinatumomab antibody formation.

**Patient Population**

Patients must have newly diagnosed, previously untreated BCR-ABL negative B cell precursor acute lymphoblastic leukemia. Patients with mature B ALL (Burkitt's-like leukemia) are not eligible. Patients must be negative for the Philadelphia chromosome.

Patients must not have a concurrent active malignancy for which they are receiving treatment. Patients must be between the age of 30 and 70 years and have an ECOG performance status of 0-3. Patients must have adequate hepatic and cardiac function. Patients must not have a history of recent myocardial infarction (within three months of registration), uncontrolled congestive heart failure, or uncontrolled cardiac arrhythmia. Patients must not have a history or presence of clinically relevant CNS pathology. Patients must not have intercurrent organ damage or medical problems that will jeopardize the outcome of therapy. Patients must not have an active uncontrolled infection. Patients with HIV infection are not eligible. Patients must not have an antecedent hematologic disorder.

**Stratification/Descriptive Factors**

At randomization (Step 3) patients will be stratified by (1) MRD status: positive vs negative; (2) white blood cell counts (WBC) at diagnosis: < 30,000/mcL vs ≥ 30,000/mcL; (3) age: < 55 years vs ≥ 55 years; and (4) whether patients intend to receive HSCT: yes vs no.

**Accrual Goals**

The accrual goal for this study is 360 eligible patients. Interim analyses will be performed annually beginning when at least 18 events (approximately 30% information) have occurred in the MRD-positive subgroup.

**Summary Statement**

ECOG-ACRIN reported a total accrual of 31 patients as of December 31, 2014, including 15 CTSU registrations from SWOG institutions. The complete Fall 2014 summary of this study from ECOG-ACRIN is available on the SWOG web site.

## Registration by Institution

Registrations ending December 31, 2014

| Institutions | Total Reg |
|---|---|
| Yale University | 6 |
| Stanford University | 5 |
| Kansas, U of | 2 |
| San Diego, U of CA | 1 |
| Wayne State Univ | 1 |
| **Total (5 Institutions)** | **15** |

# E1912 Phase III SWOG Supported CTSU Study

## Coordinating Group: ECOG-ACRIN

# A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL)

---

**Participants:**
ECOG-ACRIN, SWOG

**Date Activated:**
02/07/2014

**Study Chairs:**
T Shanafelt (ECOG-ACRIN), S O'Brien

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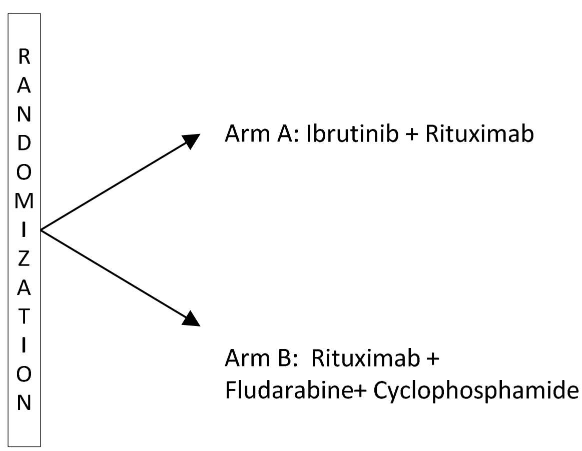
## SCHEMA




**<u>Objectives</u>**

The primary objective for the trial is to evaluate the ability of ibrutinib-based induction therapy to prolong progression free survival (PFS) compared to standard FCR chemoimmunotherapy for younger patients with CLL.

To evaluate overall survival (OS) of patients based on treatment arm.

To monitor and assess toxicity of treatment with ibrutinib-based induction relative to standard FCR chemotherapy.

To compare quality of life (QOL) in CLL patients during the first six months of treatment among patients receiving ibrutinib-based induction therapy relative to standard FCR chemoimmunotherapy.

To compare QOL over the long-term in CLL patients receiving continuous therapy using ibrutinib to that of CLL patients who completed FCR therapy.

To determine the effect of pretreatment clinical and biological characteristics on clinical outcomes of the different arms.

To determine if the minimal residual disease (MRD) status as assessed by flow cytometry at different time points during and after treatment is an effective surrogate marker for prolonged PFS and overall survival.

To compare the genetic abnormalities and dynamics of intra-clonal architecture of CLL patients before and after treatment with CIT and non-CIT approaches and explore relationships with treatment resistance.

To explore the effects of FCR and ibrutinib-based therapy on T-cell immune function.

To conduct confirmatory validation genotyping of single nucleotide polymorphisms (SNPs) associated with the efficacy and toxicity of fludarabine-based therapy as in a prior ECOG GWAS analysis in the E2997 trial.

To evaluate the ability of a prognostic model that incorporates clinical and biologic characters to predict a response to therapy and clinical outcome (PFS, OS).

To evaluate signaling networks downstream of the B-cell receptor in patients receiving ibrutinib-based therapy.

To collect relapse samples to study mechanisms of resistance to both FCR and ibrutinib-based therapy.

**Patient Population**

Patients must have a diagnosis of CLL according to the NCI/WCLLL criteria or SLL according to the WHO criteria. Patients must meet at least one of the indications for treatment of CLL or small lymphocytic leukemia (SLL) listed in the protocol. Patients must not have deletion of 17p13 on cytogenetic analysis by FISH.

Patients must not have had prior chemotherapy or monoclonal anti-body therapy for treatment of CLL or SLL. Patients must not have had previous use of corticosteroids for autoimmune complications that have developed since the intial diagnosis of CLL. Patients must not have had major surgery within the last 28 days prior to registration or minor surgery within the last five days. Patients must not have had radiation therapy within four weeks prior to registration. Patients must not have received warfarin or another vitamin K antagonist in the preceding 30 days.

Patients must be between 18 and 70 years of age and have an ECOG performance status of 0-2. Patients must have adequate renal, hepatic and cardiac function. Patients must not have active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment. Patients with HIV infection may be eligible provided they meet the criteria listed in the protocol. Patients must not have uncontrolled infection or infection with known chronic, active hepatitis C, or positive serology for hepatitis B. Patients must not have had a cerebral vascular accident or intracranial bleed within the last six months.

**Stratification/Descriptive Factors**

At randomization, patients will be stratified as follows: (1) age at registration: < 60 years vs ≥ 60 years; (2) performance status: 0 or 1 vs 2; (3) disease stage: 3 or 4 vs 1 or 2; (4) baseline cytogenetic abnormalities on FISH: deletion 11q22.3(ATM) vs other.

**Cancer Control Credits**

The NCI Division of Cancer Prevention has not assigned cancer control credit for registration to this study. There are potential cancer control credits for quality of life.

**Accrual Goals**

The accrual goal of this study is 519 patients: 346 in arm A (Ibrutinib) and 173 patients in arm B (FCR). The first interim analysis will be performed when follow-up is available through the later of five years after the start of accrual or two years after accrual is completed. If this study is not at full information at this time, then interim analyses will be performed annually until full information is reached.

**Summary Statement**

ECOG-ACRIN reported a total accrual of 148 patients as of December 31, 2014, including 35 CTSU registrations from SWOG institutions. The complete Fall 2014 summary of this study from ECOG-ACRIN is available on the SWOG web site.

# Registration by Institution

Registrations ending December 31, 2014

| Institutions | Total Reg |
|---|---|
| Stanford University | 16 |
| Rochester, Univ of | 5 |
| Kaiser NCORP | 3 |
| Wayne State Univ | 3 |
| KaiserPermanenteSCAL/Kaiser NCORP | 2 |
| Montana NCORP | 2 |
| KaiserPermanenteCOL/Kaiser NCORP | 1 |
| Northwest CCOP | 1 |
| Ozarks Reg NCORP | 1 |
| Stormont-Vail Health/Kansas, U of | 1 |
| **Total (10 Institutions)** | **35** |

# E2905 Phase III SWOG Supported CTSU Study

## Coordinating Group: ECOG-ACRIN

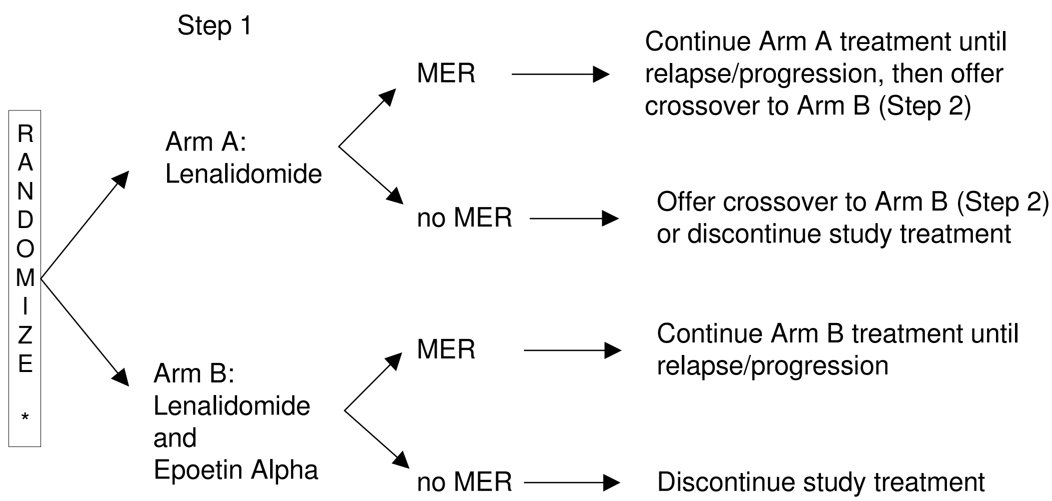
# Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
02/09/2009

**Study Chairs:**
A List (ECOG-ACRIN), C Schiffer (SWOG)

## SCHEMA




* Patients with the del 5q31.1 abnormality will not be randomized but will be assigned to Arm A.

**Objectives**

To compare the rate of major erythroid response (MER) between lenalidomide monotherapy and combined treatment of lenalidomide and epoetin alfa in EPO non-responsive Low/Int-1 risk MDS patients or EPO-treatment naive patients with low probability of EPO benefit.

To compare the time to MER by treatment assignment.

To evaluate the duration of MER by treatment assignment.

To estimate the frequency of MER to salvage combination therapy in patients who fail to experience a MER with lenalidomide monotherapy.

To evaluate and compare the frequency of minor erythroid response by treatment assignment.

To investigate the mechanism and target of lenalidomide action in patients with chromosome 5q31.1 deletion.

To evaluate the frequency of cytogenetic response and progression, and the relation between cytogenetic pattern and erythroid response.

To evaluate the frequency of bone marrow response (CR+PR).

To evaluate the relationship between erythroid response and laboratory correlates of the following: (a) Pretreatment and onstudy endogenous EPO level (Arm A); (b) To evaluate the effect of CD45 isoform profile on lenalidomide enhancement of EPO-induced STAT5 phosphorylation in CD71Hi erythroid precursors and the relationship to erythroid response; (c) To characterize molecular targets relevant to lenalidomide cytotoxicity in del5q cells; (d) To evaluate the frequency of cryptic chromosome 5q31 deletions in patients with non-del5q MDS by array-based genomic scan, and to determine the relationship to hematologic response.

**Patient Population**

Patients must have documented diagnosis of MDS lasting at least three months according to WHO criteria or non-proliferative chronic myelomonocytic leukemia. Patients must have International Prognostic Scoring System (IPSS) categories of Low- or Intermediate-1 risk disease. Patients must have IPSS score determined by cytogenetic analysis prior to randomization. Patients with cytogenetic failure and < 10% marrow blasts will be eligible. Patients with cytogenetic failure must have previous cytogenetic results (FISH is not a substitute) within the last six months post MDS treatment (in this case, not referring to growth factors as type of MDS treatment). Patients must have symptomatic anemia untransfused with hemoglobin ≤ 9.5 g/dL within eight weeks of registration or with RBC transfusion-dependence (i.e., ≥ 2 units/month) confirmed for a minimum of eight weeks before randomization. Patients must not have proliferative (WBC ≥ 12,000/mcL) chronic myelomonocytic leukemia. Patients must not have MDS secondary to treatment with radiotherapy, chemotherapy, and/or immunotherapy for malignant or autoimmune diseases. Patients without deletion 5q31.1 must have failed treatment with an erythropoietic growth factor, or have a low probability of response to rhu-EPO, as defined in the protocol, eight weeks prior to randomization. Patients must be off all non-transfusion therapy for MDS for 28 days prior to initiation of study treatment. Patients may receive hydrocortisone prophylactically to prevent transfusion reactions. Patients must not have prior therapy with lenalidomide or have used cytotoxic chemotherapeutic agents, or experimental agents for the treatment of MDS within eight weeks prior to randomization.

Patients must be at least 18 years of age. Patients must have a serum erythropoietin level documented prior to randomization and ≤ 56 days before day 1 of study treatment. Patients must not have documented iron deficiency and musthave documented marrow iron stores. If marrow iron stain is not available, the transferrin saturation must be > 20% or a serum ferritin > 100 ng/mL. Patients must have the following lab values documented on two occasions (separated by at least seven days) over 21 days prior to randomization: platelet count ≥ 50,000/mcL without platelet transfusion, ANC ≥ 500 cells/mcL, serum creatinine ≤ 1.5 x ULN, serum SGOT or SGPT ≤ 2.0 x ULN, serum total bilirubin < 3.0 mg/dL. Patients must not have had prior Grade 3 or higher allergic reaction to thalidomide, must not have had a known allergic reaction to epoetin alfa or human serum albumin, and must not have prior desquamating rash at time of study entry. Patients must not have anemia resulting from iron, B12, or folate deficiencies, autoimmune or hereditary hemolysis, or gastrointestinal bleeding. Patients must not have a history of thromboembolic events within three years prior to randomization. Patients must not have known HIV-1 seropositivity, uncontrolled seizure, or uncontrolled hypertension.

**Stratification/Descriptive Factors**

At randomization patients will be stratified by (1) serum erythropoietin level: ≤ 500 mU/mL vs > 500 mU/mL, and (2) prior erythropoietic growth factor treatment: yes vs no. All patients with del 5q31.1 karyotype will be assigned to treatment with lenalidomide monotherapy (Arm A).

**Accrual Goals**

The study requires 212 patients without 5q31.1 deletion. The estimated accrual goal is a total of 252 eligible patients.

**Summary Statement**

The study was activated at ECOG-ACRIN on January 29, 2009. Accrual was suspended December 31, 2012 due to changes in the supply of epoetin alfa and re-opened to new accrual June 6, 2013.

ECOG-ACRIN reported a total accrual of 197 patients as of December 31, 2014, including 60 CTSU registrations from SWOG institutions. The complete Fall 2014 summary of this study from ECOG-ACRIN is available on the SWOG web site.

## Registration by Institution

Registrations ending December 31, 2014

| Institutions | Total Reg |
|---|---|
| H Lee Moffitt CC | 18 |
| Greenville NCORP | 6 |
| KaiserPermanenteSCAL/Kaiser NCORP | 6 |
| Wayne State Univ | 5 |
| Davis, U of CA | 4 |
| Montana NCORP | 4 |
| Thompson Ca Surv Ctr/San Antonio, U of TX | 3 |
| Yale University | 3 |
| Kansas City NCORP | 2 |
| Colorado, U of | 1 |
| Columbia MU-NCORP | 1 |
| Kansas, U of | 1 |
| Lahey Clinic Med Ctr/Davis, U of CA | 1 |
| Providence Hosp | 1 |
| Rochester, Univ of | 1 |
| Southeast CCC NCORP | 1 |
| St Luke's Mt State | 1 |
| Winthrop-Univ Hosp/Columbia University | 1 |
| **Total (18 Institutions)** | **60** |

# E2906 Phase III SWOG Supported CTSU Study

### Coordinating Group: ECOG-ACRIN

## Phase III Randomized Trial of Clofarabine as Induction and Post-Remission Therapy vs. Standard Daunorubicin & Cytarabine Induction and Intermediate Dose Cytarabine Post-Remission Therapy, Followed by Decitabine Maintenance vs. Observation in Newly-Diagnosed Acute Myeloid Leukemia in Older Adults (Age ≥ 60 Years)

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**Participants:**
ECOG-ACRIN, CTSU

**Date Activated:**
02/24/2011

**Study Chairs:**
J Foran (ECOG-ACRIN), J Godwin (SWOG)

**Date Closed*:**
02/23/2015

*Temporary Closure

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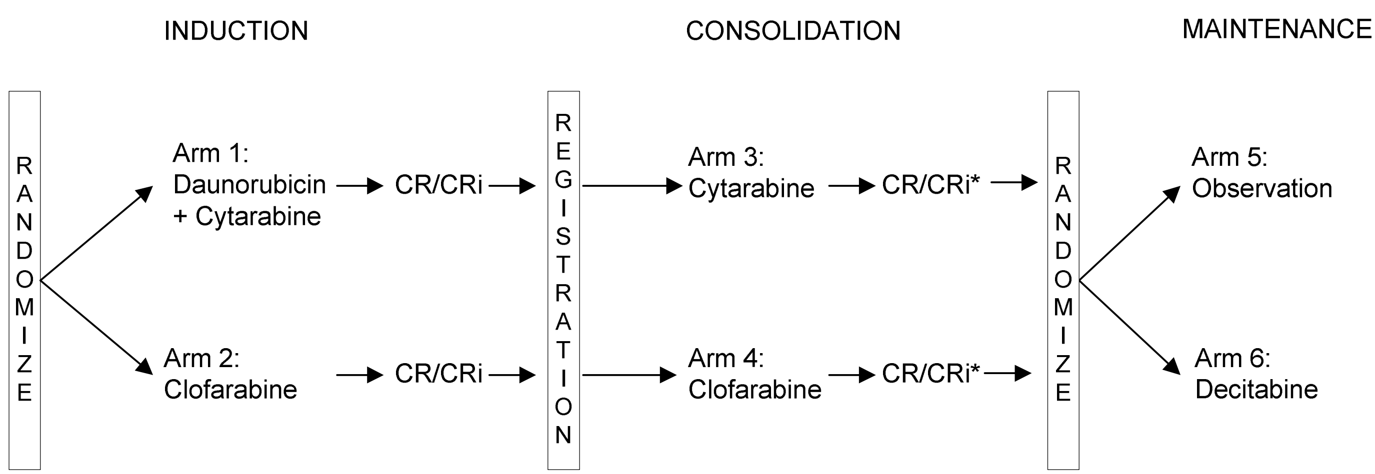
### SCHEMA




*Note: Patients with an HLA matched donor who achieve CR/CRi or morphologic leukemia-free state will proceed to allogeneic Hematopoietic Stem Cell Transplantation after consolidation.

**Objectives**
To evaluate the effect of clofarabine induction and consolidation therapy on overall survival in comparison with standard therapy (daunorubicin + cytarabine) in newly-diagnosed AML patients age 60 years and older.

To evaluate complete remission (CR) rates, duration of remission, and toxicity/treatment-related mortality of clofarabine in comparison with standard therapy (daunorubicin + cytarabine) in newly-diagnosed AML patients age 60 years and older.

To evaluate the feasibility of consolidation with reduced-intensity conditioning and allogeneic hematopoietic stem cell transplantation from HLA-identical donors in patients who achieve a response to induction therapy, including the incidence of successful engraftment, acute and chronic graft-versus-host disease, transplant-related mortality, and its impact on overall survival in comparison to patients receiving chemotherapy.

To evaluate the duration of remission and disease-free survival of patients in complete remission following completion of consolidation therapy who are subsequently randomized to receive scheduled low-dose decitabine maintenance in comparison with observation.

To perform expression and methylation profiling on all patients receiving decitabine and to correlate their integrated epigenetic signatures with response to decitabine.

To examine the epigenetic profiles of remission marrow in patients randomized to observation vs. decitabine to determine whether epigenetic signature of apparently morphologically normal bone marrow is predictive of relapse or response to decitabine maintenance.

To explore the possible association of response to clofarabine with nucleoside transporters hENT1, hCNT3, and ABC-transporter P-glycoprotein (Pgp).

To assess the expression of CXCR4 and to correlate its expression with other established prognostic factors in patients receiving induction treatments.

To compare health-related QOL (physical, functional, leukemia-specific well-being) and fatigue in elderly AML patients receiving standard induction therapy with those receiving clofarabine.

To measure the change in health-related QOL that occurs over time (within treatment groups).

To comprehensively assess patient function at the time of study enrollment.

To determine if components of a comprehensive geriatric assessment of QOL scales predict ability to complete AML treatment.

To describe the impact of transplant on QOL in AML patients above age 60.

**Patient Population**

Patients must have newly-diagnosed AML according to WHO classification and be considered candidates for intensive chemotherapy based upon examination of peripheral blood, bone marrow aspirate specimens, or touch preparations of the bone marrow biopsy. Patients must not have blastic transformation of chronic myelogenous leukemia. Patients with secondary AML are eligible. Patients with documented CNS involvement are not eligible.

Patients must not have received prior chemotherapy for AML with the exception of hydroxurea for increased blast count or leukapheresis for leukocytosis. Patients who have received a limited and short-term exposure of ATRA (all trans retinoic acid) while AML-M3 (Acute Promyelocytic Leukemia) was being ruled out, and which has been discontinued, will be eligible. Patients who have received previous treatment for antecedent hematologic disorder (AHD) with 5-azacitidine, decitabine, or low dose cytarabine are not eligible.

Patients must have an ECOG performance status 0-3 and reached their 60th birthday. Patients must have adequate cardiac, hepatic, and renal function. Patients must not have a concurrent active malignancy for which they are receiving treatment (other than MDS). Patients with known HIV infection are not eligible.

**Stratification/Descriptive Factors**

At initial randomization patients will be stratified by (1) age: 60-69 vs ≥ 70 years; (2) therapy-related AML: yes vs no; and (3) presence of AHD at the time of diagnosis of AML: yes vs no.

For the randomization to maintenance, treatment randomization will be stratified by (1) age: 60-69 vs ≥ 70 years; (2) cytogenetics: unfavorable vs other; and (3) induction treatment: arm 1 vs arm 2.

**Cancer Control Credits**

The NCI Division of Cancer Prevention has not assigned cancer control credit for registration to this study. There are potential cancer control credits for quality of life.

**Accrual Goals**

The accrual goal for this study is 747 patients. Up to nine interim analyses will be performed beginning when approximately 25% of planned full information has occurred. Interim analyses will include both futility and efficacy analyses.

**Summary Statement**

This study was temporarily closed to accrual on February 23, 2015. The Therapeutic Subcommittee of the ECOG-ACRIN Data Safety Monitoring Committee has recommended that enrollment to this study be suspended due to differences in survival rates favoring standard daunorubicin and cytarabine for induction and consolidation compared to clofarabine induction and consolidation.

ECOG-ACRIN reported a total accrual of 718 patients as of February 23, 2015, including 75 CTSU registrations from SWOG institutions. The complete Fall 2014 summary of this study from ECOG-ACRIN is available on the SWOG web site.

## Registration by Institution

Registrations ending February 23, 2015

| Institutions | Total Reg | Institutions | Total Reg |
|---|---|---|---|
| Rochester, Univ of | 27 | Cincinnati MC, U of | 3 |
| Loyola University | 9 | Columbia MU-NCORP | 3 |
| Arizona MC, U of | 7 | Upstate Carolina | 3 |
| Kentucky, U of | 7 | Mississippi, Univ of | 1 |
| Dayton NCORP | 5 | New Mexico MU-NCORP | 1 |
| Florida, Univ of/Yale University | 4 | Winthrop-Univ Hosp/Yale University | 1 |
| West Michigan NCORP | 4 | **Total (13 Institutions)** | **75** |