

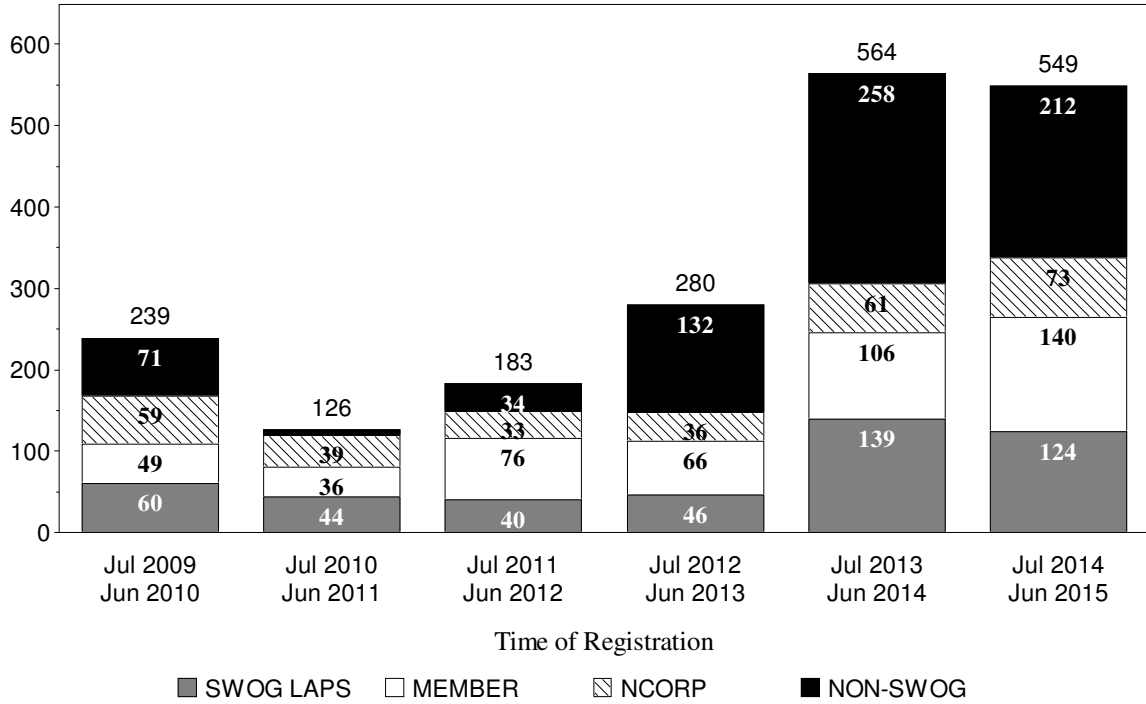
LEUKEMIA COMMITTEE

CONTENTS

S0805 Phase II.....	6
S0919 Phase II.....	12
S1117 Phase II.....	17
S1203 Phase III.....	23
S1204 Surveillance	32
S1312 Phase I	33
S1318 Phase II.....	38
A041202 Phase III SWOG Supported CTSU Study.....	40
E1910 Phase III SWOG Supported CTSU Study	43
E1912 Phase III SWOG Supported CTSU Study	45
E2905 Phase III SWOG Supported CTSU Study	48
E2906 Phase III SWOG Supported CTSU Study	51

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

	<u>Jan 2015 Jun 2015</u>	<u>Jul 2014 Dec 2014</u>	<u>Jan 2014 Jun 2014</u>	<u>All Patients</u>
S0919 Rel AML: Pravastatin+Ida+Ara-C				
Induction				
Pravastatin+Idarubicin+Ara-C	3	14	13	97
S1117 MDS/CMML, Aza+Len/Aza/Aza+Vor				
Randomization				
Azacitidine+Lenalidomide	0	0	23	97
Azacitidine	0	0	21	92
Azacitidine+Vorinostat	0	0	19	93
	<u>0</u>	<u>0</u>	<u>63</u>	<u>282</u>
S1203 AML, Age 18-60, 7+3/IA/IA+V				
Randomization				
AraC + Daunorubicin	51	66	53	219
AraC + Idarubicin	49	69	53	222
Vorinostat + AraC + Idarubicin	48	72	54	224
	<u>148</u>	<u>207</u>	<u>160</u>	<u>665</u>
S1312 ALL,CD22+,REL/REF,Inotuzumab+CVP				
Initial Registration				
CVP + Inotuzumab dose level 1	0	2	3	5
CVP + Inotuzumab dose level 2	4	1	0	5
CVP + Inotuzumab dose level 3	3	0	0	3
	<u>7</u>	<u>3</u>	<u>3</u>	<u>13</u>
S1318 ALL, Age 65+, Ph±, Blinatumomab				
Initial registration				
Induction: Ph-negative	1	0	0	1
A041202 CLL,65+, Ben+Rtx vs Ibrut±Rtx*				
Total Registrations	30	29	6	65
C10701 Ph+ ALL, Age 50+, Dasatinib+HCT*				
Total Registrations	0	9	1	13
E1910 BCR-ABL-neg B ALL, blinatumomab*				
Total Registrations	5	13	2	20

	<u>Jan 2015 Jun 2015</u>	<u>Jul 2014 Dec 2014</u>	<u>Jan 2014 Jun 2014</u>	<u>All Patients</u>
E1912 CLL, Age 18-70, Ibrutinib vs FCR*				
Total Registrations	31	19	16	66
E2905 MDS, Len vs Len + Epo*				
Total Registrations	5	9	8	65
E2906 AML, Age 60+, Clo vs Dauno+Cy*				
Total Registrations	0	16	9	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)

Participants:

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

Date Activated:

09/01/2009

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)

Date Closed:

10/01/2013

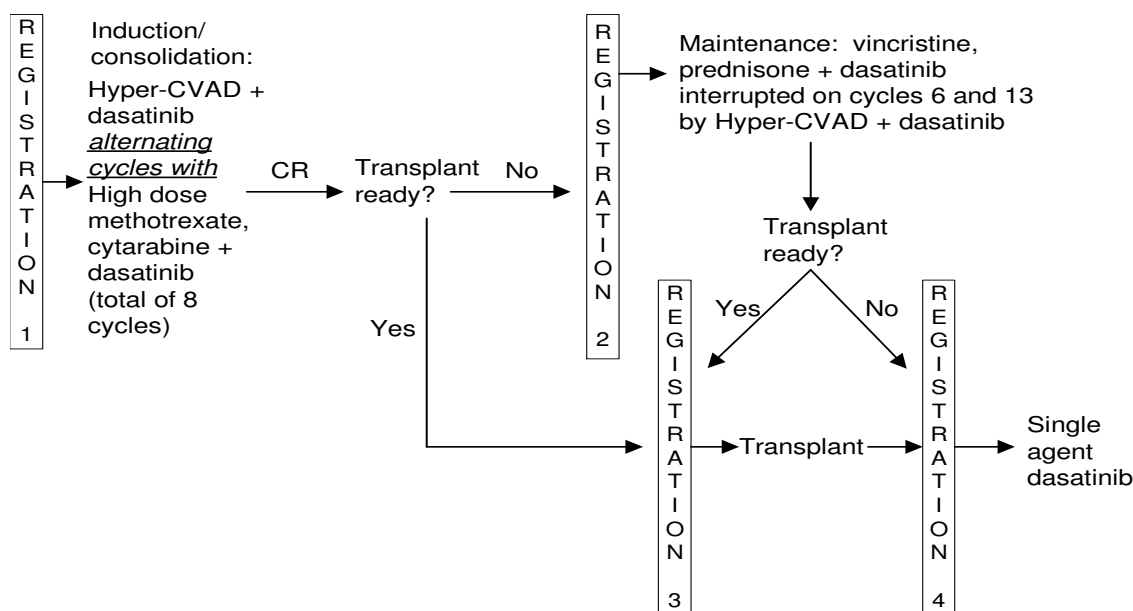
Statisticians:

H Li, M Othus

Data Coordinator:

L Kingsbury

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 due to elevated liver enzymes and effusion not due to leukemia (one each). One additional patient was denied coverage by insurance before starting protocol treatment and is not included in any analyses.

Three patients refused to continue protocol induction/consolidation therapy. Twelve other patients were removed from protocol induction/consolidation therapy for reasons not

specified in the protocol; three at physician's discretion, four to receive off protocol stem cell transplants, three were unable to find matched donors, one was unable to have remission determined within two courses of induction/consolidation therapy, 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 CC	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 July 30, 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 July 30, 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 July 30, 2015

	Induction /Consolidation
NUMBER ON PROTOCOL TREATMENT	1
NUMBER OFF PROTOCOL TREATMENT	93
REASON OFF TREATMENT	
Treatment completed as planned	67
Adverse Event or side effects	6
Refusal unrelated to adverse event	3
Progression/relapse	0
Death	4
Other - not protocol specified	12
Reason under review	1
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 July 30, 2015

ADVERSE EVENTS	Induction/Consolidation (n=92)			
	Grade			
	≤ 2	3	4	5
ALT	69	19	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	89	3	0	0
Confusion	91	1	0	0
Creatinine	90	2	0	0
DLCO	91	0	1	0
Dehydration	90	2	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
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	71	20	1	0
Hyponatremia	90	2	0	0
Hypophosphatemia	85	6	1	0
Hypotension	89	2	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

**Induction/Consolidation
(n=92)
Grade**

ADVERSE EVENTS	≤ 2	3	4	5
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	85	6	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	84	8	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
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.	90	1	1	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 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 accrual to the refractory/relapsed 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 transplantation 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. A major protocol deviation is coded for one patient who received an extra dose of AraC.

Forty-one relapsed/refractory AML patients have been assessed for adverse events. Four 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, 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, and fourth death was due to respiratory failure (reported as DLCO). An additional eight patients experienced treatment-related Grade 4 non-hematologic toxicities.

As of June 30, 2015, 16 patients have been accrued to the MDS transformed to AML cohort. One patient is ineligible due to elevated creatinine level prior to registration. Among the twelve patients assessed for adverse events, four reported treatment-related Grade 4 non-hematologic toxicities.

Two patients accrued to the refractory/relapsed 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. No Grade 3 or higher toxicity has been reported for consolidation therapy.

Registration by Institution
Registrations ending June 30, 2015

Institutions	Total Reg	Institutions	Total Reg
Stanford University	24	Birmingham, U of AL	3
Cleveland Clinic OH	22	PCRC NCORP	2
Rochester, Univ of	12	Wichita NCORP	2
H Lee Moffitt CC	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)	97
New Mexico MU-NCORP	4		

Registration, Eligibility, and Evaluability

Classified by Disease Status

Initial Registration

Registrations from April 1, 2013 through June 30, 2015; Data as of July 27, 2015

	TOTAL	MDS transformed to AML	Refractory or relapsed with previous remission < 6 months
NUMBER REGISTERED	61	16	45
INELIGIBLE	4	1	3
ELIGIBLE	57	15	42
Not Analyzable	1	0	1
RESPONSE ASSESSMENT			
Determinable	48	12	36
Not Determinable	6	1	5
Too Early	2	2	0
ADVERSE EVENT ASSESSMENT			
Evaluable	53	12	41
Too Early	3	3	0

Patient Characteristics

Classified by Disease Status

Initial Registration

Registrations from April 1, 2013 through June 30, 2015; Data as of July 27, 2015

	MDS transformed to AML (n=15)		Refractory or relapsed with previous remission < 6 months (n=41)	
AGE				
Median	66.6		54.4	
Minimum	29.6		23.1	
Maximum	71.9		75.0	
SEX				
Males	11	73%	19	46%
Females	4	27%	22	54%
HISPANIC				
Yes	0	0%	4	10%
No	13	87%	34	83%
Unknown	2	13%	3	7%
RACE				
White	14	93%	30	73%
Black	1	7%	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 June 30, 2015; Data as of July 27, 2015

	TOTAL	MDS transformed to AML	Refractory or relapsed with previous remission < 6 months
NUMBER ON PROTOCOL TREATMENT	1	1	0
NUMBER OFF PROTOCOL TREATMENT	55	14	41
REASON OFF TREATMENT			
Treatment completed as planned	48	13	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 June 30, 2015; Data as of July 27, 2015

ADVERSE EVENTS	MDS transformed to AML (n=12) Grade				Refractory or relapsed with previous remission < 6 months (n=41) Grade			
	≤ 2	3	4	5	≤ 2	3	4	5
	ALT	10	2	0	0	40	1	0
AST	11	1	0	0	40	1	0	0
Alkaline phosphatase	12	0	0	0	40	1	0	0
Colitis, infectious	12	0	0	0	40	1	0	0
Creatinine	11	1	0	0	40	1	0	0
DLCO	12	0	0	0	40	0	0	1
Diarrhea	11	1	0	0	33	8	0	0
Dyspnea	12	0	0	0	40	1	0	0
Edema-limb	11	1	0	0	41	0	0	0
Fatigue	12	0	0	0	39	2	0	0
Febrile neutropenia	3	9	0	0	14	22	5	0

ADVERSE EVENTS	MDS transformed to AML (n=12) Grade				Refractory or relapsed with previous remission < 6 months (n=41) Grade			
	≤ 2	3	4	5	≤ 2	3	4	5
	GI Inf, 3-4 ANC: stomach	12	0	0	0	40	1	0
GI Pain: abdomen	11	1	0	0	41	0	0	0
GI Pain: esophagus	12	0	0	0	40	1	0	0
GI Pain: oral cavity	12	0	0	0	38	3	0	0
GU Inf, 3-4 ANC: kidney	12	0	0	0	40	1	0	0
Hypoalbuminemia	11	1	0	0	35	6	0	0
Hypocalcemia	11	1	0	0	39	1	1	0
Hypokalemia	11	1	0	0	38	3	0	0
Hyponatremia	12	0	0	0	40	1	0	0
Hypophosphatemia	12	0	0	0	39	2	0	0
Hypotension	12	0	0	0	40	0	0	1
Hypoxia	12	0	0	0	38	3	0	0
Inf, 3-4 ANC: blood	9	0	3	0	36	1	3	1
Inf, Unk ANC: blood	10	0	2	0	38	0	2	1
Lung Hemorrhage: bronchopulm.	12	0	0	0	40	0	1	0
Lung Hemorrhage: nose	12	0	0	0	40	1	0	0
Lung Inf, 3-4 ANC: bronchus	12	0	0	0	40	1	0	0
Lung Inf, 3-4 ANC: lung	11	1	0	0	35	5	1	0
Lung Inf, Unk ANC: mucosa	12	0	0	0	40	1	0	0
Mucositis, clin: oral cavity	12	0	0	0	40	1	0	0
Mucositis, clin: pharynx	12	0	0	0	40	0	1	0
Mucositis, funct: oral cav.	12	0	0	0	40	1	0	0
Musculo. Pain: bone	12	0	0	0	40	1	0	0
Musculo. Pain: limb	12	0	0	0	40	1	0	0
Nausea	12	0	0	0	38	3	0	0
Neuro Inf, 3-4 ANC: mening.	12	0	0	0	40	0	1	0
Opportunistic infection	12	0	0	0	39	2	0	0
Rash	12	0	0	0	40	1	0	0
Renal failure	12	0	0	0	40	0	1	0
Typhlitis	12	0	0	0	40	1	0	0
Ulceration	12	0	0	0	40	1	0	0
Vomiting	11	1	0	0	41	0	0	0
Weight Loss	12	0	0	0	39	2	0	0
MAX. GRADE ANY ADVERSE EVENT	0	8	4	0	3	26	8	4

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)

Participants:

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

Date Activated:

04/03/2012

Study Chairs:

M Sekeres, A List, S Gore (ECOG-ACRIN), O Odenike (Alliance)

Date Closed:

11/14/2014

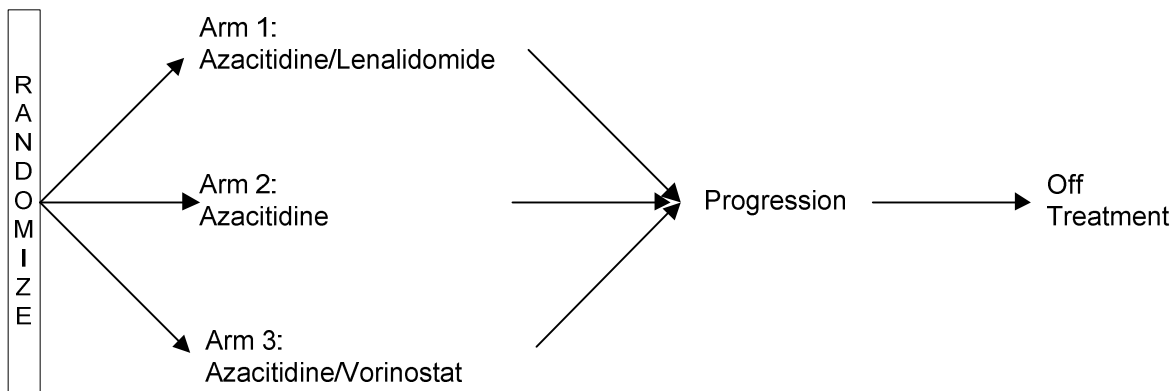
Statisticians:

M Othus, H Li

Data Coordinator:

T Maher

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 results that ruled out the pre-specified treatment benefit with high confidence, the DSMC recommended that the study do not proceed to Phase III.

The study was permanently closed to accrual on November 14, 2014 with a total of 282 patients. Five patients are ineligible due to: 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 seventy-one patients were assessed for adverse events. There have been four treatment-related deaths reported on the azacitidine + lenalidomide arm: one due to pneumonia (coded as 'Lung infection'), one due to ARDS, one due to sepsis, 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 another died of hemorrhage (coded as 'Sudden death

NOS'). Four additional patients on the azacitidine arm experienced Grade 4 non-hematologic toxicities.

toxicities, including one with pyoderma gangrenosum (coded as 'Skin infection' and 'Infections/infestations-Other').

No treatment related death occurred on the azacitidine + vorinostat arm. Six patients on the azacitidine + vorinostat arm reported Grade 4 non-hematologic

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
CRC West MI NCORP	4	Montana NCORP	1
Hawaii MU-NCORP	4	Oklahoma, Univ of	1
Kaiser Vallejo NCORP	4	Southeast COR NCORP	1
Kansas, U of	4	St Louis CCOP	1
Utah, U of	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 July 30, 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	205	64	72	69
Not Determinable	72	29	20	23
ADVERSE EVENT ASSESSMENT				
Evaluable	271	89	91	91
Not Evaluable	6	4	1	1

Patient Characteristics

Data as of July 30, 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 July 30, 2015

	Total
NUMBER ON PROTOCOL TREATMENT	32
NUMBER OFF PROTOCOL TREATMENT	245
REASON OFF TREATMENT	
Treatment completed as planned	0
Adverse Event or side effects	42
Refusal unrelated to adverse event	37
Progression/relapse	77
Death	15
Other - not protocol specified	73
Reason under review	1
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 July 30, 2015

ADVERSE EVENTS	Azacitidine+Lenalidomide (n=89) Grade				Azacitidine (n=91) Grade				Azacitidine+Vorinostat (n=91) Grade			
	≤2	3	4	5	≤2	3	4	5	≤2	3	4	5
ALT increased	89	0	0	0	91	0	0	0	86	5	0	0
ARDS	88	0	0	1	91	0	0	0	91	0	0	0
AST increased	89	0	0	0	91	0	0	0	88	3	0	0
Abdominal infection	88	1	0	0	91	0	0	0	91	0	0	0
Abdominal pain	88	1	0	0	91	0	0	0	88	3	0	0
Acute kidney injury	89	0	0	0	91	0	0	0	90	1	0	0
Anorectal infection	89	0	0	0	91	0	0	0	90	1	0	0
Anorexia	85	4	0	0	91	0	0	0	88	3	0	0
Apnea	89	0	0	0	91	0	0	0	90	1	0	0
Ascites	88	1	0	0	91	0	0	0	90	1	0	0
Ataxia	89	0	0	0	91	0	0	0	90	1	0	0
Back pain	88	1	0	0	91	0	0	0	91	0	0	0
Blood bilirubin increased	89	0	0	0	91	0	0	0	88	3	0	0
Bronchial infection	89	0	0	0	91	0	0	0	90	1	0	0
Cardiac arrest	88	0	1	0	91	0	0	0	91	0	0	0
Catheter related infection	88	1	0	0	89	1	1	0	90	1	0	0
Cecal infection	89	0	0	0	91	0	0	0	90	1	0	0
Cholecystitis	89	0	0	0	91	0	0	0	90	1	0	0
Colitis	89	0	0	0	91	0	0	0	90	1	0	0
Confusion	89	0	0	0	91	0	0	0	90	1	0	0
Constipation	87	2	0	0	90	1	0	0	90	1	0	0
Creatinine increased	87	2	0	0	91	0	0	0	91	0	0	0
Dehydration	84	5	0	0	90	1	0	0	88	3	0	0
Delirium	89	0	0	0	91	0	0	0	90	1	0	0
Diarrhea	84	5	0	0	91	0	0	0	88	3	0	0
Dizziness	88	1	0	0	91	0	0	0	91	0	0	0
Dyspnea	85	3	1	0	89	2	0	0	88	3	0	0
Epistaxis	89	0	0	0	91	0	0	0	90	1	0	0
Esophageal pain	89	0	0	0	91	0	0	0	90	1	0	0
Esophagitis	88	1	0	0	91	0	0	0	91	0	0	0
Fall	89	0	0	0	91	0	0	0	90	1	0	0
Fatigue	80	9	0	0	86	5	0	0	78	13	0	0
Febrile neutropenia	74	12	3	0	80	10	1	0	78	12	1	0
Fever	89	0	0	0	91	0	0	0	89	2	0	0
Flushing	89	0	0	0	91	0	0	0	90	1	0	0
Gastric hemorrhage	89	0	0	0	91	0	0	0	90	1	0	0
Gastrointestinal pain	88	1	0	0	91	0	0	0	90	1	0	0
Gen disorders/admin site cond	88	1	0	0	91	0	0	0	91	0	0	0
Generalized muscle weakness	86	3	0	0	90	1	0	0	88	3	0	0
Hallucinations	89	0	0	0	91	0	0	0	90	1	0	0
Headache	89	0	0	0	91	0	0	0	90	1	0	0
Heart failure	89	0	0	0	91	0	0	0	90	1	0	0
Hematoma	89	0	0	0	91	0	0	0	90	1	0	0

OCTOBER 7 - 10, 2015

SWOG

LEUKEMIA 21

S1117/II

ADVERSE EVENTS	Azacitidine+Lenalidomide (n=89) Grade				Azacitidine (n=91) Grade				Azacitidine+Vorinostat (n=91) Grade			
	≤2	3	4	5	≤2	3	4	5	≤2	3	4	5
Hematuria	88	1	0	0	91	0	0	0	89	2	0	0
Hyperglycemia	88	1	0	0	90	0	1	0	89	2	0	0
Hypernatremia	89	0	0	0	90	1	0	0	91	0	0	0
Hypertension	88	1	0	0	91	0	0	0	89	2	0	0
Hyperuricemia	89	0	0	0	91	0	0	0	90	0	1	0
Hypoalbuminemia	86	3	0	0	91	0	0	0	91	0	0	0
Hypokalemia	85	4	0	0	91	0	0	0	90	1	0	0
Hypomagnesemia	88	0	1	0	91	0	0	0	91	0	0	0
Hyponatremia	84	5	0	0	90	1	0	0	87	4	0	0
Hypophosphatemia	88	1	0	0	91	0	0	0	89	2	0	0
Hypotension	85	4	0	0	91	0	0	0	88	3	0	0
Hypoxia	89	0	0	0	91	0	0	0	90	0	1	0
Infections/infestations-Other	85	3	1	0	89	2	0	0	86	4	1	0
Intracranial hemorrhage	88	0	0	1	91	0	0	0	91	0	0	0
Investigations-Other, specify	88	1	0	0	91	0	0	0	91	0	0	0
Lower GI hemorrhage	89	0	0	0	91	0	0	0	89	2	0	0
Lung infection	85	3	0	1	90	1	0	0	89	1	1	0
Mucosal infection	89	0	0	0	91	0	0	0	90	1	0	0
Mucositis oral	88	1	0	0	91	0	0	0	91	0	0	0
Nausea	88	1	0	0	89	2	0	0	89	2	0	0
Pain	88	1	0	0	91	0	0	0	91	0	0	0
Papulopustular rash	88	1	0	0	91	0	0	0	91	0	0	0
Pericardial effusion	88	0	1	0	91	0	0	0	91	0	0	0
Pneumonitis	89	0	0	0	91	0	0	0	90	1	0	0
Pruritus	88	1	0	0	91	0	0	0	91	0	0	0
Pulmonary edema	89	0	0	0	91	0	0	0	90	1	0	0
Purpura	88	1	0	0	91	0	0	0	91	0	0	0
Rash maculo-papular	76	13	0	0	88	3	0	0	90	1	0	0
Renal/urinary disorders-Other	89	0	0	0	91	0	0	0	90	1	0	0
Respiratory failure	89	0	0	0	91	0	0	0	90	0	1	0
Sepsis	85	0	3	1	89	0	1	1	88	0	3	0
Sinus bradycardia	88	1	0	0	91	0	0	0	91	0	0	0
Skin infection	86	2	1	0	90	1	0	0	89	1	1	0
Soft tissue infection	88	1	0	0	90	1	0	0	91	0	0	0
Sudden death NOS	89	0	0	0	90	0	0	1	91	0	0	0
Syncope	87	2	0	0	91	0	0	0	87	4	0	0
Thromboembolic event	88	1	0	0	91	0	0	0	90	1	0	0
Tooth infection	89	0	0	0	91	0	0	0	90	1	0	0
Upper GI hemorrhage	89	0	0	0	91	0	0	0	90	1	0	0
Upper respiratory infection	89	0	0	0	90	1	0	0	91	0	0	0
Urinary tract infection	88	1	0	0	90	0	1	0	90	1	0	0
Vasc disorders-Other, spec	89	0	0	0	91	0	0	0	90	1	0	0
Vomiting	88	1	0	0	90	1	0	0	90	1	0	0
Weight loss	88	1	0	0	91	0	0	0	91	0	0	0
MAX. GRADE ANY ADVERSE EVENT	31	48	6	4	62	23	4	2	40	45	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, J Radich, M Fang, D Rizzieri (Alliance), M Savoie (NCIC-CTG), S Strickland (ECOG-ACRIN)

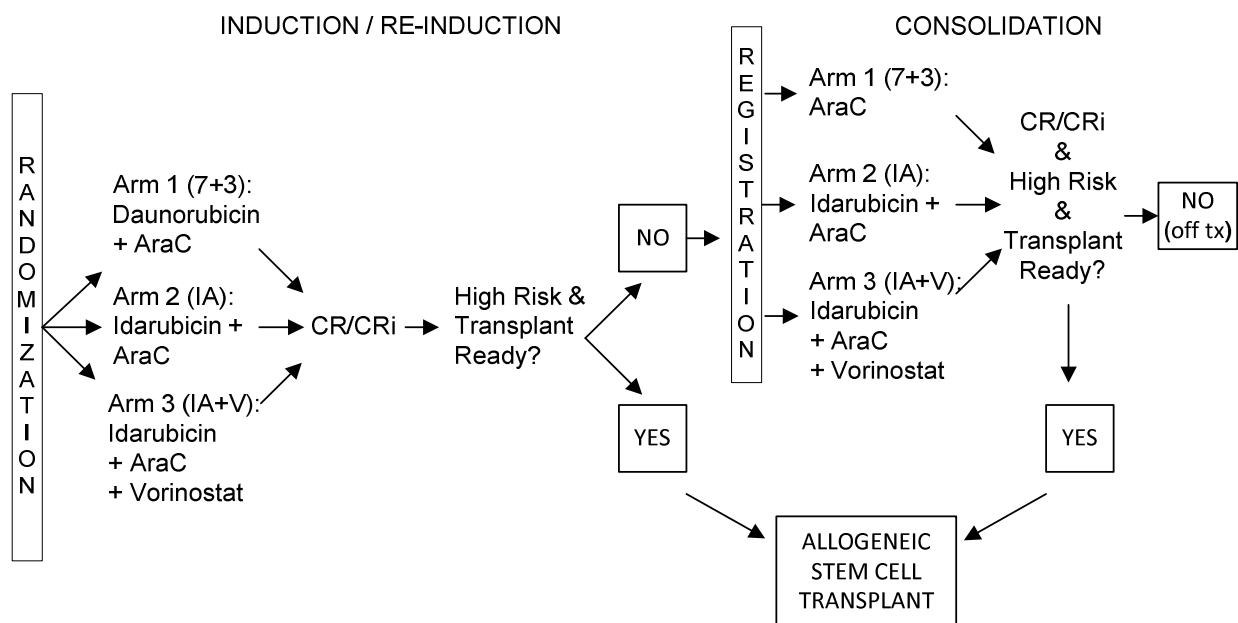
Statisticians:

M Othus, H Li

Data Coordinators:

T Maher, L Kingsbury, L Highleyman

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) with blood or bone marrow disease, as defined in the protocol. Patients with only extramedullary disease in the absence of bone marrow or blood involvement are not eligible.

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/m² daunorubicin or equivalent. Prior ATRA for suspected APL is allowed. Prior methotrexate for CNS involvement is allowed. Patients with prior history of MDS must not have received azacitidine, decitabine, lenalidomide or vorinostat.

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/mL.

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 initial accrual goal of this study was 705 eligible patients (235 eligible patients per arm). Arm 3 (Idarubicin +AraC +Vorinostat) was permanently closed to accrual on May 22, 2015, with a total of 224 patients enrolled. Arm 1 (AraC + Daunorubicin) and Arm 2 (AraC + Idarubicin) remain open to accrual until 235 eligible patients enrolled on each 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

The study was temporarily closed to accrual on May 22, 2015, due to the outcome of interim analysis conducted by the SWOG Data Safety and Monitoring Committee (DSMC) on May 1, 2015. The DSMC analysis showed futility for Arm 3 (Idarubicin +AraC +Vorinostat) being better than either Arm 1 (AraC + Daunorubicin) or Arm 2 (AraC + Idarubicin). The DSMC recommended the closure of Arm 3. Patients currently receiving treatment on Arm 3 who choose to continue protocol treatment may do so with or without vorinostat. If a patient chooses to remain on Arm 3 without vorinostat, the treatment schedule should follow that of Arm 2. The study was reactivated on June 19, 2015 with randomization to either Arm 1 or Arm 2.

As of June 30, 2015, 665 patients have enrolled. Fifteen patients are currently ineligible due to the following reasons: insufficient blasts (7), no evidence of AML (3), positive Philadelphia chromosome in

bone marrow, having APL, receiving valproic acid at the time of registration, being intubated prior to registration, and inadequate heart function (1 patient each). Eight eligible patients who 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.

Six hundred ten patients were assessed for adverse events on protocol induction treatment. Six treatment-related deaths occurred on the 7+3 arm (AraC + Daunorubicin) due to the following reasons: cardiac arrest, platelet decreased (coded as 'Death NOS'), venous occlusive disease (coded as 'Hepatobil disorder-Other'), multi-organ failure, respiratory failure, and typhlitis (one each). An additional 28 patients on the 7+3 arm experienced Grade 4 non-hematologic toxicities as maximum degree, including *Stenotrophomonas* and *E. coli* from central line (coded as 'Infections/infestations-Other'),

Seventeen treatment-related deaths occurred on the IA arm (AraC + Idarubicin) due to the following reasons: sepsis (7), respiratory failure (3), cardiac arrest (3), multi-organ failure (2), and one case each of ARDS, bronchopulmonary hemorrhage, gastric hemorrhage, hematoma, septic shock (coded as 'Infections/infestations-Other'), and uncal herniation, tonsillar herniation, and edema herniation (coded as 'Nervous system disorders-Other'). An additional 21 patients experienced Grade 4 non-hematologic toxicities as maximum degree, including colostomy and ischemic bowel (coded as 'GI disorders-Other, specify'), monocyte count decreased (3) (coded as 'Investigations-Other, specify'), and acute respiratory distress (coded as 'Respiratory, thoracic and mediastinal disorders-Other').

Sixteen treatment-related deaths occurred on the IA+V arm (AraC + Idarubicin + Vorinostat) due to the following reasons: sepsis (8), respiratory failure (5), multi-organ failure (2), and one case each of bronchopulmonary hemorrhage, cardiac arrest, and intracranial hemorrhage. An additional 34 patients

experienced Grade 4 non-hematologic toxicities, including sepsis (coded as 'Infections and infestations - Other, specify'), monocyte count decreased and lactate (coded as 'Investigations-Other, specify').

Twelve patients are currently ineligible for consolidation due to the following reasons: not meeting protocol defined remission (5), being ineligible for induction (5), persistent leukemia cutis, and evidence of residual extramedullary disease. One patient on the IA arm who did not receive any consolidation treatment, coded as a major protocol deviation, is not evaluable for adverse events. Another patient on the IA arm who progressed after registration to consolidation therapy and before treatment started is also coded as a major protocol deviation.

Two possibly treatment related deaths occurred on the 7+3 consolidation arm: one due to seizure and one is reported as both 'Respiratory, thoracic and mediastinal disorders-Other' and 'Death NOS'. Seventeen additional patients on the 7+3 consolidation arm experienced Grade 4 non-hematologic toxicities, including cardiomyopathy (coded as 'Cardiac disorders-Other'), acute hepatic failure (coded as 'GI disorders-Other'), *Klebsiella pneumoniae* (coded as 'Infections/infestations-Other'), and elevated lactate dehydrogenase (coded as 'Investigations-Other, specify').

One treatment related death occurred on the IA consolidation arm due to sepsis. Eighteen additional patients experienced Grade 4 non-hematologic toxicities during consolidation, including monocyte count decreased (2) and decreased granulocytes (coded as 'Investigations-Other, specify').

Five treatment-related deaths occurred on the IA+V consolidation arm due to the following reasons: respiratory failure (2), sepsis (2), and intracranial hemorrhage. Twenty-one additional patients experienced Grade 4 non-hematologic toxicities during consolidation, including monocyte count decreased (coded as 'Investigations-Other, specify').

Registration by Institution
Registrations ending June 30, 2015

Institutions	Total Reg	Institutions	Total Reg
Alliance	196	Dayton NCORP	5
ECOG-ACRIN	139	MD Anderson CC	5
Stanford University	47	Prov Portland MC/PCRC NCORP	4
Birmingham, U of AL	25	Providence Hosp	4
NCIC-CTG	24	Florida, Univ of/Yale University	3
Kansas, U of	23	Montana NCORP	3
Cleveland Clinic OH	21	Northwestern Univ/San Diego, U of CA	3
Rochester, Univ of	20	Upstate Carolina	3
Davis, U of CA	14	Wayne State Univ	3
NRG	12	Baylor College	2
Yale University	12	Kansas City NCORP	2
MUSC MU-NCORP	11	Michigan, U of	2
Kentucky, U of	9	New Mexico MU-NCORP	2
Loyola University	9	Heartland NCORP	1
Mississippi, Univ of	9	Michigan CRC NCORP	1
Oregon Hlth Sci Univ	9	Ozarks NCORP	1
H Lee Moffitt CC	7	PCRC NCORP	1
Irvine, U of CA	7	San Diego, U of CA	1
City of Hope Med Ctr	6	Southeast COR NCORP	1
CRC West MI NCORP	6	St Luke's Mt State/PCRC NCORP	1
Oklahoma, Univ of	6	Total (42 Institutions)	665
Arizona MC, U of	5		

Registration, Eligibility, and Evaluability

Registrations ending June 30, 2015; Data as of July 30, 2015

	TOTAL	AraC + Daunorubicin	AraC + Idarubicin	Vorinostat + AraC + Idarubicin
NUMBER REGISTERED	665	219	222	224
INELIGIBLE	15	2	6	7
ELIGIBLE	650	217	216	217
Analyzeable, Pend. Elig.	6	4	2	0
RESPONSE ASSESSMENT				
Determinable	560	194	184	182
Not Determinable	37	4	14	19
Too Early	53	19	18	16
ADVERSE EVENT ASSESSMENT				
Evaluable	610	201	206	203
Not Evaluable	8	0	2	6
Too Early	32	16	8	8

Patient Characteristics

Registrations ending June 30, 2015; Data as of July 30, 2015

	AraC + Daunorubicin (n=217)		AraC + Idarubicin (n=216)		Vorinostat + AraC + Idarubicin (n=217)	
AGE						
Median	49.3		51.4		48.8	
Minimum	19.2		18.8		19.6	
Maximum	60.6		60.9		61.0	
AGE						
< 40 years	57.0	26%	56.0	26%	56.0	26%
≥ 40 years	160.0	74%	160.0	74%	161.0	74%
SEX						
Males	112	52%	111	51%	114	53%
Females	105	48%	105	49%	103	47%
HISPANIC						
Yes	18	8%	18	8%	21	10%
No	185	85%	178	82%	186	86%
Unknown	14	6%	20	9%	10	5%
RACE						
White	184	85%	180	83%	178	82%
Black	17	8%	15	7%	17	8%
Asian	4	2%	4	2%	8	4%
Pacific Islander	1	0%	1	0%	0	0%
Native American	1	0%	0	0%	3	1%
Multi-Racial	0	0%	1	0%	0	0%
Unknown	10	5%	15	7%	11	5%
ONSET						
De novo	195	90%	195	90%	194	89%
Treatment related and/or AML arising from antecedent hematologic disease	22	10%	21	10%	23	11%

Treatment Summary

Registrations ending June 30, 2015; Data as of July 30, 2015

	Total
NUMBER ON PROTOCOL TREATMENT	29
NUMBER OFF PROTOCOL TREATMENT	621
REASON OFF TREATMENT	
Treatment completed as planned	470
Adverse Event or side effects	18
Refusal unrelated to adverse event	15
Progression/relapse	4
Death	32
Other - not protocol specified	72
Reason under review	10
MAJOR PROTOCOL DEVIATIONS	10

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

Registrations ending June 30, 2015; Data as of July 30, 2015

ADVERSE EVENTS	AraC + Daunorubicin (n=201) Grade				AraC + Idarubicin (n=206) Grade				Vorinostat + AraC + Idarubicin (n=203) Grade			
	≤ 2	3	4	5	≤ 2	3	4	5	≤ 2	3	4	5
ALT increased	191	9	1	0	195	11	0	0	184	18	1	0
ARDS	200	0	1	0	203	1	1	1	199	0	4	0
AST increased	193	7	1	0	197	9	0	0	192	10	1	0
Abdominal distension	200	1	0	0	206	0	0	0	203	0	0	0
Abdominal infection	200	1	0	0	205	0	1	0	202	1	0	0
Abdominal pain	198	3	0	0	201	5	0	0	197	6	0	0
Acidosis	200	0	1	0	206	0	0	0	201	1	1	0
Acute kidney injury	199	0	2	0	202	2	2	0	199	2	2	0
Alkaline phosphatase increased	199	2	0	0	204	2	0	0	202	1	0	0
Alkalosis	200	1	0	0	205	1	0	0	201	2	0	0
Allergic reaction	201	0	0	0	206	0	0	0	201	2	0	0
Anal hemorrhage	201	0	0	0	206	0	0	0	202	1	0	0
Anal pain	201	0	0	0	205	1	0	0	203	0	0	0
Anal ulcer	201	0	0	0	206	0	0	0	202	1	0	0
Anorectal infection	201	0	0	0	206	0	0	0	199	4	0	0
Anorexia	197	3	1	0	197	9	0	0	192	11	0	0
Atelectasis	201	0	0	0	206	0	0	0	202	1	0	0
Atrial fibrillation	201	0	0	0	204	0	2	0	202	0	1	0
Atrial flutter	201	0	0	0	206	0	0	0	202	1	0	0
Blood bilirubin increased	193	7	1	0	197	7	2	0	187	13	3	0
Bone infection	200	1	0	0	206	0	0	0	203	0	0	0
Bronchopulmonary hemorrhage	201	0	0	0	205	0	0	1	200	1	1	1

OCTOBER 7 - 10, 2015

SWOG

LEUKEMIA 28

S1203/III

ADVERSE EVENTS	AraC + Daunorubicin (n=201)				AraC + Idarubicin (n=206)				Vorinostat + AraC + Idarubicin (n=203)			
	Grade				Grade				Grade			
	≤2	3	4	5	≤2	3	4	5	≤2	3	4	5
Bullous dermatitis	201	0	0	0	204	2	0	0	203	0	0	0
Cardiac arrest	200	0	0	1	203	0	0	3	201	0	1	1
Cardiac disorder-Other, spec	201	0	0	0	206	0	0	0	202	0	1	0
Cardiac troponin I increased	201	0	0	0	205	1	0	0	203	0	0	0
Catheter related infection	200	1	0	0	201	5	0	0	198	5	0	0
Chills	200	1	0	0	206	0	0	0	203	0	0	0
Chronic kidney disease	201	0	0	0	205	0	1	0	203	0	0	0
Cognitive disturbance	201	0	0	0	206	0	0	0	202	1	0	0
Colitis	199	2	0	0	200	6	0	0	199	2	2	0
Colonic hemorrhage	200	1	0	0	206	0	0	0	202	1	0	0
Colonic perforation	201	0	0	0	206	0	0	0	202	0	1	0
Conduction disorder	200	0	1	0	206	0	0	0	203	0	0	0
Conjunctivitis	200	1	0	0	206	0	0	0	203	0	0	0
Constipation	201	0	0	0	205	1	0	0	203	0	0	0
Constrictive pericarditis	200	1	0	0	206	0	0	0	203	0	0	0
Creatinine increased	200	1	0	0	204	2	0	0	199	3	1	0
DIC	200	1	0	0	206	0	0	0	202	1	0	0
Death NOS	200	0	0	1	206	0	0	0	203	0	0	0
Dehydration	200	1	0	0	206	0	0	0	201	2	0	0
Dental caries	200	1	0	0	206	0	0	0	203	0	0	0
Device related infection	200	1	0	0	205	1	0	0	203	0	0	0
Diarrhea	190	11	0	0	190	16	0	0	170	32	1	0
Dry skin	201	0	0	0	204	2	0	0	203	0	0	0
Duodenal hemorrhage	200	0	1	0	206	0	0	0	203	0	0	0
Dyspepsia	200	1	0	0	206	0	0	0	203	0	0	0
Dysphagia	200	1	0	0	206	0	0	0	203	0	0	0
Dyspnea	198	2	1	0	204	1	1	0	195	5	3	0
ECG QT corrected int prolong	201	0	0	0	206	0	0	0	201	2	0	0
Edema cerebral	201	0	0	0	206	0	0	0	202	0	1	0
Edema limbs	201	0	0	0	205	1	0	0	201	2	0	0
Ejection fraction decreased	200	1	0	0	202	4	0	0	200	3	0	0
Enterocolitis	200	1	0	0	201	3	2	0	199	4	0	0
Enterocolitis infectious	201	0	0	0	202	4	0	0	199	4	0	0
Epistaxis	200	1	0	0	205	1	0	0	201	2	0	0
Esophageal hemorrhage	201	0	0	0	206	0	0	0	202	1	0	0
Esophageal pain	200	1	0	0	205	1	0	0	203	0	0	0
Esophagitis	199	2	0	0	205	1	0	0	202	1	0	0
Eye infection	201	0	0	0	205	1	0	0	203	0	0	0
Fatigue	190	11	0	0	194	12	0	0	191	12	0	0
Febrile neutropenia	81	114	6	0	83	117	6	0	98	101	4	0
Fever	198	2	1	0	202	4	0	0	197	5	1	0
GERD	200	1	0	0	206	0	0	0	203	0	0	0
GGT increased	199	2	0	0	205	1	0	0	199	4	0	0
GI disorders-Other, specify	200	1	0	0	203	1	2	0	202	1	0	0
Gastric hemorrhage	201	0	0	0	205	0	0	1	200	2	1	0
Gastritis	200	1	0	0	206	0	0	0	203	0	0	0
Gen disorders/admin site cond	201	0	0	0	206	0	0	0	202	1	0	0
Generalized muscle weakness	199	2	0	0	206	0	0	0	202	1	0	0
Genital edema	201	0	0	0	206	0	0	0	202	1	0	0
Gum infection	200	1	0	0	206	0	0	0	203	0	0	0

ADVERSE EVENTS	AraC + Daunorubicin (n=201)				AraC + Idarubicin (n=206)				Vorinostat + AraC + Idarubicin (n=203)			
	Grade				Grade				Grade			
	≤2	3	4	5	≤2	3	4	5	≤2	3	4	5
Hand-Foot syndrome	201	0	0	0	205	1	0	0	203	0	0	0
Headache	199	2	0	0	205	1	0	0	199	4	0	0
Heart failure	200	1	0	0	204	2	0	0	200	1	2	0
Hematoma	201	0	0	0	205	0	0	1	203	0	0	0
Hematuria	201	0	0	0	204	2	0	0	203	0	0	0
Hepatic failure	200	0	1	0	206	0	0	0	203	0	0	0
Hepatic infection	200	1	0	0	205	1	0	0	203	0	0	0
Hepatobil disorders-Other	200	0	0	1	206	0	0	0	202	1	0	0
Hyperglycemia	197	4	0	0	199	6	1	0	188	14	1	0
Hyperhidrosis	200	1	0	0	205	1	0	0	203	0	0	0
Hyperkalemia	201	0	0	0	205	0	1	0	202	1	0	0
Hypermagnesemia	201	0	0	0	205	1	0	0	203	0	0	0
Hypernatremia	201	0	0	0	206	0	0	0	202	0	1	0
Hypertension	194	7	0	0	203	3	0	0	198	4	1	0
Hyperuricemia	201	0	0	0	205	1	0	0	202	0	1	0
Hypoalbuminemia	198	2	1	0	200	6	0	0	196	7	0	0
Hypocalcemia	195	5	1	0	196	10	0	0	181	19	3	0
Hypoglycemia	201	0	0	0	206	0	0	0	202	1	0	0
Hypokalemia	187	11	3	0	192	14	0	0	180	21	2	0
Hypomagnesemia	201	0	0	0	206	0	0	0	202	1	0	0
Hyponatremia	185	14	2	0	191	15	0	0	195	8	0	0
Hypophosphatemia	182	18	1	0	184	19	3	0	175	26	2	0
Hypotension	199	2	0	0	199	3	4	0	194	4	5	0
Hypoxia	199	1	1	0	204	1	1	0	195	4	4	0
Ileus	201	0	0	0	206	0	0	0	202	1	0	0
Infections/infestations-Other	189	11	1	0	193	12	0	1	192	10	1	0
Infective myositis	200	1	0	0	206	0	0	0	203	0	0	0
Intracranial hemorrhage	201	0	0	0	206	0	0	0	202	0	0	1
Investigations-Other, specify	200	1	0	0	202	1	3	0	200	1	2	0
Jejunal obstruction	201	0	0	0	206	0	0	0	202	1	0	0
Kidney infection	201	0	0	0	205	1	0	0	203	0	0	0
LV systolic dysfunction	200	1	0	0	205	1	0	0	203	0	0	0
Laryngeal edema	200	1	0	0	206	0	0	0	203	0	0	0
Laryngeal mucositis	201	0	0	0	206	0	0	0	202	1	0	0
Lipase increased	201	0	0	0	206	0	0	0	201	2	0	0
Lower GI hemorrhage	201	0	0	0	206	0	0	0	200	3	0	0
Lung infection	186	15	0	0	196	8	2	0	190	11	2	0
MS/connective tissue disorder	201	0	0	0	206	0	0	0	202	1	0	0
Menorrhagia	200	1	0	0	206	0	0	0	203	0	0	0
Metab/nutrition disorders-Oth	200	1	0	0	206	0	0	0	203	0	0	0
Middle ear inflammation	200	1	0	0	206	0	0	0	203	0	0	0
Mucosal infection	200	1	0	0	206	0	0	0	202	1	0	0
Mucositis oral	188	12	1	0	198	8	0	0	195	8	0	0
Multi-organ failure	200	0	0	1	203	0	1	2	198	1	2	2
Nausea	195	6	0	0	194	12	0	0	198	5	0	0
Neck edema	201	0	0	0	206	0	0	0	202	1	0	0
Nervous sys disorders-Other	201	0	0	0	205	0	0	1	203	0	0	0
Non-cardiac chest pain	201	0	0	0	206	0	0	0	202	1	0	0
Oral pain	198	3	0	0	202	4	0	0	203	0	0	0
Pain	200	1	0	0	206	0	0	0	203	0	0	0

ADVERSE EVENTS	AraC + Daunorubicin (n=201)				AraC + Idarubicin (n=206)				Vorinostat + AraC + Idarubicin (n=203)			
	Grade				Grade				Grade			
	≤2	3	4	5	≤2	3	4	5	≤2	3	4	5
Pain in extremity	200	1	0	0	206	0	0	0	203	0	0	0
Papulopustular rash	201	0	0	0	205	1	0	0	203	0	0	0
Pericardial effusion	201	0	0	0	206	0	0	0	202	1	0	0
Pericardial tamponade	201	0	0	0	206	0	0	0	202	0	1	0
Periorbital edema	201	0	0	0	205	1	0	0	203	0	0	0
Pharyngeal mucositis	200	1	0	0	206	0	0	0	203	0	0	0
Pleural effusion	200	1	0	0	206	0	0	0	202	1	0	0
Pneumonitis	200	1	0	0	203	3	0	0	201	2	0	0
Pruritus	201	0	0	0	206	0	0	0	202	1	0	0
Pulmonary edema	200	1	0	0	204	1	1	0	198	4	1	0
Purpura	201	0	0	0	205	1	0	0	203	0	0	0
Rash acneiform	201	0	0	0	205	1	0	0	203	0	0	0
Rash maculo-papular	194	7	0	0	186	20	0	0	195	8	0	0
Rectal hemorrhage	200	1	0	0	206	0	0	0	203	0	0	0
Rectal pain	200	1	0	0	206	0	0	0	202	1	0	0
Resp/thoracic/mediastinal ds	200	1	0	0	204	1	1	0	201	1	1	0
Respiratory failure	199	0	1	1	199	0	4	3	190	0	8	5
Restrictive cardiomyopathy	200	1	0	0	206	0	0	0	203	0	0	0
Scrotal infection	201	0	0	0	206	0	0	0	202	0	1	0
Seizure	200	1	0	0	206	0	0	0	202	1	0	0
Sepsis	188	0	13	0	187	0	12	7	174	0	21	8
Sinus bradycardia	201	0	0	0	206	0	0	0	202	1	0	0
Sinus tachycardia	201	0	0	0	204	2	0	0	201	2	0	0
Sinusitis	199	2	0	0	206	0	0	0	203	0	0	0
Skin infection	197	4	0	0	205	1	0	0	201	2	0	0
Skin ulceration	201	0	0	0	206	0	0	0	202	1	0	0
Skin/subq tissue ds-Other	201	0	0	0	205	1	0	0	202	1	0	0
Soft tissue infection	200	0	1	0	206	0	0	0	203	0	0	0
Sore throat	200	1	0	0	204	2	0	0	201	2	0	0
Stomach pain	200	1	0	0	206	0	0	0	203	0	0	0
Stroke	201	0	0	0	205	1	0	0	202	0	1	0
Supraventricular tachycardia	201	0	0	0	205	1	0	0	202	1	0	0
Syncope	200	1	0	0	204	2	0	0	200	3	0	0
TTP	199	0	2	0	206	0	0	0	202	1	0	0
Testicular disorder	201	0	0	0	205	1	0	0	203	0	0	0
Thromboembolic event	200	1	0	0	206	0	0	0	203	0	0	0
Tumor lysis syndrome	198	3	0	0	200	6	0	0	195	8	0	0
Typhlitis	194	6	0	1	195	11	0	0	182	20	1	0
Upper GI hemorrhage	200	1	0	0	206	0	0	0	202	1	0	0
Upper respiratory infection	199	2	0	0	206	0	0	0	201	2	0	0
Urinary tract infection	197	4	0	0	205	1	0	0	198	5	0	0
Urine output decreased	201	0	0	0	206	0	0	0	202	1	0	0
Vaginal hemorrhage	201	0	0	0	206	0	0	0	202	1	0	0
Vascular access complication	201	0	0	0	205	1	0	0	202	0	1	0
Vasovagal reaction	201	0	0	0	205	1	0	0	202	0	1	0
Ventricular tachycardia	201	0	0	0	205	1	0	0	203	0	0	0
Vomiting	199	2	0	0	201	5	0	0	199	4	0	0
Weight loss	200	1	0	0	206	0	0	0	202	1	0	0
MAX. GRADE ANY ADVERSE EVENT	50	117	28	6	44	124	21	17	37	116	34	16

OCTOBER 7 - 10, 2015

SWOG

LEUKEMIA 31

S1203/III

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

Date Activated:

08/29/2013

Statisticians:

J Unger, K Arnold

Data Coordinator:

M Yee

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 solid or hematologic cancer malignancy. Confirmed diagnosis date must be within 120 days prior to first clinic visit as a newly diagnosed cancer patient at the registering clinic. Patients presenting for "second opinions" of confirmed malignancies are eligible, including those who have started cancer treatment at other facilities. Patients must be registered within 90 days after their first clinic visit. Patients must not 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. Patients must have no evidence of disease for a prior malignancy for at least five years prior to randomization except as noted above.

Patients must be 18 years of age or older. Patients must have had their blood drawn for viral status testing for HIV, HBV and HCV or provide acceptable viral status documentation prior to registration, as defined in the protocol. Note that patients must have blood drawn for testing prior to registration for any of the three viruses not covered by the documentation. Patients are allowed to participate in other clinical trials.

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 with bilineal leukemia are excluded. 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 second or third 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 one week prior to registration; (2) Chimeric antigen receptor (CAR) T-cells must not have been received for 28 days prior to registration; (3) Steroids, vincristine, 6-mercaptopurine, methotrexate, thioguanine and intrathecal chemotherapy are permitted within any time frame prior to registration. FDA-approved tyrosine kinase inhibitors may also be administered until one day prior to start of study therapy (C1, D1). All drug-related toxicities must have resolved to \leq Grade 2.

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 is reached or the highest dose tested is judged tolerable. This study will accrue 3-30 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 in five separate cohorts. The initial dose level of 0.4 mg/m² inotuzumab 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/m² cohort, no DLTs were observed. Among five patients on the dose 0.4 mg/m² cohort assessed for toxicity, no Grade 4 or higher non-hematologic toxicities reported.

The second cohort evaluating inotuzumab at 0.6 mg/m² at day 1 and 0.4 mg/m² at day 15 was closed to accrual on May 15, 2015, with five patients registered. One patient was ineligible due to inadequate liver function. Another patient who was removed from study early was not evaluable for prolonged myelosuppression and therefore is not evaluable for DLT. Of the three evaluable patients, no DLTs were observed. Among four patients assessed for toxicity, no Grade 4 or higher non-hematologic toxicities reported.

The third cohort evaluating inotuzumab at 0.8 mg/m² at day 1 and 0.4 mg/m² at day 15, was open to accrual on June 1, 2015. As of August 24, 2015, five patients have been registered. Three patients were not evaluable for DLT: one due to persistent disease, one patient died and did not receive a full cycle of treatment, and one patient continued to take tyrosine kinase inhibitor (TKI) while on protocol and is coded as a major protocol deviation. No DLTs were observed in the evaluable patients. Among five patients assessed for toxicity, no Grade 4 or higher non-hematologic toxicities reported.

Registration by Institution

Registrations ending August 24, 2015

Institutions	Total Reg
Cleveland Clinic OH	7
Rochester, Univ of	3
Baylor College	2
Stanford University	2
City of Hope Med Ctr	1
Total (5 Institutions)	15

Registration, Eligibility, and Evaluability

Registrations ending August 24, 2015; Data as of August 24, 2015

	TOTAL	CVP + Inotuzumab dose level 1	CVP + Inotuzumab dose level 2	CVP + Inotuzumab dose level 3
NUMBER REGISTERED	15	5	5	5
INELIGIBLE	1	0	1	0
ELIGIBLE	14	5	4	5
Analyzeable, Pend. Elig.	2	0	0	2
RESPONSE ASSESSMENT				
Determinable	10	5	4	1
Not Determinable	1	0	0	1
Too Early	3	0	0	3
ADVERSE EVENT ASSESSMENT				
Evaluable	14	5	4	5
DOSE-LIMITING TOXICITY ASSESSMENT				
Evaluable	7	3	3	1
Not Evaluable	6	2	1	3
Too Early	1	0	0	1

Patient Characteristics

Registrations ending August 24, 2015; Data as of August 24, 2015

	CVP + Inotuzumab dose level 1 (n=5)		CVP + Inotuzumab dose level 2 (n=4)		CVP + Inotuzumab dose level 3 (n=5)	
AGE						
Median	48.9		42.3		35.6	
Minimum	22.4		20.7		22.4	
Maximum	73.7		56.4		74.5	
SEX						
Males	4	80%	0	0%	3	60%
Females	1	20%	4	100%	2	40%
HISPANIC						
Yes	2	40%	2	50%	1	20%
No	3	60%	2	50%	4	80%
RACE						
White	4	80%	3	75%	3	60%
Black	1	20%	1	25%	1	20%
Unknown	0	0%	0	0%	1	20%

Treatment Summary

Registrations ending August 24, 2015; Data as of August 24, 2015

	TOTAL	CVP + Inotuzumab dose level 1	CVP + Inotuzumab dose level 2	CVP + Inotuzumab dose level 3
NUMBER ON PROTOCOL TREATMENT	2	0	0	2
NUMBER OFF PROTOCOL TREATMENT	12	5	4	3
REASON OFF TREATMENT				
Treatment completed as planned	3	1	2	0
Adverse Event or side effects	1	0	0	1
Refusal unrelated to adverse event	0	0	0	0
Progression/relapse	2	1	1	0
Death	1	0	0	1
Other - not protocol specified	5	3	1	1
Reason under review	0	0	0	0
MAJOR PROTOCOL DEVIATIONS	1	0	0	1

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 August 24, 2015; Data as of August 24, 2015

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

Registrations ending August 24, 2015; Data as of August 24, 2015

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

Participants:

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

Date Activated:

01/12/2015

Study Chairs:

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

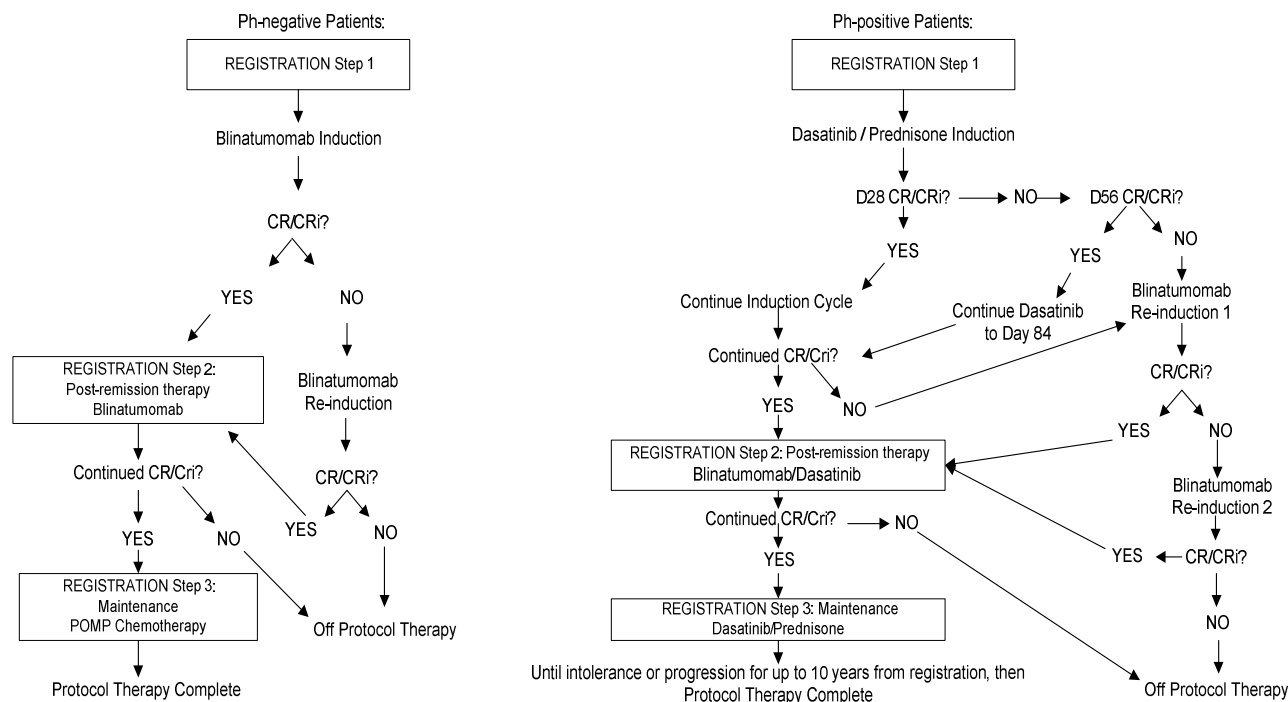
Statisticians:

H Li, M Othus

Data Coordinator:

T Maher

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-idiotypic 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. As of June 30, 2015, one patient from Alliance has been enrolled to the Ph-negative cohort.

A041202 Phase III SWOG Supported CTSU Study

Coordinating Group: Alliance

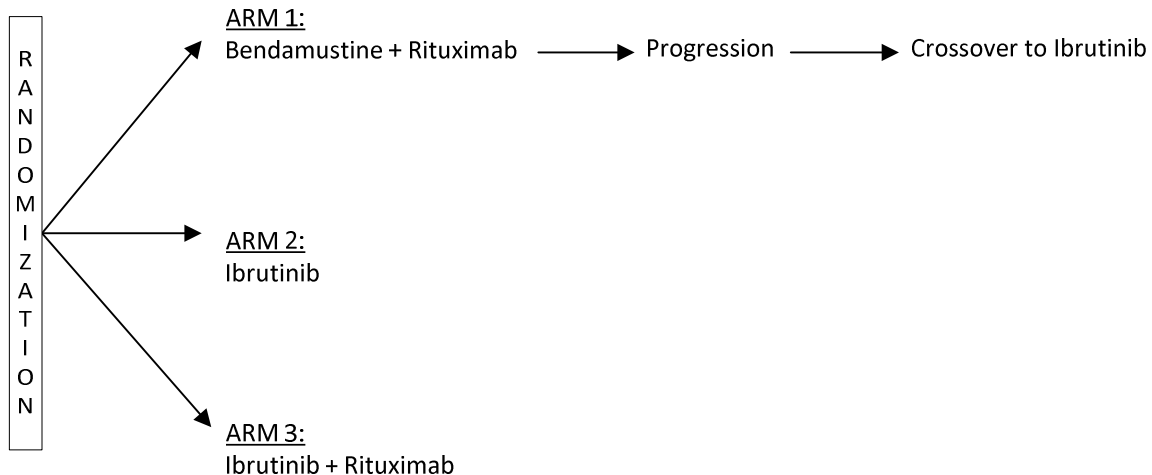
A Randomized Phase III Study of Bendamustine plus Rituximab Versus Ibrutinib plus Rituximab Versus Ibrutinib Alone In Untreated Older Patients (≥ 65 Years of Age) With Chronic Lymphocytic Leukemia (CLL)

Participants:
Alliance, CTSU

Date Activated:
12/10/2013

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

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 functional status 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 any prior history of Richter's transformation or prolymphocytic leukemia.

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 not be receiving active systemic anticoagulation with heparin or warfarin. Patients must be off warfarin therapy for at least 30 days prior to enrollment. Patients must not have had major surgery within ten days or minor surgery within seven days of enrollment.

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 ≥ 350 cells/mm³ 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.

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 $\geq 20\%$. In the event that a sample does not yield a Zap-70 methylation status, data will be input based on IgVH mutation status: > 20 if IgVH mutated or < 20 for unmutated.

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 339 patients as of June 30, 2015, including 65 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 June 30, 2015

Institutions	Total Reg	Institutions	Total Reg
Kaiser Vallejo NCORP	13	Boston Medical Ctr	1
KaiserPermanenteSCAL/Kaiser Vallejo NCORP	8	Columbus NCORP	1
City of Hope Med Ctr	6	Fowler Family Center/Baptist MU-NCORP	1
Stanford University	6	KaiserPermanenteCOL/Kaiser Vallejo NCORP	1
Rochester, Univ of	5	Northwestern Univ/San Diego, U of CA	1
Cleveland Clinic OH	4	Poudre Valley Hosp/Colorado, U of	1
Kansas, U of	4	Sacred Heart Hosp/Arkansas, U of	1
Arizona MC, U of	3	St Luke's Mt State/PCRC NCORP	1
Yale University	3	Wayne State Univ	1
Orange Reg Med Ctr	2	Total (20 Institutions)	65
Presbyterian Hosp/Irvine, U of CA	2		

E1910 Phase III SWOG Supported CTSU Study

Coordinating Group: ECOG-ACRIN

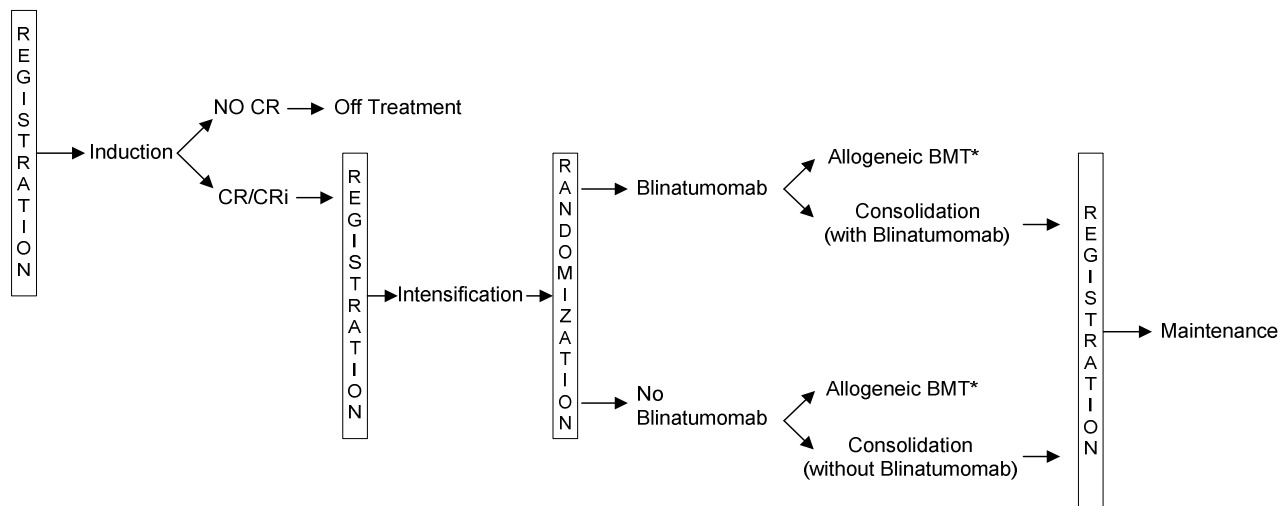
A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL-negative B Lineage Acute Lymphoblastic Leukemia in Adults

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 conjunction 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 55 patients as of June 30, 2015, including 20 registrations from SWOG institutions. The complete Spring 2015 summary of this study from ECOG-ACRIN is available on the SWOG web site.

Registration by Institution

Registrations ending June 30, 2015

Institutions	Total Reg
Yale University	7
Stanford University	6
Cleveland Clinic OH	2
Kansas, U of	2
Rochester, Univ of	1
San Diego, U of CA	1
Wayne State Univ	1
Total (7 Institutions)	20

E1912 Phase III SWOG Supported CTSU Study

Coordinating Group: ECOG-ACRIN

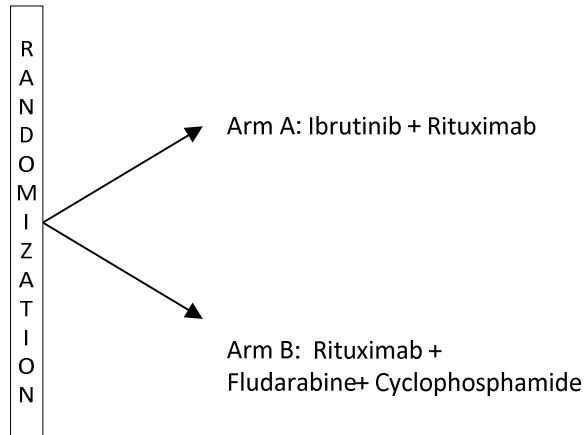
A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL)

Participants:
ECOG-ACRIN, SWOG

Date Activated:
02/07/2014

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

SCHEMA



Objectives

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 initial 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, life expectancy of at least 12 months, 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) ECOG 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.

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 290 patients as of June 30, 2015, including 66 registrations from SWOG institutions. The complete Spring 2015 summary of this study from ECOG-ACRIN is available on the SWOG web site.

Registration by Institution
 Registrations ending June 30, 2015

Institutions	Total Reg	Institutions	Total Reg
Stanford University	20	KaiserPermanenteCOL/Kaiser Vallejo NCORP	1
Rochester, Univ of	12	Loyola University	1
Kaiser Vallejo NCORP	8	Northwest NCORP	1
Beaumont NCORP	4	Orange Reg Med Ctr	1
KaiserPermanenteSCAL/Kaiser Vallejo NCORP	3	Ozarks NCORP	1
Montana NCORP	3	San Antonio, U of TX	1
Wayne State Univ	3	St Joseph Med Ctr/PCRC NCORP	1
Arkansas, U of	2	Stormont-Vail Health/Kansas, U of	1
Cancer Ctr South Bay/Stanford University	1	Yale University	1
Greenville NCORP	1	Total (19 Institutions)	66

E2905 Phase III SWOG Supported CTSU Study

Coordinating Group: ECOG-ACRIN

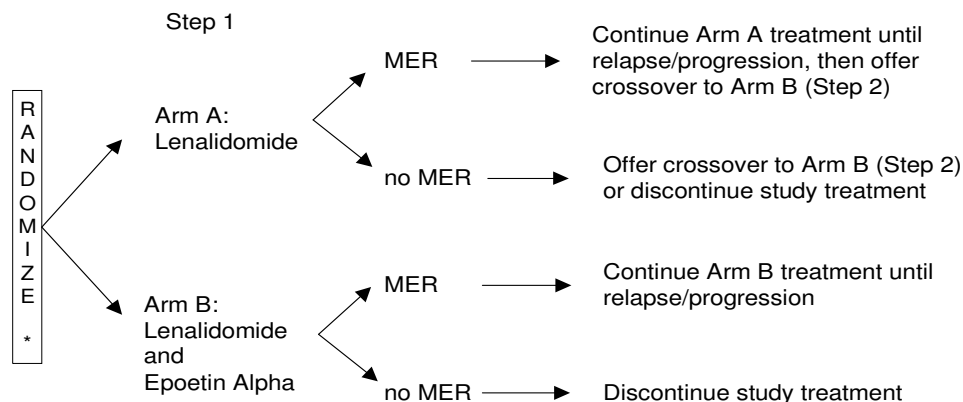
Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment with Lenalidomide (Revlimid®) Alone and in Combination with Epoetin Alfa (Procrit®) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

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 $\geq 12,000$ /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 must have 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 $\geq 50,000$ /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 212 patients as of June 30, 2015, including 65 registrations from SWOG institutions. The complete Spring 2015 summary of this study from ECOG-ACRIN is available on the SWOG web site.

Registration by Institution
 Registrations ending June 30, 2015

Institutions	Total Reg	Institutions	Total Reg
H Lee Moffitt CC	20	Rochester, Univ of	2
Greenville NCORP	6	Columbia MU-NCORP	1
KaiserPermanenteSCAL/Kaiser Vallejo NCORP	6	CORA NCORP	1
Wayne State Univ	5	Kansas, U of	1
Davis, U of CA	4	Lahey Clinic Med Ctr/Davis, U of CA	1
Montana NCORP	4	Providence Hosp	1
Thompson Ca Surv Ctr/San Antonio, U of TX	3	Southeast COR NCORP	1
Yale University	3	St Luke's Mt State/PCRC NCORP	1
Colorado, U of	2	Winthrop-Univ Hosp/Columbia University	1
Kansas City NCORP	2	Total (19 Institutions)	65

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)

Participants:
ECOG-ACRIN, CTSU

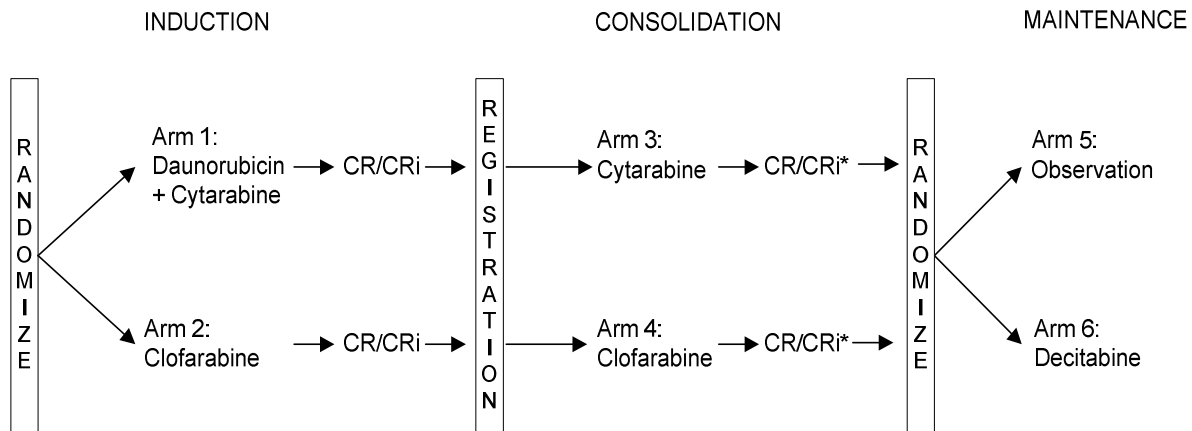
Date Activated:
02/24/2011

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

Date Closed*:
02/23/2015

*Temporary closure

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.

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.

registrations from SWOG institutions. The complete Spring 2015 summary of this study from ECOG-ACRIN is available on the SWOG web site.

ECOG-ACRIN reported a total accrual of 727 patients as of February 23, 2015, including 75

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
CRC West MI NCORP	4	Winthrop-Univ Hosp/Yale University	1
Florida, Univ of/Yale University	4	Total (13 Institutions)	75