ABSTRACT
During the last grant period (January, 2003 through July, 2008) the Southwest Oncology Group Leukemia Committee and its Leukemia Translational Medicine Subcommittee have contributed to 34 manuscripts published or in press, and 22 abstracts presented at national meetings. The manuscripts have or will appear in Blood (13), British Journal of Hematology (4), Leukemia (4), Journal of Clinical Oncology (2), Proceedings of the National Academy of Science (1), Nature Medicine (1), Leukemia Research (1), American Journal of Hematology (3), and Genes, Chromosomes, and Cancer (2).

In acute promyelocytic leukemia (APL), an intergroup prospective randomized trial was completed that demonstrates superior disease-free and overall survival with the addition of arsenic trioxide as consolidation therapy for patients with newly diagnosed disease (1). This trial has changed the standard of care for patients with APL and forms the basis for two active intergroup studies in this disease. Our Translational Medicine Subcommittee initiated the intergroup laboratory consortium (SWOG, CALGB, ECOG, COG) that developed and standardized quantitative RT-PCR assays for measurement of minimal residual disease (MRD) in APL. These assays are integrated into the new intergroup APL studies where quantitative MRD is used for randomization and targeting to specific treatment arms.

In acute myeloid leukemia (AML) in younger patients (age < 61), we completed and published a phase II trial of the addition of high-dose cytarabine during the last three days of induction, and found the regimen to be less active than described in the previous single institution report (2). In an active randomized trial in younger patients with previously untreated AML, we are testing whether the addition of gemtuzumab ozogamicin to induction and post-consolidation therapy improves remission and survival. Correlative studies are investigating whether molecular genetics (NPM, FLT3 mutations), flow cytometric measures of MRD, and/or gene expression classifiers predictive of response can be used to target patients who fail this regimen to experimental therapies or transplantation in the future. Our prior studies demonstrating that functional multidrug resistance (MDR) is a highly significant predictor of treatment failure in AML, associated with advancing age and unfavorable cytogenetics, led to the design of a series of SWOG trials testing cyclosporine as an MDR-reversing agent. Based on results of a randomized trial in patients with recurrent or high-risk AML, we completed two sequential phase 2 trials of continuous infusion cytarabine and daunomycin with and without cyclosporine as initial therapy for older patients with AML who were candidates for intensive chemotherapy. For older patients not felt to be candidates for intensive chemotherapy, we conducted a randomized phase 2 trial of four different dose/schedules of the farnsyl transferase inhibitor, tipifarnib (3). In AML we have also described the clinical spectrum of core binding factor leukemias as well as AMLs associated with t(6;9) (4,5); how the nature of AML changes with age and the powerful interaction of age and performance status on the ability of a patient to tolerate initial induction chemotherapy (6); on novel gene expression profiles and cluster groups in older AML patients; and on the prognostic significance of FLT3 and NPM mutations (10-12). Laboratory investigations focused on the significance of adhesion molecule expression including VLA-4 and on how cholesterol metabolism is perturbed in AML provide the scientific rationale for proposed and active clinical trials (7-9).

In acute lymphocytic leukemia (ALL), the results of a phase II trial of nelarabine in T-cell ALL were published (13). We also reported a new cytogenetic classification scheme for adult ALL, defining 4 prognostic categories and demonstrating that cytogenetics is the most important prognostic factor in this disease (14). In currently active studies, we are validating gene expression classifiers predictive of MRD and outcome in adult ALL and we have identified specific genes (such as CTGF and CRLF2) that are strongly associated with outcome (15).

In chronic myeloid leukemia (CML), we reported gene expression profiles associated with disease progression, highlighting differences in chronic, accelerated and blast crisis (16). Quantitative RT-PCR assays for BCR-ABL are being used in our active CML study as the primary endpoint to measure the molecular depth of remission to imatinib at varying doses and dasatinib.
The results of a retrospective comparison of a combination of rituximab plus fludarabine versus fludarabine alone for treatment of previously untreated chronic lymphocytic leukemia (CLL) were reported (17). A phase II trial of cyclophosphamide followed by fludarabine was conducted and reported, as were the results of a randomized trial of simultaneous cyclophosphamide plus fludarabine versus fludarabine alone (18,19). Other studies in CLL described the prognostic significance of CD38 and CD20 expression, the very poor outcome associated with del(17p), and the impact of mutations in p53, BCL2 and other genes on treatment outcome (20, 21).

Currently, the Leukemia Committee has a full roster of clinical trials and associated translational medicine studies addressing major issues in the treatment of all categories of leukemia and myelodysplasia. In addition to this U01 Cooperative Group Agreement, we have been successful in obtaining additional peer-reviewed funding in support of our correlative science and translational investigations that drive the design of our studies (NIH NCI CA U01 CA88361; NIH NCI CA U01CA114762; LLS SCOR 7388-06; NIH NCI P01 CA18029).

**MEMBERSHIP**

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<td>Vice Chair:</td>
<td>Alan F. List, M.D.</td>
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<td>Executive Officer:</td>
<td>Harry P. Erba, M.D., Ph.D.</td>
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<td>Statisticians:</td>
<td>Kenneth J. Kopecky, Ph.D.</td>
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<td>Golly Gundacker, M.S.</td>
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**Scientific Leadership**

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<th>Translational Medicine:</th>
<th>Cheryl L. Willman, M.D.</th>
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<td>Jerald P. Radich, M.D.</td>
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<td>Pathology:</td>
<td>David R. Head, M.D.</td>
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**Designates**

| Clinical Research Associates: | Emilia G. Cantu |
|                              | Gaye L. Winakur, CCRA |
|                              | Connie Sparks       |
| Data Coordinators:           | Amy Edwards         |
|                              | Tracy Maher         |

| Nurse:                      | Keisha C. Humphries, R.N., B.S.N. |
| Protocol Coordinator:       | Sandi Fredette       |

The Southwest Oncology Group Leukemia Committee is chaired by Frederick R. Appelbaum, and Alan F. List serves as Co-chair. The Leukemia Translational Medicine Subcommittee is chaired by Cheryl L. Willman with Jerry P. Radich serving as Co-Chair. Biostatisticians leading the Committee include Kenneth J. Kopecky, PhD and Holly Gundaker, MS, while David Head oversees Leukemia Pathology. Diane Roulston assists when needed with Leukemia Cytogenetics activities. The Committee encourages membership by all SWOG investigators with an interest in clinical or translational science aspects of leukemia. The entire Committee membership meets twice each year in a one half-day Leukemia Committee retreat held simultaneously with the Southwest Oncology Group meeting. At this retreat, approximately half of the time is devoted to laboratory and pre-clinical studies of leukemia with an agenda developed by Cheryl L. Willman, while the other half of the meeting is devoted to the development and performance of clinical trials, an agenda which is overseen by Frederick R. Appelbaum. This meeting is open to all Leukemia Committee members.

Among the broad membership of the Leukemia Committee are a number of individuals who have been particularly active in the activities of the Leukemia Committee. These individuals form a voluntary working committee and are further subdivided into work groups devoted to specific diseases. Thus, there is a working
group devoted to AML (Chauncey, Erba, Sekeres, Lancet, Nand, Petersdorf, and Willman), ALL (Advani, Thomas, Forman, Kantarjian, Radich, Radvani, and Willman), CML (Drs. Druker and Radich), CLL (Drs. Stewart, Godwin and Kalycio), and MDS (Schiffer, List, Komrokji, and Willman). Each of these disease specific subgroups is charged with identifying important questions that might be addressed in clinical studies in their specific disease area. All members of these working groups join the leadership of the Leukemia Committee and the Leukemia Biology Subcommittee on a monthly conference call on the second Wednesday of each month at 12:00 noon eastern time. On these calls, the progress of current trials is reviewed and ideas developed by the working groups are discussed.

The following is a summary of the Southwest Oncology Group Leukemia Committee and the Leukemia Translational Medicine Subcommittee membership.

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### RELEVANT PAST, CURRENT AND FUTURE STUDIES

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*Registrations are through 12/30/2008

**Other Includes non-tx Intervention (symptom control), "Pilot", "Quality of Life", "Treatment (Prevention)" and "Treatment (Symptom)"

LEUKEMIA COMMITTEE
**Acute Promyelocytic Leukemia (APL)**

**C9710**  Phase III Randomized Study of Concurrent Tretinoin and Chemotherapy with or without Arsenic Trioxide (As₂O₃) (NSC #706363) as Initial Consolidation Therapy Followed by Maintenance Therapy with Intermittent Tretinoin Versus Intermittent Tretinoin Plus Mercaptopurine and Methotrexate for Patients with Untreated Acute Promyelocytic Leukemia (APL) (Activated: 7/15/99; Accrual Completed)

**Schema:** Patients with previously untreated acute promyelocytic leukemia and confirmed as molecularly positive for PML-RARα fusion transcripts in the SWOG Leukemia Reference Laboratory received standard induction using a combination of tretinoin, daunomycin and cytarabine. Patients were randomized to standard consolidation using tretinoin plus daunomycin or to first receive two cycles of arsenic trioxide followed by standard consolidation. Following completion of consolidation therapy, patients were randomized to maintenance with intermittent tretinoin alone or a combination of tretinoin plus 6-mercaptopurine and methotrexate.

**Rationale:** Previous studies, including the last American intergroup study (SWOG-9129, E2491), have established a role for tretinoin during induction and maintenance therapy of acute promyelocytic leukemia. Arsenic trioxide has high activity in patients with recurrent acute promyelocytic leukemia. This study, C9710, was designed to test the efficacy and determine the toxicities of two cycles of arsenic trioxide given as initial consolidation therapy. By giving arsenic trioxide early in the treatment course, effects on molecular markers of disease, particularly levels of molecular MRD, could be evaluated in addition to determining the impact of treatment on disease-free and overall survival. A European study using less intensive induction has suggested a benefit of adding 6-mercaptopurine and methotrexate to maintenance. Whether a similar benefit exists for patients treated more aggressively during consolidation is unknown but was also tested in this study.

**Objectives:** 1) To compare event-free survival and toxicities of two induction/consolidation therapies for patients with untreated acute promyelocytic leukemia: tretinoin, cytarabine and daunomycin with or without arsenic trioxide; 2) To evaluate the event-free survival and toxicities of maintenance therapy using tretinoin with or without the addition of mercaptopurine plus methotrexate; 3) In addition, the effects of these therapies on MRD and leukemia residual disease burden using standardized quantitative RT-PCR assays was studied.

**Statistical endpoints and results:** The planned accrual for this study was 506 adult patients. 518 adults and 64 children were entered (children were assigned to the non-arsenic arm). The overall CR rate for adults was 89% and did not differ by treatment arm; CR rate for children was also 89%. Event-free survival was 77% at 3 years on the arsenic arm compared with 59% at 3 years on the standard arm (P=0.0013). Overall survival was 86% at 3 years on the arsenic arm compared with 77% at 3 years on the standard arm (P=0.029). Event-free survival and overall survival for pediatric patients did not differ significantly from the adult patients without arsenic. Thus, the addition of two courses of arsenic trioxide consolidation following remission induction significantly improved event-free and overall survival in adults with acute promyelocytic leukemia.

In the correlative studies accompanying this trial, the association of pre-treatment WBC and platelet count, age, t(15;17)/PML-RARα transcript levels, and PML-RARα isoform type with disease free (DFS) and overall survival (OS) was studied in the first 180 patients accrued to the trial (22). PML-RARα transcripts were measured using real-time quantitative RT-PCR and expressed as a normalized quotient (NQ) of PML-RARα/GAPDH. Using a multivariate proportional hazards regression model, pre-treatment PML-RARα transcript levels and WBC count were independently associated with DFS; p = 0.0073 and p = 0.05. Pre-treatment WBC count was the only feature significantly associated with OS; p<0.0001. Patients with presenting WBC > 10K/µl had both shorter DFS and OS with hazard ratios of 2.3 and 5.5, respectively. Analyses of end-of-induction and post-consolidation quantitative MRD monitoring data are ongoing. In the prior APL intergroup study SWOG-9129, we detected mutations in the ligand binding domain of the RARα-region of PML-RARα that appear to confer therapeutic resistance in 33% of patients relapsing after ATRA treatment (23). Despite the use of more intensive therapy and the introduction of arsenic on C9710, the
frequency of these mutations do not appear to be reduced, occurring in 38% of patients who have relapsed to date (24). Among the mutations identified, 5 were novel (Leu224Pro, Lys238Glu, Ile273Phe, Arg276Gln x2, Gly289Glu x2). In relapsing patients, serial monitoring of post-consolidation samples did not detect the mutation until or just prior to clinical relapse (see Figure 1, plotting the quantitative increase in PML-RARα transcripts (red) with the detectable mutant clone (blue) in a relapsing patient). These studies suggest that proximate ATRA selection is not involved in the emergence of PML-RARα mutant subclones and the late emergence of these leukemic clones contributes to disease recurrence.

![Case 11](image)

**Figure 1. Quantitative Molecular Monitoring of Minimal Residual Disease in APL (C9710).** After decreasing to undetectable levels within 5 months of treatment (PML-RARα transcript levels in red), the leukemic clone re-emerged at approximately 20 months. Simultaneously, a new PML-RARα mutation, associated with therapeutic resistance, appeared and quantitatively increased (blue). This patient was determined to be in clinical/morphologic relapse at 42 months.

**S0521** A Randomized Trial of Maintenance Versus Observation for Patients with Previously Untreated Low and Intermediate Risk Acute Promyelocytic Leukemia (APL), phase III. *(Activated 6/1/07; Currently accruing)*

**Schema:** Patients with previously untreated acute promyelocytic leukemia of low or intermediate risk (white count ≤10,000/mm³) receive induction using a combination of tretinoin, daunomycin and cytarabine. Patients achieving complete remission receive consolidation using two cycles of arsenic trioxide followed by two cycles of tretinoin plus daunomycin. Those patients who are RT-PCR negative for the PML/RARα fusion gene product following consolidation therapy are randomized between observation versus one year of maintenance using tretinoin, methotrexate and 6-mercaptopurine.

**Rationale:** Using modern therapies, at least 95% of patients with low or intermediate risk acute promyelocytic leukemia (25) can be expected to enter complete remission, and the risk of relapse during the first year is less than 5%, as demonstrated by the recently completed North American Intergroup Study, **C9710**. Given these outstanding results, attention has shifted to how one might decrease toxicities of treatment without placing patients at undue risk for higher relapse rates. Recently, the Japanese Adult Leukemia Study Groups conducted a trial, APL 97, which randomized patients who were RT-PCR negative for the PML/RARα fusion gene product after consolidation to then receive maintenance versus observation (26). They have witnessed no difference in outcome between the groups, suggesting that one year of expensive and potentially toxic therapy might be avoided.
Objectives: 1) To compare disease-free survival among patients with previously untreated low and intermediate risk APL who are PCR-negative for PML-RARα after consolidation therapy and receive maintenance therapy versus patients who receive no maintenance therapy; 2) To assess toxicities of induction, consolidation and maintenance therapies; 3) To test whether gene expression profiles assessed prior to treatment are predictive of resistance to remission induction chemotherapy, correlate with detectable minimal residual disease post-consolidation, and predict relapse-free survival in patients who respond to induction chemotherapy; 4) To investigate in a preliminary manner the outcomes of patients who fail to achieve or maintain PCR-negativity after consolidation therapy, when treated with gemtuzumab ozogamicin. In addition we will estimate the proportions of maintenance and observation patients for whom quantitative RT-PCR monitoring identifies increasing disease burden, and to test whether such increasing burden is associated with increased risk of relapse (supported by the NCI Strategic Partnerships to Evaluate Cancer Gene Signatures Program (SPECS); NIH NCI CA U01CA114762; PI: C. Willman, Co-PI: J Radich).

Statistical endpoints: This study will continue accrual until a total of 400 patients have been randomized to maintenance versus observation. Assuming that 80% of patients will be randomized, this implies a total accrual of 500 patients onto study. The study is designed as a non-inferiority study, testing whether observation is, at worst, inferior to maintenance by a margin of 10% in 3-year disease-free survival. Based on accrual rates of the last North American Intergroup study, accrual should require four years to complete. The Cancer and Acute Leukemia Group B, the Eastern Cooperative Oncology Group and the National Cancer Institute of Canada are participating in this trial. As of December 12, 2008, 25 patients have been entered.

S0535 A Phase II Study of Tretinoin, Arsenic Trioxide and Gemtuzumab Ozogamicin in Previously Untreated High-Risk Acute Promyelocytic Leukemia. (Activated 11/15/07; currently accruing).

Schema: Patients with previously untreated high-risk acute promyelocytic leukemia (WBC >10,000/mm^3) receive induction therapy with a combination of gemtuzumab ozogamicin, tretinoin and arsenic trioxide. Patients achieving a complete response will receive consolidation with two cycles of arsenic trioxide, followed by two cycles of tretinoin plus daunomycin, followed by two cycles of gemtuzumab ozogamicin. Patients then receive one year of maintenance using tretinoin, methotrexate and mercaptopurine.

Rationale: Although there have been dramatic improvements in the therapy of acute promyelocytic leukemia, for patients presenting with white blood cell counts in excess of 10,000/mm^3, the risk of death during induction is approximately 20%, and in most studies at least 25% of patients who achieve a complete remission will recur with their disease. Results from the recently completed North American Intergroup trial C9710 are consistent with this expectation. The two most active single agents in the treatment of acute promyelocytic leukemia are tretinoin and arsenic trioxide, and encouraging results combining the two as induction therapy have been reported, albeit not in a study restricted to high risk patients. Recently, gemtuzumab ozogamicin has been shown to also have high activity in this disease, and accordingly Estey, et al, at MD Anderson have combined these three drugs as induction for high risk acute promyelocytic leukemia, achieving an 86% complete response rate, a figure superior to any they have achieved in the past (27 and personal communication). Thus, we are testing this novel induction strategy in an intergroup phase II trial to estimate its activity. We have maintained the same consolidation and maintenance used in C9710 but have added an additional cycle of gemtuzumab ozogamicin. Thus, comparison of S0535 patients to the high-risk patients on C9710 will aid in our interpretation of results.

Objectives: 1) To assess the event-free survival and death during the first six weeks in patients with previously untreated high-risk acute promyelocytic leukemia treated with a combined regimen of all trans retinoic acid (ATRA), arsenic trioxide, and gemtuzumab ozogamicin; 2) To estimate the frequency and severity of toxicities of this regimen in this group of patients; and 3) To investigate the molecular response rate utilizing this regimen in high-risk patients.
**Statistical endpoints:** Historical data suggest that high-risk patients have a 3-year probability of relapse-free survival of 60%. The proposed regimen would be of interest if it produces a true 3-year continuous complete remission (CCR) rate of at least 70% and 6-week mortality rate of 15% (alternative hypothesis) or less but not if the 3-year CCR rate was 50% or less and the 6-week mortality rate was 30% or more (null hypothesis). A total of 70 patients will be registered in two stages of accrual. In the first stage of accrual, 32 eligible patients will be accrued. If more than seven patients die within the first 6 weeks, then the study will be terminated early with the conclusion that the study does not warrant Phase III study. Otherwise an additional 38 eligible patients will be accrued. If, among the total of 70 eligible patients, at least 41 are alive and in CCR at 3 years and fewer than 17 die in the first 6 weeks, then Phase III study will be warranted. The power of this study is 0.89 under the alternative hypothesis above, and the critical level is 0.033 under the null hypothesis. The Cancer and Acute Leukemia Group B and the Eastern Cooperative Oncology Group have joined us in this study. As of December 12, 2008, 2 patients have been entered.

**Acute Myeloid Leukemia**

**S0106** A phase III Study of the Addition of Gemtuzumab Ozogamicin (Mylotarg®) During Induction Therapy versus Standard Induction Therapy with Daunomycin and Cytarabine followed by Consolidation and Subsequent Randomization to Post-Consolidation Therapy with Gemtuzumab Ozogamicin or No Additional Therapy for Patients Under Age 61 with Previously Untreated De Novo Acute Myeloid Leukemia (AML) (Activated: 5/15/04; Currently Accruing)

**Schema:** Patients under age 61 with previously untreated acute myeloid leukemia are randomized to induction therapy using either standard daunomycin and cytarabine or the same combination with gemtuzumab ozogamicin added on Day 4. Patients achieving complete remission on both arms receive three cycles of high-dose cytarabine as consolidation therapy. Following completion of consolidation, patients are re-randomized to gemtuzumab (receiving an additional three doses of the drug) versus observation.

**Rationale:** Standard induction therapy for adult acute myeloid leukemia remains 3 days of an anthracycline plus 7 days of conventional dose cytarabine, which in cooperative group settings results in complete response rates of approximately 70%. Previous attempts to improve complete response rates by adding, for example, etoposide or high-dose cytarabine to the induction regimen, have not been successful. Gemtuzumab ozogamicin is a humanized anti-CD33 monoclonal antibody linked to a potent anti-tumor antibiotic, calicheamicin. As a single agent, gemtuzumab ozogamicin induces complete responses in approximately 30% of patients with acute myeloid leukemia in first relapse (28). Two phase II trials have explored the use of gemtuzumab ozogamicin in combination with conventional chemotherapy for initial induction therapy. A regimen of daunomycin 45 mg/m^2^ Days 1-3, cytarabine 100 mg/m^2^ by continuous infusion Days 1-7 and gemtuzumab ozogamicin 6 mg/m^2^ on Day 4, was found to have an acceptable toxicity profile in a phase I study and subsequently was tested as de novo therapy in adults age 20-60. Among the first 21 patients studied, 18 (86%) achieved a complete response (29). Time to hematopoietic recovery appeared similar to conventional induction regimens. Grade 3 or 4 liver function test abnormalities were not seen nor was there any case of veno-occlusive disease observed. Similar encouraging results have been obtained by the British Medical Research Council, who reported an 87% complete response rate among 62 patients, using gemtuzumab ozogamicin at a dose of 3mg/m^2^ on day 1 of induction (30). Based on their encouraging results, the British Medical Research Council performed a prospective randomized trial of standard induction therapy with or without the addition of gemtuzumab ozogamicin, the MRC AML15 Trial. This trial was initiated shortly before S0106 was opened and has since achieved its accrual goal. The preliminary results, presented in abstract form at the American Society of Hematology, involved 1113 randomized patients (31). There was no difference in complete response rates (84% with gemtuzumab and 86% without). However, the addition of gemtuzumab significantly lengthened disease-free survival (P=0.007) and significantly reduced the risk of relapse (P=0.002). There was no appreciable difference in overall toxicities with the addition of gemtuzumab ozogamicin, and in the 107 patients who proceeded to hematopoietic cell transplantation because of very high risk leukemia, there was no increase in the incidence of liver disease among those induced with the addition of
gemtuzumab. On October 13, 2008, the MRC shared an update of results of their AML15 trial with the SWOG Leukemia committee. The disease-free survival advantage with the addition of gemtuzumab ozogamicin continues, but is most noticeable in intermediate and favorable risk patients, where the addition of gemtuzumab is associated with an improvement in overall survival (P=0.01), but there appears to be no advantage with the addition of gemtuzumab in patients with unfavorable risk cytogenetics (Burnett, personal communication 10-13-08).

**Objectives:** 1) To compare disease-free survival of patients under age 61 with previously untreated, de novo, non-M3 acute myeloid leukemia who receive gemtuzumab ozogamicin as post-consolidation therapy chemotherapy versus patients who receive no post-consolidation therapy; 2) To compare complete remission rates with gemtuzumab ozogamicin plus chemotherapy versus chemotherapy alone; 3) To estimate the frequency and severity of toxicities associated with the addition of gemtuzumab ozogamicin; and 4) To evaluate the prognostic significance of CD33 expression on the response rate, and of cytogenetics, FLT3 and NPM1 mutations prior to therapy, and of flow cytometric measures of minimal residual disease in remission specimens collected before and after consolidation therapy. In addition we will use gene expression profiling to develop molecular classifiers predictive of response, focusing on classifiers that are predictive of failure on first line therapy that can be used to target patients at initial diagnosis to more experimental regimens or transplantation in future clinical trials (supported by the NCI SPECS Program; NIH NCI CA U01CA114762).

**Statistical endpoints and results:** The planned accrual on this study is 684 patients. This will provide a 90% power to detect an increase in complete response rate of 11% (e.g., 70% to 81%) and an 90% power to detect a hazard ratio of 1.5 in disease-free survival (e.g. an increase in one-year DFS from 50% to 63% with unfavorable cytogenetics and from 75% to 83% with favorable/intermediate cytogenetics). The National Institute of Canada and the Leukemia Group of Middle Sweden have joined this study. As of December 12, 2008, 488 patients have been randomized and the accrual rate is approximately 17 per month.

The correlative studies integrated into the design of this trial, testing the ability of various methodologies (flow cytometric MRD, FLT3 and NMP1 gene mutations, and gene expression classifiers) to prospectively identify patients at risk for treatment failure, are ongoing. We and others have determined that AML patients whose blasts contain NPM1, but lack FT3 internal tandem duplication (ITD) mutations have the best overall survival on standard regimens (Figure 2); even in elderly AML patients where survival is traditionally very low (10). The frequency of these mutations and their prognostic significance in younger AML patients will be determined in S0106.
We have developed highly sophisticated and sensitive multi-parametric, 9-color flow cytometric assays to detect rare leukemic cells (at a sensitivity of 0.0001) and quantitate levels of residual disease (MRD) at the end of induction in patients registered S0106 (Figures 3A and B). The instrument platform, reagents, and methods have been fully validated in over 25,000 assays. To date, 350 samples from S0106 patients have been assessed by these methods and analyses are in progress.

Fig. 3A: Flow Cytometric MRD
9-Color Panel Design

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Fig. 3B: 9 Color Flow Cytometric MRD

Figure 3 A and 3B. Multi-Parameter, 9-Color Flow Cytometric Measurement of Minimal Residual Disease in AML (S0106). Fig. 3A. Each row in this table provides the 9 antibodies directed to cell surface antigens and their direct fluorochrome conjugates (such as CD33-PE or CD117-PE55) that in combination are used to distinguish AML blasts from myelomonocytic precursors, normal stem cells, and T cells in bone marrow and peripheral blood. Fig 3B. Using these combinations, residual AML cells (purple) are easily detected and quantified relative to normal marrow cells (green, grey, and red).
At our current rate of accrual, S0106 is projected to complete accrual in approximately 15 months. The current front line trial for adults age <60 at ECOG will also complete accrual at about the same time. CALGB is currently participating in a randomized trial for FLT3+ patients, but has no randomized phase III trial for the remainder. This provides an opportunity for all three cooperative groups, along with the NCIC, to coordinate planning for the next upfront study of AML in patients age <60. Accordingly, the Leukemia Committee chairs of CALGB, ECOG, SWOG and NCIC, along with representatives of their translational medicine subcommittees, the BMT/CTN and CTEP, met in Chicago on November 3, 2008 to discuss future plans. We are well on our way to developing the next trial as a North American Intergroup study. The current concept would involve risk-adapted treatment asking the following questions: (1) In patients with CBF AML, does inhibition of cKIT using a potent tyrosine kinase inhibitor prolong disease-free survival; (2) In patients with FLT3 mutations, does the use of a FLT3 inhibitor improve outcome; (3) In patients with unfavorable cytogenetics, what proportion can rapidly be brought to allogeneic transplant using related, unrelated or cord blood donors, and what is the outcome of such transplants; and (4) In patients with intermediate risk disease, does maintenance with a demethylating agent prolong disease-free and overall survival.

S0112 A Phase II Study of Daunomycin and Ara-C, Both Given by Continuous IV Infusion for Previously Untreated Non-M3 Acute Myeloid Leukemia (AML) in Patients of Age 56 or Older (Activated: 8/1/01; Accrual Completed)

Schema: Patients age 56 or older with previously untreated acute myeloid leukemia received a regimen of daunomycin 45 mg/m$^2$/day for 3 days by continuous infusion and cytarabine 200 mg/m$^2$/day for 7 days by continuous infusion. Patients achieving a complete response received two cycles of consolidation using the same drugs and doses, but for 2 and 5 days, respectively.

Rationale: In a prior study, SWOG-9031, we found a very high incidence of p-glycoprotein (MDR1; multidrug resistance gene 1) expression and functional drug efflux in leukemic blasts in older patients with acute myeloid leukemia (71%) and also noted that this phenotype was highly associated with failure to achieve a complete remission (p=0.0041) (6,32-33). We further found in SWOG-9126 that the addition of cyclosporine, a competitive inhibitor of multidrug resistance mediated efflux, to a regimen of continuous infusion daunomycin and high dose cytarabine, led to improved disease-free and overall survival in younger patients with high-risk (recurrent or secondary) AML (34). In SWOG-9126, there was no increase in serious toxicities or in treatment-related mortality with the addition of cyclosporine, perhaps because the daunomycin was given by continuous infusion, since prior studies have suggested that toxicities to daunomycin are particularly associated with high peak levels of drug exposure. We wished to test this approach as up-front therapy for patients over age 55 with newly diagnosed acute myeloid leukemia. However, there are almost no data available about the efficacy and toxicity of standard-dose daunomycin and cytarabine given by continuous infusion alone in this patient group. Although we do not expect that in the absence of cyclosporine giving daunomycin by continuous infusion would lead to dramatically different results than when given by bolus infusion, we needed to test this regimen since it would constitute the appropriate control arm for a subsequent randomized trial testing the addition of cyclosporine.

Objective: 1) To test whether an induction regimen of daunomycin and cytarabine, both given by continuous intravenous infusion, is sufficiently effective for previously untreated patients age 55 or over with acute myeloid leukemia to warrant further investigation in phase III trials; 2) To estimate the frequency and severity of toxicities with this regimen; and 3) To assess in a preliminary manner the frequency and prognostic effects of functional and phenotypic P-glycoprotein expression, cytogenetics, and pharmacokinetic characteristics in these patients.
Statistical endpoints and results: This regimen would warrant further testing if the true complete response rate were greater than 50% and would not warrant testing if the rate were less than 30%. The study was designed in two stages. In the first stage, 30 eligible patients were registered and if 9 complete responses were seen, we would complete the planned accrual of 55 patients and the results would be considered favorable if 23 or more complete responses. This design had 91% power and 4.1% critical level if the true complete response rate is 50% or 30%, respectively. A total of 60 eligible and evaluable patients were registered to this trial, and sufficient activity and safety were seen to warrant further testing. Specifically, 21 complete responses were documented in the first 55 eligible and evaluable patients; however, an additional 4 patients who had insufficient material on marrow aspiration to document remission but were registered for post remission therapy and survived between 301 and 1182 days after study entry are considered likely complete responders. Among all 60 eligible and evaluable patients, the estimated complete response rate was 40% (95% confidence interval 28-53%), and 47% (34-60% with the likely responders included). Relapse-free and overall survival at 24 months were 22 (95% confidence interval 5-39%) and 15% (6-24%), respectively.

**S0301** A Phase II Study of Induction with Daunorubicin, Cytarabine, and Cyclosporine All by Continuous IV Infusion for Previously Untreated Non-M3 Acute Myeloid Leukemia (AML) in Patients Age 56 or Older (Activated 12/2/03; Accrual Completed)

Schema: Patients with previously untreated acute myeloid leukemia, age 56 or older, received daunomycin 45 mg/m²/day for 3 days, cyclosporine 6 mg/m²/day for 3 days, and cytarabine 200 mg/m²/day for 7 days, all by continuous intravenous infusion. Patients achieving a complete response received the same drugs at the same doses but with the daunomycin and cyclosporine shortened to two days, and the cytarabine to 5.

Rationale: In a prior study, SWOG-9031, we found a very high incidence of p-glycoprotein expression and functional drug efflux in leukemic blasts from older patients with acute myeloid leukemia (71%) and also noted that this phenotype was highly associated with failure to achieve a complete remission (p=0.0041) (6,32-33). We further found in SWOG-9126 that the addition of cyclosporine, a competitive inhibitor of p-glycoprotein mediated drug efflux, to a regimen of daunomycin by continuous infusion and high-dose cytarabine led to an improved outcome in younger patients with high risk disease (34). We also saw no increase in life-threatening or total toxicities with the addition of cyclosporine, perhaps because we gave the anthracycline by continuous infusion. In S0112 we tested whether a regimen of daunomycin 45 mg/m²/day for 3 days with cytarabine 200 mg/m²/day for 7 days, both by continuous intravenous infusion, was sufficiently safe and effective to be studied in a subsequent phase III trial. The results obtained were consistent with that conclusion. Thus, following the completion of S0112, we initiated S0301, another phase II study of the same chemotherapy regimen but with the addition of cyclosporine.

Objectives: 1) To test whether a regimen with daunomycin, cytarabine, and cyclosporine, all given by continuous intravenous infusion, is sufficiently safe and effective for patients age 56 and older with previously untreated non-M3 acute myeloid leukemia to warrant phase III investigation; 2) To estimate the frequency and severity of toxicities in this group of patients; 3) To investigate in a preliminary manner the frequency and prognostic importance of p-glycoprotein expression, functional drug efflux, and cytogenetics in this group of patients, and the pharmacokinetics of daunomycin in this patient population.

Statistical endpoints and results: This study differed slightly from S0112, since it included simultaneous assessment of both response and toxicity in its primary test criterion. Initially, 25 patients were treated. Based on the results in these 25 patients, the regimen was deemed sufficiently safe and effective to complete the full accrual of 50 patients. Among these 50 patients, 22 achieved a CR (44%, 95% CI 30-59%). Three others had insufficient material or cellularity but recovered normal counts, if these are included as responders the CR rate was 50% (36-64%). Relapse-free and overall survival at 24 months were 38% (17-60%) and 24% (10-37%), respectively. Although further analysis is ongoing, based on these preliminary results, this regimen does not appear sufficiently encouraging as induction therapy to warrant the conduct of a randomized trial. However, the possible prolongation of relapse-free and overall survival seen in S0301 compared to S0112 suggests that
the addition of cyclosporin to continuous infusion anthracycline may be worth further study as a method of consolidation. Correlation of response with MDR1/p-glycoprotein expression and functional drug efflux, assays that were first developed in our SWOG Leukemia Reference Laboratory (32-33) have been completed and the results are being correlated with response.

**S0432** Phase II Studies of Two Different Schedules and Two Different Doses of the Farnesyl Transferase Inhibitor R115777 (Tipifarnib, Zarnestra®) (NSC-702818) for Previously Untreated Acute Myeloid Leukemia (AML) in Patients of Age 70 or Older. **(Activated 9/15/04; Accrual Completed)**

**Schema:** Patients age 70 or older with newly diagnosed acute myeloid leukemia were randomized to treatment with R115777 using one of four regimens: Arm 1 – 600 mg bid x 21 days q 28 days; Arm 2 – 600 mg bid x 7 days every other week q 28 days; Arm 3 – 300 mg bid x 21 days q 28 days; Arm 4 – 300 mg bid x 7 days every other week q 28 days.

**Rationale:** R115777 is a farnesyl transferase inhibitor that has been studied in acute myeloid leukemia and shown to have activity. In a phase I trial at the Universities of Rochester and Maryland, R115777 resulted in a 30% response rate in patients with relapsed, refractory or secondary acute leukemia (35). The optimal dose and schedule of R115777 remains uncertain; doses in excess of 600 mg bid were not easily tolerated in the phase I trial and inhibition of farnesylation was seen at 300 mg bid. Whether continuous dosing for 3 weeks is necessary is likewise uncertain and may be associated with more toxicity than dosing on a week on, week off basis. Accordingly, we conducted a four armed phase II trial.

**Objectives:** 1) To test whether any of the four regimens of R115777 is sufficiently effective therapy for previously untreated non-M3 acute myeloid leukemia in patients of age 70 or older to warrant phase III investigation; 2) To estimate the frequency and severity of toxicities of these four regimens in this group of patients; 3) To investigate in a preliminary manner the relationship of cytogenetics with response to R115777 (tipifarnib) and assess whether karyotype represents a potential prognostic factor among older AML patients who are not candidates for chemotherapy and are treated with R115777; and 4) To investigate in a preliminary manner the effect of R115777 on the inhibition of RAS and downstream targets in this population. In addition we will investigate gene expression profiles predictive of response to this agent.

**Statistical endpoints and results:** The primary measure of effectiveness was the total response rate, defined as the proportion of patients who achieved CR or PR. Any of the regimens would be considered to be of interest if it resulted in a response rate of 30% or greater but not if the response rate were 10% or less. The study was designed as a two-step procedure with 15 patients initially treated in each arm. Had there been no responses, the arm would have been closed. Otherwise an additional 59 patients would be accrued for a total of 74 patients per arm. To warrant further investigation, 15 or more responses would be required. All four treatment arms proceeded to the second step, and a total of 348 patients were accrued in 18 months. The complete response rates for arms 1, 2, 3 and 4 were 8%, 4% 11% and 1% respectively, and the overall response rates (CR, CRi, and PR) were 14%, 11%, 20% and 6% (3). Median survivals for the four arms were 104 days, 111 days, 120 days and 106 days. Survivals at one year for the four arms were 14%, 25%, 28% and 14%. Thus, although tipifarnib has activity in the treatment of this disease, none of the dose-schedules was sufficiently active to warrant further investigation as a single agent in this population of patients. However, there may be specific subsets of patients who could be identified who might benefit from this agent, and active combinations may be developed. Among the four dose schedules, arm 3 (300 mg bid x 21 days q 28 days) appeared to be the most active.

**S0605** A phase II Study of Lenalidomide (Revlimid®) (NSC-703813) for Previously Untreated Non-M3, Deletion 5q Acute Myeloid Leukemia (AML) in Patients Age 60 or Older Who Decline Remission Induction Chemotherapy. **(Activated 6/15/06; Currently accruing)**
Schema: Patients receive lenalidomide as a single daily agent for a 28-day course of therapy, at a dose of 50mg po/day. Patients are assessed for response at day 35, and if there is improvement or lack of progression, patients receive subsequent cycles of therapy.

Rationale: Older patients with acute myeloid leukemia with 5q- have a very poor prognosis; in the last Southwest Oncology Group Study, complete responses were seen in 12 of 44 patients (27%), and the median duration of the response was less than 6 months. Lenalidomide has been extensively studied in patients with myelodysplasia, and in patients with lower risk transfusion-dependent myelodysplasia with 5q31.1 deletion, a 75% response rate was seen including a 44% complete cytogenetic response (36). Among 8 patients with 5q31.1 deletion and complex karyotypes, 6 experienced a cytogenetic response including 4 complete responses. Whether the surprisingly high activity of lenalidomide seen in myelodysplasia with 5q- will occur in acute myeloid leukemia with a similar genetic background is uncertain, but worthy of testing.

Objectives: 1) To test whether lenalidomide is sufficiently effective therapy for previously untreated acute myeloid leukemia in patients age 60 or older with del5q to warrant phase III investigation; 2) To investigate the frequency and severity of toxicities with this regimen in this group of patients; 3) To investigate in a preliminary manner the effect of cytogenetic abnormalities in addition to del 5q on response of these patients to lenalidomide; and 4) To estimate the total (complete plus partial) response rate and the cytogenetic response rate in this group of patients.

Statistical endpoints: This regimen would be considered of interest if the true response rate were at least 20% and not of interest if the true response rate were 5% or less. Initially 20 patients were to be entered and if none achieved CR or CRi, the study would be closed, otherwise accrual would continue to 35 patients. Sufficient activity was observed in the first stage and accrual to the second stage is ongoing. A total of 31 patients have so far been accrued.

S0703 A Phase II Trial of Azacitidine (NSC-102816) plus Gemtuzumab Ozogamicin As Induction and Post-remission Therapy in Patients of Age 60 or Older with Previously Untreated Non-M3 Acute Myeloid Leukemia

Schema: Patients age 60 or older with previously untreated non-M3 acute myeloid leukemia will be treated with azacitidine 75 mg/m² subcutaneously days 1-7 and gemtuzumab ozogamicin 3 mg/m² intravenously on day 8. Patients presenting with WBC over 10,000/mm³ will be treated with hydroxyurea 1500 mg orally twice daily to reduce counts prior to starting the azacitidine. A second induction course will be given to patients with greater than 5% blasts on a day 14 marrow exam. Patients achieving a CR or CRi will receive one consolidation course identical to induction and then be placed on azacitidine maintenance.

Rationale: Previous studies from our group, similar to those of others, found that CR rates fall dramatically as patients age, dropping from 70% in patients younger than age 56 to 46% in patients age 56-65, 39% in patients age 66-75 and 26% in those over age 75 (6). Median survivals likewise fall from 18.8 months in younger patients, to 9, 6.9 and 3.9 months in the older age groups. Reasons for these changes include both inherent drug resistance and a lower tolerance for the toxicities of chemotherapy in older individuals (6,32-33). Both azacitidine and gemtuzumab ozogamicin have activity as single agents in AML. In limited experience, azacitidine as a single agent results in CR or CRi in 10-20% of patients. In patients with AML in first relapse, gemtuzumab ozogamicin as a single agent results in CR in 15% and CRi in an additional 10-15%. Further, in vitro studies document that exposure of leukemic blasts to azacitidine increases CD33 expression and sensitizes AML blasts to killing by gemtuzumab ozogamicin. In addition to the increased CD33 expression, several other mechanisms have been proposed to explain this increased killing. Ball’s group have demonstrated that exposure to 5-azacytidine restores SHP-1 expression which, in turn sensitizes AML blasts to killing with anti-CD33 antibodies alone or with gemuzumab (37). Efferth et al. have demonstrated that 5-azacytidine reduces expression of MDR1, which can efflux calechiamicin (38). Based, in part, on these observations, SWOG investigators at Loyola University initiated a trial using the exact regimen to be tested in S0703 in older patients with previously untreated AML. The results on the first 20 patients treated are
promising (39). Among these patients, median age 77, there were no treatment related deaths and 75% achieved a CR. Most required two cycles of induction therapy to achieve remission. We therefore are testing this regimen in two groups of patients – those considered fit for chemotherapy where previous CR rates have been in the 40-50% range, and those considered unfit for chemotherapy.

**Objectives:** 1) To test whether outcomes of patients of age 60 or older with previously untreated non-M3 acute myeloid leukemia treated with azacitidine plus gemtuzumab ozogamicin are sufficient to warrant phase III investigation. This will be tested independently in two groups of patients: (1) good risk patients, defined as those of age 60-69 years OR with Zubrod performance status 0-1, and (2) poor risk patients, defined as those who are at least 70 years old AND have Zubrod performance status 2-3. 2) To estimate the frequency and severity of toxicities of this regimen in the good and poor risk groups of patients. 3) To investigate in a preliminary manner the disease-free survival of patients who achieve complete remission and receive post-remission therapy on this study. 4) To investigate in a preliminary manner the cytogenetic response rates of patients treated with this regimen. 5) To investigate in a preliminary manner the effects of cytogenetic abnormalities, gene promoter and global methylation changes at pre-treatment and in response to therapy, and P-Glycoprotein/MDR expression and functional drug efflux on overall survival and response to azacitidine plus gemtuzumab ozogamicin therapy. We will also investigate the prognostic significance of FLT3 and NPM1 mutations in these patients.

**Statistical Endpoints:** The primary objective of this study is to test whether the induction regimen incorporating azacitidine and gemtuzumab ozogamicin is sufficiently safe and effective among older patients with previously untreated AML to warrant phase III study. This objective will be met by analyzing the probabilities of achieving CR or CRp and of surviving more than 30 days after study registration. Due to the differences in expected outcomes between the two risk groups, the regimen will be investigated independently in the two risk groups as described below. Each of the risk groups will accrue independently which means that one group may be closed upon reaching its accrual goal, while the other group remains open to accrual.

**Good Risk Group:**
If the CR+CRp rate is 35% or less OR the 30-day survival rate is 75% or less, then phase III study would not be warranted for good risk patients. The test criterion is based on both outcomes, with the null hypothesis as defined above and the alternative hypothesis that the CR+CRp rate exceeds 35% AND the 30-day survival rate exceeds 75%. Initially 30 patients will be accrued. If 12 or more achieve CR or CRp AND 23 or more survive 30 days, then a total of 73 patients will be enrolled.

**Poor Risk Group:**
The regimen would not warrant phase III study if its true CR+CRp rate is 10% or less OR its true survival rate at day 30 is 50% or less. In a two-stage design similar to that for the Good Risk patients, initially 15 patients will be accrued. If 2 or more achieve CR or CRp AND 8 or more survive 30 days, then a total of 66 patients will be enrolled.

**S0804** A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myeloid Leukemia (AML)

**Schema:** Adults with relapsed AML, defined as those who achieved a complete response of at least 90 days' duration with their last regimen but who have since relapsed, will be treated with high dose pravastatin (1280 mg/day orally days 1-8) followed by idarubicin 12 mg/m2 intravenously days 4-6, and cytarabine 1.5 g/m2/day by continuous infusion days 4-7. Patients achieving a complete response will receive two cycles of consolidation similar to the induction regimen except that the idarubicin and cytarabine are given only on days 4 and 5, and the pravastatin is given only on days 1-6.

**Rationale:** Little headway has been made in developing improved therapies for recurrent AML. Laboratory studies have found that cholesterol homeostasis is abnormal in AML cells, with cholesterol synthesis and LDL
processing being hyperactive compared with normal myeloid cells of similar differentiation status. Further, we have determined that inhibiting cholesterol synthesis markedly sensitizes AML blasts to cytotoxic therapy without having a similar effect on normal myeloid progenitors (8-9). These findings were the scientific rationale for a phase I-II trial conducted by investigators at two SWOG institutions (MD Anderson and the UW/FHCRC) (40). This trial found that high doses of pravastatin (1280 mg orally per day) could be safely combined with idarubicin and high-dose cytarabine. Further, the CR and CRp rates were higher than predicted based on historical controls for similar patients treated at these institutions, suggesting that a phase II evaluation of this approach is warranted.

**Objectives:** 1) To test whether the complete remission (CR) rate (including CR with incomplete recovery [CRi]) in patients with relapsed acute myeloid leukemia (AML) treated with a combination of chemotherapy and pravastatin is sufficiently high to warrant further investigation. The regimen would be of no further interest if it yields a true CR rate of 30%, and would be of interest if it yields a true CR rate of 50%. Fifty eligible patients will be accrued in a single step. If 21 or more patients achieve CR or CRi then the regimen will be considered sufficiently effective to warrant further investigation, assuming toxicity findings and other pertinent results are favorable. This design has critical level 4.8% if the true CR rate is 30%, and 90% power if the true CR rate is 50%. With 50 patients in the study, the probability of any particular toxicity of the induction regimen can be estimated to within at most ±14% (95% confidence interval). Any toxicity having a true occurrence rate of 5% or more is very likely to be observed in at least one patient (probability ≥ 92%). Based on SWOG-9216 and S0117, the expected accrual rate is 2 patients per month. Therefore, accrual to this study is estimated to be complete in approximately 25 months after study activation.

**Statistical Endpoints:** The primary objective of this study is to test whether the CR rate (CR+CRi) among adult patients with relapsed AML treated with this regimen is sufficient to warrant further investigation. The regimen would be of no further interest if it yields a true CR rate of 30%, and would be of interest if it yields a true CR rate of 50%. Fifty eligible patients will be accrued in a single step. If 21 or more patients achieve CR or CRi then the regimen will be considered sufficiently effective to warrant further investigation, assuming toxicity findings and other pertinent results are favorable. This design has critical level 4.8% if the true CR rate is 30%, and 90% power if the true CR rate is 50%. With 50 patients in the study, the probability of any particular toxicity of the induction regimen can be estimated to within at most ±14% (95% confidence interval). Any toxicity having a true occurrence rate of 5% or more is very likely to be observed in at least one patient (probability ≥ 92%). Based on SWOG-9216 and S0117, the expected accrual rate is 2 patients per month. Therefore, accrual to this study is estimated to be complete in approximately 25 months after study activation.

**Additional Translational Medicine Studies in AML**

In addition to the correlative science and translational medicine studies described above in the context of various completed and active SWOG AML trials, we completed a number of laboratory and correlative science studies in the past funding period that have provided new insights into leukemogenesis or therapeutic responsiveness and resistance. Many of these studies have provided the scientific rationale for active or newly proposed clinical trials and correlative studies.

- **AML in the Elderly:** We defined the unique biologic and genetic features of this highly resistant form of disease, how the nature of AML changes with age, and the powerful interaction of age and performance status on the ability of patients to tolerate initial induction chemotherapy (6).

- **The Biologic and Clinical Significance of Multidrug Resistance Gene (MDR; P-glycoprotein) Expression and Functional Drug Efflux in AML.** As discussed in prior sections, the SWOG Translational Medicine Subcommittee’s initial discovery that functional MDR was a highly significant predictor of treatment failure in AML provided the scientific basis for numerous publications and the rationale for the design of a series of prior and recently completed SWOG trials (S9032, S9126, S9333, S9617, S0112, S0301) and for related trials in other Cooperative Groups in the U.S. and Europe.

- **Gene Expression Profiling in AML.** We discovered distinct gene expression profiles, novel biologic clusters, and potential distinct pathways for targeting in AML in the elderly (10,41). To determine if gene expression profiling could improve risk classification and outcome prediction in older AML patients, expression profiles were obtained in pre-treatment leukemic samples from 170 patients whose median age was 65 years. Unsupervised clustering methods were used to classify patients into six cluster groups (designated A-F, Figure 4) that varied significantly in rates of resistant disease (RD, P<.0001), complete remission (CR, P=.023), and disease free survival (DFS, P=.023). Cluster A (n=24), dominated by NPM1 mutations (78%), normal karyotypes (75%), and genes associated with
signaling and apoptosis, had the best DFS (27%) and overall survival (OS, 25% at 5 years). Patients in clusters B (n=22) and C (n=31) had the worst OS (5% and 6%, respectively), cluster B was distinguished by the highest rate of RD (77%) and multidrug resistant gene expression (ABCG2, MDR1). Cluster D was characterized by a “proliferative” gene signature with the highest proportion of detectable cytogenetic abnormalities (76%; including 83% of all favorable and 34% of unfavorable karyotypes). These gene expression signatures provide insights into novel groups of AML not predicted by traditional studies that impact prognosis and potential therapy.

- **Quantitative Monitoring of MRD in APL.** SWOG Translational Medicine investigators initiated the intergroup laboratory consortium that developed and standardized automated quantitative PCR assays for MRD detection in APL and defined thresholds predictive for remission vs. relapse that have been incorporated into the series of prior and current intergroup APL studies (S0129, C9710, S0521, S0535). (42-44).

- **Clinical Significance of Genetic Polymorphisms.** SWOG Translational Medicine Investigators collaborating with Dr. Christine Ambrosone defined the association of genetic polymorphisms in GSST1, GSTA1 and DNA repair genes with treatment outcomes and toxicities. Patients with XPD Gln751C/Asp312G (‘D’) haplotype were more likely to have complete responses (OR = 3.06; 95% CI, 1.44-6.70) and less likely to have resistant disease (OR = 0.32; 95%CI, 0.14-0.72) than patients with other haplotypes. ERCC1 polymorphisms were significantly associated with lung (P = .037) and metabolic (P = .041) toxicities (45-46).

- **Determined the Clinical Relevance of Novel Genetic Mutations in AML.** We reported on the clinical and biologic significance of novel FLT3 mutations as well as the length of the FLT3 ITD mutation (11-12); the cloning of a novel transcript in AML (AML1-FOG in AML and MDS; 47); the clinical spectrum of core binding factor leukemias (4); and the poor outcomes and distinct features of AML cases with t(6;9) (5). Of particular interest was the discovery of a novel C-terminal splice variant of the t(8;21) / AML1-ETO transcript (AE9a) that is sufficient to promote AML in animal models (unlike the full length transcript) and which may be associated with a more aggressive form of leukemia in humans. Recent studies have determined that CD45, a negative regulator of cytokine/growth factor receptor signaling is downregulated and JAK/STAT signaling is greatly enhanced in t(8;21) cells. Interestingly, these cells are more susceptible to JAK2 inhibitors than wild type cells. Our results indicate that AE9a enhances JAK/STAT signaling by directly modulating regulators of this signaling pathway, which provides a potential novel approach to treating t(8;21) AML. (48).

- **Cholesterol Metabolism in AML.** Our studies demonstrating how cholesterol metabolism is perturbed in AML and cholesterol-modulating agents such as pravastatin kill AML cells provided the scientific rationale for early phase clinical trials conducted at the Group institutions FHCRC and M.D. Anderson, leading to the newly proposed SWOG phase II study S0804 (8-9,49).
Acute Lymphoblastic Leukemia

C10403  An Intergroup Phase II Clinical Trial for Adolescents and Young Adults with Untreated Acute Lymphoblastic Leukemia (ALL). (Activated 1/15/08; Currently accruing)

Schema: Adolescents and young adults up to age 31 with newly diagnosed acute lymphoblastic leukemia were initially to be treated on one arm (DC) of the current Children’s Oncology Group Study AALL0232. Therapy included induction with daunomycin, vincristine, dexamethasone, pegylated L-asparaginase and intrathecal cytarabine and methotrexate; consolidation included cyclophosphamide, cytarabine, 6-mercaptopurine, dexamethasone and pegylated L-asparaginase; interim maintenance contained vincristine, methotrexate and pegylated L-asparaginase; delayed intensification included daunomycin, vincristine, dexamethasone pegylated L-asparaginase, cyclophosphamide, cytarabine and 6-thioguanine, and continued maintenance was the same as interim maintenance. Shortly after the study was opened, Children’s Oncology Group alerted us of an increased incidence of skeletal events following induction. Accordingly, both the Children’s Group and the CALGB-SWOG trial substituted prednisone for dexamethasone during induction.

Rationale: Several retrospective studies have highlighted the fact that adolescent patients (ages 16-21) with ALL had improved outcomes when enrolled and treated on pediatric cooperative group studies rather than when enrolled and treated on adult cooperative group protocols (50). The differences were sizable, with outcomes, for example, of 64% 6 year event-free survival on Children’s Cancer Study Group trials compared to 39% on Cancer and Acute Leukemia Group B studies. The reasons for these differences are not known, but could relate to the actual treatment protocols, the behavior of the physicians, or differences in the patient population. We will attempt to better understand this difference by treating adolescents and young adults at adult institutions using exactly the same treatment regimen being used by the Children’s Oncology Group (AALL0232). In addition, we will collect information about the manner in which drugs are administered (dose and schedule) as well as biologic, demographic, and socio-economic data about the patients in order to allow for a comparison with results of the Children’s Oncology Group Study.

Objectives: 1) To improve the outcome of adolescents and young adults with acute lymphoblastic leukemia; 2) To compare the outcome of patients treated on this CALGB/SWOG study with the outcomes seen using the same regimen on COG AALL0232; 3) To evaluate the toxicities and efficacy of this regimen when applied to young adults up to age 30; 4) To evaluate the adherence of adult hematologist/oncologists to a “pediatric” acute lymphoblastic leukemia treatment protocol; 5) To describe the outcome of adolescents and young adults treated on this study according to pre-treatment characteristics and biologic features, such as age, gender, white cell count, blood chemistry, cytogenetics, molecular genetic characteristics, gene expression profiles, treatment variables, and socio-economic status.

Statistical endpoints: Up to 300 untreated ALL patients between ages 16 and 30 will be enrolled onto this phase II trial over a 5 year period. The main hypothesis is that, using event-free survival as a primary endpoint of this trial, we can detect an improved median event-free survival of 31 months versus our previous experience of a median event-free survival of 24 months. The study will have a power of 0.85 to detect such a difference.

S0333  A Phase II Study of Double Induction Chemotherapy for Newly Diagnosed Non-L3 Adult Acute Lymphoblastic Leukemia with Investigation of Minimal Residual Disease and Risk of Relapse Following Maintenance Chemotherapy (Activated 4/15/05: currently accruing)

Schema: Patients with newly diagnosed non-L3 acute lymphoblastic leukemia are treated with an initial standard induction regimen consisting of daunomycin, vincristine, prednisone and pegylated L-asparaginase. All patients, including those who achieve a complete remission and those who don’t, then receive a second
induction cycle of high dose cytarabine plus mitoxantrone. Patients in complete remission after the second induction then receive standard consolidation with cyclophosphamide, cytarabine, 6-mercaptopurine and methotrexate, and then go on to maintenance for 2 years.

**Rationale:** Although a high percentage of adults with acute lymphoblastic leukemia achieve a complete response with standard four-drug induction therapy, the majority will subsequently relapse and die of their disease. A variety of different multi-agent consolidation and maintenance schemas have been studied with most reporting between 35-40% cure and no one regimen clearly defined as being superior. A report from Memorial Sloan-Kettering showed that a regimen of high dose cytarabine plus mitoxantrone is highly active in adult lymphoblastic leukemia inducing as many patients into complete remission as standard induction (51). Also, a report from the Medical Research Council and the Eastern Cooperative Oncology Group suggests that allogeneic marrow transplantation may be superior to conventional chemotherapy both for high risk and intermediate risk disease, albeit with a greater immediate risk of mortality and more long-term toxicities (52). Thus, the current trial is designed to test the feasibility of combining the two most active chemotherapy regimens as treatment early in the disease and the possibility of using molecular markers of minimal residual disease (IgH, TCR gene clonal gene rearrangements) after this intensive induction regimen to identify patients for whom the risk of early transplantation is particularly justified.

**Objectives:** 1) To test whether the probability of continuous complete remission at one year among adult patients with non-L3, Ph-negative, BCR/ABL-negative acute lymphoblastic leukemia treated with a double induction therapy is sufficiently high to warrant further investigation; 2) To estimate the frequency and severity of toxicities with this double induction regimen; 3) To evaluate in a preliminary manner the significance of detecting cytogenetic and molecular measures of minimal residual disease (clonal IgH and TCR rearrangements) as prognostic factors for survival and relapse-free survival of patients receiving this chemotherapy regimen; and 4) To evaluate in a preliminary manner the pattern of gene expression of patients entered onto this trial and its relationship to cytogenetic/FISH risk classification, overall survival and relapse-free survival (supported by the NCI SPECS Program (NIH NCI CA U01CA114762) and a Leukemia & Lymphoma Society Specialized Center of Research Program Grant (7388-06), PI: C. L. Willman; co-PI: J. Radich).

**Statistical endpoints:** In SWOG-9400, 53% of patients with Ph- non-L3 disease remained in continuous complete remission one year after entering the study. The regimen described here would be of interest if the true continuing complete remission rate at one year were 65%, but not if it were 45%. Planned accrual is for 58 Ph- patients, and if 33 or more are alive in continuous remission at one year, then the regimen would be concluded to be of interest. This study will have critical level 4.6% if the true continuous remission rate at one year is 45%, and power 92% if the true rate is 65%. As of December 12, 2008, 73 patients had been registered, and given the frequency of Ph+ disease, an additional 5 patients will be registered before accrual is completed. Following completion of S0333, we plan to join ECOG in the conduct of E2907. This trial, which is still in development, presumably will be testing, in precursor B-cell ALL the addition of antibodies against CD20 and CD22, and in T-cell ALL the impact of the addition of nelarabine to standard therapy.
as the most important prognostic factor in adult ALL. Thus, cytogenetic correlates are currently being assessed in S0333.

Supported by an NCI SPECS and an LLS SCOR Center Grant, Willman and Radich are performing gene expression profiling studies in high risk pediatric and adult ALL cohorts from patients registered to COG and SWOG trials. Willman and colleagues recently obtained expression profiles in pre-treatment samples from 207 uniformly treated children and adolescents with high risk ALL (mean age: 11.5 yrs) treated in COG Trial 9906. Molecular classifiers predictive of outcome were developed with robust statistical methods and extensive cross validation procedures. A 38 gene molecular risk classifier predictive of relapse free survival (MRC-RFS) distinguished two groups of high risk pediatric ALL patients with different relapse risks: low (4 yr RFS: 81%, n=109) vs. high (4 yr RFS: 50%, n=98) (P< 0.0001). In multivariate analysis, the best predictor combined MRC-RFS and day 29 flow MRD data, classifying children into low (87% RFS), intermediate (62% RFS), or high risk (29% RFS) groups (P<0.0001). A 21 gene molecular classifier predictive of MRD could effectively substitute for day 29 flow MRD, yielding a combined classifier that similarly distinguished three risk groups at pre-treatment (low: 82% RFS; intermediate: 63% RFS; and high risk: 45% RFS) (P<0.0001) (Figure 5). This combined molecular classifier was further validated on an independent cohort of 84 children with high risk ALL registered to COG/CCG Trial 1961 (P = 0.006) (Willman et al, Blood, submitted). As shown in Figure 5, using this combined classifier we are able to identify, at pre-treatment, a group of pediatric ALL patients (approximately 30% of high risk ALL cases) that have a 5 year RFS approaching 0%, indicating that these patients are receiving no benefit from current treatment regimens and should be targeted at diagnosis and potentially after first remission to novel therapies or transplantation. Interestingly, children of Hispanic/American Indian race were over-represented in this extremely poor outcome group.

Like high risk, relatively older, pediatric ALL patients, the outcome of adult ALL is dismal. While allogeneic transplantation is effective in this disease, it is toxic. The ability to use molecular classifiers at pre-treatment to
prospectively identify those patients who have a high likelihood of failure on current regimens may provide a specific means to target patients to transplantation or other experimental approaches. Thus, Willman and Radich are currently testing the ability of the molecular classifiers for RFS and MRD developed in high risk pediatric ALL cases in adult cohorts derived from SWOG Trials 9400 and S0333. One of the most powerful genes identified in the pediatric molecular classifier for RFS was connective tissue growth factor (CTGF) (15). Interestingly, in preliminary gene expression profiling studies in the adult ALL cohorts, CTGF was found to be expressed at high levels and was significantly associated with outcome (Figure 6). CTGF is a secreted protein that promotes changes in cell adhesion, migration, and the properties of the extracellular matrix and has been reported to play a role in invasion and metastasis in solid tumors suggesting that it may be an interesting therapeutic target.

In addition, Radich has determined that two other genes originally found by Willman in the pediatric ALL molecular classifiers were prognostically significant in SWOG adult ALL cases. Two genes, Neuropeptide Y (NPY) and midkine (MDK), had high expression in adult ALL compared to normal hematopoietic cells, and have enough heterogeneity at diagnosis to be potentially prognostic. Both were statistically significant predictors of response (Figure 7).
These continued collaborative efforts should lead to the validation of molecular classifiers and specific genes that can be integrated into future SWOG ALL studies to target patients to specific treatment regimens or transplantation.

**S0530** A Phase II Trial of Cytarabine and Clofarabine in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL). (Activated 10/1/06: completed accrual on 8/1/08)

**Schema:** Patients with relapsed or refractory non-L3 acute lymphoblastic leukemia (ALL) received clofarabine 40mg/m²/day intravenously over one hour on days 1-5, and starting 4 hours after each dose of clofarabine they received cytarabine 1 gm/m²/day intravenously over 2 hours. Up to two cycles of induction were permitted. Patients achieving a complete response received one cycle of consolidation using the same doses of clofarabine and cytarabine as used for induction, but given only on days 1-4.

**Rationale:** Therapy for recurrent and refractory ALL in adults remains challenging. Clofarabine has recently been approved for the treatment of relapsed/refractory ALL in children, based on data from two multicenter phase II trials that reported overall response rates of 31% (CR or CRp rates were 20% and an additional 11% had PRs). Clofarabine causes depletion of normal deoxynucleotides by inhibiting ribonucleotide reductase. This, in turn, leads to a decrease in feedback inhibition of deoxycytidine kinase and should allow increased production and accumulation of cytarabine triphosphates, thereby increasing the activity of cytarabine. Based on the single-agent activity of clofarabine and the hypothesized interaction of clofarabine and cytarabine, Faderl and colleagues conducted phase I/II trials of a combination of clofarabine plus cytarabine in adults with refractory AML or ALL. The conclusions of that trial supported a dosing regimen of cytarabine 1 gm/m²/day combined with clofarabine 40mg/m²/day, both for 5 days, which is the schedule used in S0530. Further, the response rate of 38% seen in the Faderl trial was concluded by the authors to be encouraging, given the relapse profile of their patients (53). However, only a minority of their patients had ALL (the majority were AML), thus posing the question of the activity of this regimen in adults with recurrent and refractory ALL.

**Objectives:** 1) To test whether the complete remission rate (CR + CRi) in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) is sufficiently high following treatment with cytarabine and clofarabine to warrant further investigation. 2) To estimate the frequency and severity of toxicities associated with the dosing schedule of cytarabine and clofarabine outlined by this protocol. 3) To investigate in a preliminary manner the prognostic effects of laboratory correlates (expression of nucleoside transporters, expression of other pertinent genes by tissue microarray) and cytogenetic/FISH features on response to treatment in this patient population.
Statistical endpoints and results: The primary objective of this study is to test whether the rate of complete response (CR + CRi) among patients who have relapsed or refractory ALL is sufficiently high to warrant further investigation. Such further investigation might be warranted if the true complete response rate is 30% or greater, provided that other factors such as toxicity and duration of response are acceptable, and would likely be unwarranted if the true response rate is 10% or less. Patients were accrued in two stages to allow for early termination of accrual if there was evidence that the regimen was not sufficiently effective to warrant further investigation. In the first stage, 20 eligible patients were registered, and sufficient activity was seen to allow the study to go to completion. The results would be considered favorable to further investigation of cytarabine/clofarabine in ALL if 8 or more of the total 35 patients achieve complete response. This design has a critical level 2.0% if the true response rate is 10% and power 87% if the true rate is 30%. Total accrual was reached recently and final analysis will be conducted when data are mature.

S0910 Phase II Study of Epratuzumab in Combination with Cytarabine and Clofarabine for Patients with Relapsed or Refractory Precursor B-Cell Acute Lymphoblastic Leukemia

Schema: Patients with relapsed or refractory precursor B-cell ALL will receive a combination of cytarabine plus clofarabine exactly as administered in the recently completed S0530, and in addition will receive epratuzumab 360 mg/m2 on days 4, 11, 18 and 25. Up to two cycles of induction are permitted. Patients achieving a complete response will receive one cycle of consolidation using the same doses of drugs used for induction.

Rationale: Therapy for recurrent and refractory ALL in adults remains unsatisfactory. In S0530, we showed that a combination of clofarabine (40 mg/m2/d1-5) and high-dose cytarabine (1 gm/m2/d1-5) was tolerable and had encouraging activity against recurrent ALL. Epratuzumab is a humanized monoclonal antibody against CD22, an antigen that is expressed on the cell surface of the large majority of precursor B-cell ALLs. A Phase I study of epratuzumab combined with standard chemotherapy for childhood ALL showed that the agents could be safely combined and the Phase II portion of this trial is ongoing.

Objectives: 1) To test whether the complete remissions rate (CR + CRi) in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) is sufficiently high following treatment with cytarabine, clofarabine, and Epratuzumab to warrant further investigation. 2) To estimate the frequency and severity of toxicities associated with the dosing schedule of cytarabine, clofarabine, and Epratuzumab outlined by this protocol. 3) To investigate in a preliminary manner the prognostic effects of laboratory correlates (expression of nucleoside transporters, expression of other pertinent genes by tissues microarray) and minimal residual disease on prognosis in this patient population.

Statistical endpoints: The primary objective of this study is to test whether the complete response rate among patients who have relapsed or refractory non T-cell ALL is sufficiently high to warrant further investigation. Such further investigation might be warranted if the true complete response rate is 30% or greater, provided that other factors such as toxicity and duration of response are acceptable, and would likely be unwarranted if the true response rate is 10% or less. Patients will be accrued in two stages to allow for early termination of accrual if there is evidence that the regimen is not sufficiently effective to warrant further investigation. In the first stage, 20 eligible patients will be registered. The results will be considered favorable to further investigation of this regimen in ALL if 8 or more of the total 35 patients achieve complete response. This design has a critical level (probability of falsely concluding that an agent with a 10% true response probability warrants further study) of 2.0% and a power (probability of correctly concluding that an agent with a 30% response probability warrants further study) of 87%.

S0805 Phase II Study of a 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)
**Schema:** Patients age 50 or less with newly diagnosed Ph+ ALL and those who are found to be Ph+ and have received no more than a single cycle of induction therapy will be treated with Hyper-CVAD plus dasatinib induction and consolidation (for a total of 8 cycles) and then received maintenance with vincristine, prednisone and dasatinib for a total of 24 months. Patients who achieved a complete remission and are found to have either a matched related donor or a 10/10 matched unrelated donor will be allocated to allogeneic hematopoietic cell transplantation while in first remission to be followed by dasatinib maintenance.

**Rationale:** Prior to the availability of the newer tyrosine kinase inhibitors including imatinib and dasatinib, the outcome of patients with Ph+ ALL treated only with chemotherapy was very poor, with expected survival at three years less than 20%. Allogeneic transplantation from matched related or matched unrelated donors yielded better results with five-year survival rates of 50% or more in most studies and registry data. Thus, allogeneic transplantation in first remission has become the standard of care for adults age 50 or less with this disease. BCR/ABL specific tyrosine kinase inhibitors have activity as single agents in patients with recurrent Ph+ ALL, and accordingly, several investigators have added imatinib or dasatinib to upfront chemotherapy regimens. Thomas et al initially reported the outcome of 20 patients treated with hyper-CVAD plus imatinib (54). All achieved a CR and the results appeared better than historical controls, whether or not the patients subsequently underwent an allogeneic transplant. Similar encouraging results involving relatively small patient numbers have been presented by Towatari from Japan and by the German group in their GRAAPH-2003 study (55-56). Recently, the MD Anderson group has conducted a phase II trial combining hyper-CVAD with dasatinib. To date, 15 patients have been treated and no dose limiting toxicities have been observed. The depth of molecular remission appears somewhat greater than what they previously saw using hyper-CVAD plus imatinib, and no patient has developed evidence of pleural effusions or prolonged myelosuppression. Although results combining potent tyrosine kinase inhibitors with conventional chemotherapy for adults Ph+ ALL appear encouraging, there are no large studies with prolonged follow-up showing that cure is possible in a substantial number of patients. And thus there is a strong rationale for conducting such a study in those patients without appropriate donors. Recent studies suggest that it is also possible to treat patients who have undergone stem cell transplantation with maintenance therapy using tyrosine kinase inhibitors. Although there are as yet no controlled randomized trials addressing this issue, the results so far obtained suggest that such an approach may decrease the risk of relapse following transplantation. Thus, in this trial, we will be testing the feasibility and estimating the impact of adding the potent tyrosine kinase inhibitor dasatinib to conventional chemotherapy and to allogeneic stem cell transplantation.

**Objectives:**

1) 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 given in combination with the tyrosine kinase inhibitor dasatinib is sufficiently high to warrant further investigation. 2) 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 further investigation. 3) 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 with the hyper-CVAD+dasatinib regimen and/or allogeneic stem cell transplantation. 4) To estimate the frequency and severity of toxicities of the intensive short-term chemotherapy regimen in these patients. 5) To estimate the overall survival of all patients on this study.

**Statistical endpoints:** There will be two primary objectives for this study. The first primary objective is to test whether the regimen incorporating an allogeneic stem cell transplant preceded by an intensive short-term chemotherapy of Hyper-CVAD given in combination with the tyrosine kinase inhibitor dasatinib and followed by dasatinib maintenance is sufficiently effective among patients with Ph+ and/or BCR-ABL+ acute lymphoblastic leukemia (ALL) to warrant further use and investigation. This objective will be met by analyzing the probably of relapse free survival (RFS) at 12 months after transplant. The regimen would not warrant further use if its true 12-month RFS rate is 40% or less and would warrant further use if its true 12-month RFS rate is 65% or
higher. Accrual will continue until 34 patients have received an allogeneic stem cell transplant. If 40% of registered patients receive the transplant, total accrual to the study will be 85 patients. If 19 or more transplanted patients remain alive and relapse-free at 12 months, further study of the regimen will be considered. This study will have critical level 4.4% if the true 12-month PFS is 40% and power of 90% if the true 12-months RFS is 65%.

The second primary objective of this study is to test whether the regimen incorporating an intensive short-term chemotherapy of Hyper-CVAD given in combination with the tyrosine kinase inhibitor dasatinib is sufficiently effective among patients with previously untreated Ph+ and/or BCR-ABL+ acute lymphoblastic leukemia (ALL) to warrant further use and investigation. This objective will be met by analyzing the probability of patients being alive and in continuous complete remission (CCR) at 18 months. If the 18-month CCR rate is sufficiently effective, then further use of the regimen might be warranted; otherwise further study would not be recommended. The regimen would not warrant further use if its true 18-month CR rate is 50% or less and would warrant further use if its true 18-month CCR rate is 70% or higher. The primary analysis for this objective will be based on patients with no ALL therapy prior to entering the study, expected to number 68. If 42 or more of the 68 remain alive and event-free at 18 months, further study of the regimen will be considered. This study will have critical level of 3.2% if the true 18-month EFS is 50%, a power of 90% if the true 18-months CCR is 70%. ECOG and CALGB will join us in the conduct of this trial.

Chronic Lymphocytic Leukemia (CLL)

**E2997** Phase III Randomized Trial of Fludarabine and Cyclophosphamide Versus Fludarabine for Previously Untreated Chronic Lymphocytic Leukemia *(Activated: 10/15/02; Accrual Completed)*

**Schema:** Patients with previously untreated chronic lymphocytic leukemia were randomized to receive 6 cycles of a combination of cyclophosphamide 600 mg on Day 1 and fludarabine 20mg/m² Days 1-5 every 28 days versus fludarabine alone 25 mg/m² Days 1-5 every 28 days.

**Rationale:** The prior intergroup trial SWOG-9108 established fludarabine as the most active single agent for initial therapy of patients with chronic lymphocytic leukemia. Nonetheless, the complete response rate with fludarabine was only 20% and overall response rate was 60%, leaving considerable room for improvement. Cyclophosphamide is an active agent in this disease, and has a mechanism of action distinct from fludarabine. Phase I and II trials of concurrent therapy with cyclophosphamide and fludarabine have demonstrated safety and, in a small group of patients, a level of activity potentially superior to that achieved with fludarabine alone. Specifically, Flinn et al. reported a 100% overall response rate and 47% complete response in 17 patients with intermediate or high-risk disease (57).

**Objectives:**
1) To evaluate the complete response rate of a combination of fludarabine and cyclophosphamide versus that of fludarabine alone in patients with previously untreated chronic lymphocytic leukemia;
2) To evaluate the overall survival of patients treated with fludarabine and cyclophosphamide versus fludarabine alone;
3) To evaluate the toxicities associated with these two forms of therapy;
4) To determine whether expression of proteins that have been specifically implicated in regulation of DNA damage of lymphoid cells correlates with response;
5) To conduct additional studies examining the relationship of gene expression profiles, FISH, immunophenotype, and therapeutic response.

**Statistical endpoints and results:** This study was designed to detect an improvement in complete response rates from 25% to 45%. The proposed sample size of 252 eligible cases provided 90% power in detecting such an improvement. Two interim analyses were conducted. Accrual was completed by the end of 2004. A total of 278 patients were randomized in this intergroup study. Treatment with fludarabine plus
cyclophosphamide was associated with a significantly higher complete response rate (23% versus 4%, P<0.001) and a higher overall response rate (74% versus 60%, P=0.013) than seen with fludarabine alone. Progression-free survival was also superior with the combination than seen with single agent fludarabine (31.6 versus 19.2 months, P<0.0001), but no difference in overall survival was apparent at the time of the last analysis. (19). The occurrence of del(17p13.1) or del(11q22.3) was associated with markedly reduced progression-free survival (21).

**C10404** A Randomized phase II Study of Three Fludarabine/Antibody Combinations for Patients with Symptomatic, Previously Untreated Chronic Lymphocytic Leukemia

**Schema:** Patients with previously untreated symptomatic chronic lymphocytic leukemia will be randomized to one of three treatment arms: Arm A includes 6 monthly cycles of concurrent fludarabine plus rituximab followed by observation, Arm B includes 6 monthly cycles of concurrent fludarabine plus rituximab followed by 12 months of maintenance using lenalidomide, Arm C includes 6 monthly cycles of fludarabine, rituximab and cyclophosphamide followed by observation.

**Rationale:** A prior large intergroup trial showed that fludarabine is the single most active agent identified for treatment of chronic lymphocytic leukemia but leads to few complete responses and essentially no cures of the disease. Two phase II studies from CALGB including either the concurrent or sequential addition of rituximab to fludarabine showed a substantially higher response rate and duration than seen previously with fludarabine monotherapy (17). The recently completed intergroup trial (E2997) also showed improved response rates and progression-free survival with a combination of fludarabine plus cyclophosphamide compared with fludarabine alone (19). The MD Anderson group has combined rituximab with fludarabine and cyclophosphamide and reported a 100% overall response rate and a 68% complete response rate with acceptable toxicity (58). These response rates are among the highest ever reported in this disease and substantially higher than the 20% complete response rate previously reported with fludarabine alone or the 38% complete response rate seen with the combination of fludarabine plus rituximab. Lenalidomide has high activity in myeloma (another mature B cell disease) and in a small phase II study in patients with relapsed or refractory chronic lymphocytic leukemia appeared to have high activity with 6 of the first 9 patients exhibiting either partial or complete responses (59). While there is considerable interest in determining if any of these alternative regimens (fludarabine plus rituximab, fludarabine plus rituximab plus cyclophosphamide, or fludarabine plus rituximab plus lenalidomide) are superior to fludarabine alone, greater experience with these regimens in a group-wide setting is needed as well as further confirmation of their separate activities in genetically low and high risk disease.

**Objectives:** 1) To determine the two-year progression-free survival (PFS) of three different chemo-immunotherapy combinations for patients with untreated, symptomatic, lower risk and high risk chronic lymphocytic leukemia (CLL) and to select the top two therapies in each risk cohort for further phase III investigation, provided their PFS is also superior to previous results with fludarabine alone; 2) To determine the toxicity from these three chemoimmunotherapy combinations; 3) To determine the effect of pretreatment characteristics, such as interphase cytogenetic abnormalities, V_{H} gene mutational status, ZAP-70 expression, p53 dysfunction, and specific anti-apoptotic gene polymorphisms on clinical outcomes, such as attaining a complete response to induction therapy and progression-free survival; 4) To prospectively validate that positive ZAP-70 expression by flow cytometry/presence of methylated promoter is a surrogate endpoint for V_{H} mutational status for future risk stratified treatment studies; 5) To determine patterns of resistance that emerge in relapsing or refractory CLL patients following receipt of chemoimmunotherapy relative to clonal evolution, p53 dysfunction, gene expression-profile and epigenetic changes in methylation; 6) To determine if flow cytometry negative status 24 months after study entry is an effective surrogate marker for prolonged progression-free survival and overall survival.

**Statistical endpoints:** Planned accrual is 300 patients over an accrual period of about 2.5 years. The primary endpoint of interest is 2-year progression-free survival, the probability of which was 0.45 with the single
agent fludarabine on the previous intergroup trial. In order to be of interest for further study, a treatment arm would have to show a significant improvement over that, specifically if the lower 95% confidence bound around an arm’s estimated 2-year progression-free survival includes 0.45, that arm would no longer be considered of interest for further study. Assignment to treatment arm (A, B, or C) will not be stratified according to disease risk, but IgVH mutational status will be obtained and if, after accrual of 300 patients has been achieved, one or another arm shows dramatic imbalance, we will consider extending accrual.

C10501  CALGB Intergroup CLL Study of Asymptomatic Patients with Untreated Chronic Lymphocytic Leukemia: A Randomized Study of Early Intervention in the Subset with High-Risk Genetic Features.

Schema: Patients with asymptomatic CLL within 6 months of diagnosis are eligible for study. Those with low risk disease (mutated IgVH gene) will be observed until disease progression. Those with high-risk disease (unmutated IgVH gene) will be randomized for early intervention with fludarabine plus rituximab for 6 monthly treatments followed by observation until progression using NCI '96 criteria, or observation until NCI '96 criteria are met followed by six cycles of fludarabine plus rituximab.

Rationale: Prior to the availability of fludarabine and rituximab, optimal therapy of chronic lymphocytic leukemia included chlorambucil with or without additional agents. Based on several individual studies and a large retrospective analysis, no advantage could be found for early treatment with chlorambucil for patients with asymptomatic chronic lymphocytic leukemia. There have been two major changes since these early studies that warrant reexamination of the issue of early treatment. First, a number of disease markers, including IgVH mutational status, CD 38 expression, and expression of ZAP-70 are able to distinguish a population of patients with a markedly higher probability of a shorter duration of disease stability before progression. Second, therapies considerably more active than chlorambucil now exist. Presumably, disease progression is due to the existence or emergence of a subclone of the disease resistance to available therapies. This leads to the hypothesis that early intervention with the highly active combination of fludarabine plus rituximab with the subsequent reduction in tumor mass should prolong the time to the development of treatment resistant disease clones, compared to the alternative strategy of allowing for the continued accumulation and persistence of disease while the patient is being observed before initiating treatment.

Objectives: 1) To determine if early treatment with chemoimmunotherapy extends the time to second treatment (TT2T) and overall survival in genetically high-risk (un-mutated IgVH), newly diagnosed, asymptomatic CLL patients; 2) To measure the proportions of asymptomatic untreated CLL patients who have mutated and un-mutated IgVH genes; 3) To determine the differences in acute and chronic toxicity of administering chemoimmunotherapy early to asymptomatic genetically high-risk CLL patients enrolled on this trial compared to waiting until symptoms develop; 4) To determine the effect of pretreatment clinical and biological characteristics [such as interphase cytogenetic abnormalities, ZAP-70 expression, p53 dysfunction (primary and secondary), over-expression of anti-apoptotic protein expression and/or mcl-1 promoter insertions and microRNA gene expression] in genetically high-risk disease patients randomized to early treatment with respect to response, time to second treatment, and overall survival; 5) To determine the effect of pretreatment clinical and biological characteristics [such as interphase cytogenetic abnormalities, ZAP-70 expression, p53 dysfunction (primary and secondary), over-expression of anti-apoptotic protein expression and/or mcl-1 promoter insertions and microRNA gene expression] in genetically high-risk disease patients randomized to early treatment with respect to response, time to second treatment, and overall survival; 6) To describe the natural history of asymptomatic untreated CLL patients with genetically low risk (mutated IgVH genes) disease and their response to initial treatment after development of symptoms; 7) To determine the effect of pretreatment characteristics [interphase cytogenetic abnormalities, ZAP-70 expression, p53 dysfunction (primary and secondary), over-expression of anti-apoptotic protein expression and/or mcl-1 promoter insertions and microRNA gene expression] in genetically low-risk patients with respect to time to first treatment; 7) To determine patterns of resistance that emerge in relapsing or refractory CLL patients following receipt of chemoimmunotherapy relative to clonal evolution including acquisition of high-risk karyotype abnormalities, p53 mutations, p53 dysfunction (primary and secondary), over-
expression of anti-apoptotic protein expression and/or mcl-1 promoter insertions, microRNA gene expression, and methylation changes; 9) To determine whether clone specific PCR (or highly sensitive flow cytometry) negativity at completion of therapy is an effective surrogate marker for prolonged time to second treatment, overall survival, and other clinical benefits.

**Statistical endpoints:** The primary objective of this trial is to test for a difference in time to second treatment or death associated with early treatment versus delayed treatment. A hazard ratio of 1.4 is considered a clinically meaningful effect, and we are only interested in testing if early treatment is of benefit. Under these assumptions 320 events would be needed to have 91% power. The study will require accrual of approximately 600 high-risk patients to observe 320 events, and since the ratio of high risk to low risk disease is slightly less than 1:1, overall 1200 patients will be required to complete this study.

**S0902 Phase II Study of Bendamustine Plus Rituximab for the Treatment of Advance Chronic Lymphocytic Leukemia**

**Schema:** Patients with CLL who are refractory to or have relapsed after treatment with a purine analog will receive bendamustine 70 mg/m² intravenously day 1 and 2 every 28 days for 6 courses of therapy and rituximab 375 mg/m² intravenously on day 1 of the first cycle and then 500 mg/m² on day 1 of all subsequent cycles.

**Rationale:** Treating CLL with purine analogs inevitably leads to resistance. Patients with purine analog refractory disease have a very poor prognosis. New agents are needed for this population of patients. Bendamustine is a bifunctional alkylating agent with activity similar to purine analogs, but possessing a different mechanism of action (60). A phase I/II study was done to help determine the maximally tolerated dose in patients with advanced CLL. The optimal therapeutic dose was eventually found to be 70mg/m² for 2 days(61). The response rate in this trial was 56%. Impressively, the median duration of response in the trial was 42 months.

In vitro, rituximab was shown to improve the cytotoxicity profile of bendamustine.(62) In vivo, the combination of bendamustine plus rituximab was shown to be tolerable in a population of patients with lymphoma.(63) These observations preceded a German study of bendamustine plus rituximab for patients with relapsed CLL. In a preliminary report of 31 patients with a median age of 66 years, substantial myelosuppressive and infectious complications were reported.(64) Nonetheless, responses were achieved in 65% of patients. The intriguing activity of bendamustine plus rituximab reported in this study suggests that this combination should be studied further.

**Objectives:** 1) To determine the complete and partial response rate in patients with recurrent and refractory CLL to a regimen of Bendamustine plus rituximab. 2) To estimate the frequency and severity of toxicities associated with this combination of drugs in this patient population.

**Statistical endpoints:** A total accrual of 49 patients is planned. Twenty-five will be accrued in the first stage and if 5 or more achieve a CR or PR, 24 additional patients will be accrued. If the true CR+PR rate is > 45%, the regimen would warrant further investigation, while if the true remission rate were < 25%, it would not. The current design gives a power of 90% and a critical level of 4.5%.

**Chronic Myelogenous Leukemia (CML)**

**S0325 A Phase IIb Study of Molecular Responses to Imatinib, at Standard or Increased Doses, or Dasatinib (BMS-354825) (NSC-732517) for Previously Untreated Patients with Chronic Myelogenous Leukemia (CML) in Chronic Phase. (Activated 8/15/04; Currently accruing)**

**Schema:** Patients with newly diagnosed chronic myeloid leukemia in chronic phase will be randomized to one year of therapy with imatinib 400 mg/day, imatinib 800 mg/day or dasatinib 100 mg/day.
Rationale: Based on a completed phase III study comparing imatinib 400 mg/day with interferon-alpha plus cytarabine, imatinib is now the non-transplant treatment of choice for patients with newly diagnosed chronic myeloid leukemia in chronic phase (65). With standard dose imatinib, 96% of patients will achieve a complete hematologic response, and only approximately 4% of patients will progress with each year of follow-up. Nonetheless, few if any patients are cured with this therapy. The long duration of response makes the use of progression-free survival as an endpoint for future studies searching for improved therapies difficult and published data suggest that the rate of molecular response may serve as a surrogate likely to predict for clinical benefit (66). Phase II data suggest that the rate of molecular response (>3 log reduction in BCR-ABL transcript level) may be higher for patients treated with imatinib at 800 mg QD than previously reported using imatinib at 400 mg/day (67). Recently, a high potency ABL inhibitor, dasatinib, has completed phase I trials in patients with imatinib resistance (68). Complete hematologic responses were seen in 87% of 40 evaluable patients, with cytogenetic responses in 59%. Given the significant increase in potency seen with dasatinib and its activity in imatinib resistant patients, it makes sense to likewise evaluate this drug as upfront therapy for CML in chronic phase. The detection of BCR-ABL mRNA by RT-PCR was first demonstrated to be a powerful predictor of relapse in CML patients following transplantation. The landmark IRIS study of newly diagnosed CML, randomized to either imatinib or IFN/Ara-C, became the proving grounds of the use of quantitative PCR (QPCR) to study both the depth of response to therapy and predicting outcome in a non-transplant setting (66). In summary, patients on either study arm had peripheral blood analyzed by QPCR for the BCR-ABL mRNA. Samples were taken every 3 months once complete cytogenetic remission (CCR) was achieved. The study demonstrated several important points: 1) for patients who achieved a CCR, imatinib cases achieved ~1 log greater response than the IFN/Ara-C arm as measured by MRD; 2) molecular response could be used to predict future outcome, and thus, potentially influence treatment decisions. Thus patients who did not achieve a CCR by 12 months of imatinib had a 30% risk of progression over the next 3 years, while patients who achieved a CCR could be further stratified into two groups, those who had a > 3 log reduction in BCR-ABL mRNA (a so-called “major molecular remission” or MMR), or a less than 3 log reduction. The risk of progression of the MMR group was 0%, compared to 8% in the later group. As a result of the IRIS study, the SWOG Leukemia group proposed the design of the current CML Intergroup trial, a randomization of imatinib 400 mg/d v. 800 mg/d v. the new tyrosine kinase dasatinib, using the molecular response at 12 months as the primary efficacy endpoint. This represented the first study to use a molecular endpoint in an efficacy trial.

Objectives: 1) To compare the molecular response rates, as measured by the decrease in BCR-ABL transcripts after 12 months of treatment, in patients with previously untreated CML in chronic phase who are treated with either dasatinib 100 mg/day or imatinib (STI571, Gleevec®) 400 mg/day; 2) To test whether increasing the dose of imatinib (STI571, Gleevec®) from 400 mg/day to 800 mg/day increases the rate of molecular response, as measured by the decrease in BCR-ABL transcripts after 12 months of treatment, in patients with previously untreated CML in chronic phase; 3) To estimate the rates of cytogenetic and hematologic responses to imatinib 400 mg/day, imatinib 800 mg/day, and dasatinib 100 mg/day; 4) To evaluate in a preliminary manner the prognostic effects of der(9) and der(22) chromosome deletions on response in patients treated with imatinib or dasatinib; 5) To investigate in a preliminary manner changes in gene expression pattern at relapse or progression compared to pre-treatment expression pattern; 6) To estimate the frequency and severity of toxicities of these three treatment regimens; and 7) To evaluate in a preliminary manner the overall survival and relapse-free survival of patients treated with these regimens.

Statistical endpoints: The primary objectives of this study is to test whether the molecular response rate in patients with previously untreated chronic myeloid leukemia in chronic phase treated with imatinib at 800 mg/day or with dasatinib at 100 mg/day is sufficiently higher than that produced by imatinib at standard dose to warrant further investigation of these new regimens. For this purpose a molecular response will be defined as a 4-log reduction in the BCR-ABL/bcr ratio after 12 months of therapy, which, in a large published series, was 15% with imatinib at 400 mg/day. This study is designed to ensure adequate statistical power (≥ 90%) of correctly concluding that imatinib at 800 mg/day or dasatinib at 100 mg/day significantly improves the molecular response rate, if in fact, the true molecular response rate is improved by at least 20%, i.e., from 15%
to 35%. A total of 400 patients will be accrued to this study. As of December 12, 2008, 380 patients were registered. The imatinib 800 mg/day arm met its accrual goal and has been closed to further accrual.

**Additional Translational Medicine Studies in CML**

Radich and colleagues have completed extensive studies of gene expression profiles during CML progression (16) using SWOG samples of various phases of CML derived from prior treatment trials as well as in normal, un-stimulated CD34+ hematopoietic progenitor cells. These studies demonstrated that CML appears to be a two-step rather than three-step disease. That is, of the gene expression changes that occur with different phases of disease, the vast majority of changes are from chronic phase (CP) to accelerated phase (AP), while the gene expression profiles of AP and blast crisis (BC) are very similar (Figure 8). This has obvious clinical implications, suggesting that at the time of transition into AP, the genetic changes associated with progression to blast crisis are already present.

![Figure 8. In unsorted blood ~3,000 genes were differentially expressed in CP vs. BC. The normal CD34+ signature was subtracted from the CML cases to give ~350 progression-specific genes. Note BC-r = blast crisis in remission, and AP-c = AP by cytogenetic criteria (both have <5% blasts).](image)

Genes with profound differences in expression level between CP, AP and BP CML (p<10⁻⁸) were identified that could be both markers of progression in diagnostic assays, as well as potential therapeutic targets (Table 1). For example, dysregulation of the Wnt/Beta-catenin pathway was found, as well as entire sets of genes regulated by specific transcription factors, e.g., genes controlled by the myeloid zinc finger (MZF) transcription factor. Finally, patients who obtained a CCR on imatinib, but then lost response and returned to morphologic

<table>
<thead>
<tr>
<th>Gene</th>
<th>LogR</th>
<th>Gene name</th>
<th>Gene function</th>
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<tbody>
<tr>
<td>GLI2</td>
<td>+0.8</td>
<td>GLI-Kuppel family</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>PRAME</td>
<td>+0.8</td>
<td>Preferentially expressed antigen in melanoma</td>
<td>Differentiation</td>
</tr>
<tr>
<td>SOCS2</td>
<td>+0.7</td>
<td>Suppressor of cytokine signaling 2</td>
<td>Signal transduction</td>
</tr>
<tr>
<td>WT1</td>
<td>+0.7</td>
<td>Wilms tumor 1</td>
<td>Cell cycle/apoptosis</td>
</tr>
<tr>
<td>GAS2</td>
<td>+0.7</td>
<td>Growth arrest specific 2</td>
<td>Cell cycle/apoptosis</td>
</tr>
<tr>
<td>IL8</td>
<td>-0.8</td>
<td>Interleukin 8</td>
<td>Cytokine</td>
</tr>
<tr>
<td>FOSB</td>
<td>-0.9</td>
<td>FBJ murine osteosarcoma virus homolog B</td>
<td>Nuclear protein</td>
</tr>
<tr>
<td>FOS</td>
<td>-0.9</td>
<td>v-fos osteosarcoma virus homolog</td>
<td>Proto-onocogene, nuclear protein</td>
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<tr>
<td>EREG</td>
<td>-1.0</td>
<td>Epiregulin</td>
<td>Angiogenesis</td>
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chronic phase had a gene expression signature consistent with advanced phase rather than CP disease (Figure 9). This observation agrees with the clinical observation, noted above, that such cases tend to have a short time to progression and death, despite their benign clinical and pathological appearance of CP.

| HSPA1A | -1.1 | Heat shock 70 | Chaperone |

### Table 1: The “top ten” genes up- and down-regulated in CML progression. “LogR” is the log ratio of expression in blast phase compared to chronic phase. For example, PRAME is 8-fold over-expressed, and HSPA1A 11-fold under-expressed, in blast phase compared to chronic phase.

Major Erythroid Response (MER) to Treatment with Lenalidomide (CC-5013) Alone and in Combination with Darbopoietin Alfa (DA) in Subjects with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia

**Schema:** Patients with low or intermediate risk myelodysplasia who are either erythropoietin non-responsive or have a low probability of responding to erythropoietin will be randomized between the two arms. Arm A consists of lenalidomide 10 mg po/day for 21 days, to be repeated every 28 days for 4 cycles while Arm B consists of lenalidomide given on the same schedule plus erythropoietin.

**Rationale:** Lenalidomide is an oral 4-amino glutaramide derivative of thalidomide with apparent activity in myelodysplasia. In an early dose finding study of 43 patients with myelodysplasia who had failed...
erythropoietin or were unlikely to respond based on high endogenous erythropoietin levels, among 36 patients completing more than one cycle, 67% experienced an erythroid response according to International Workshop Group criteria. Two phase II trials evaluated lenalidomide in patients with low risk or intermediate risk 1 disease with or without 5q31.1 deletions. In patients with deletion 5q31.1, there was a 66% major erythroid response and a 27% response in patients without 5q31.1 deletion (36). Preclinical studies suggest that lenalidomide may sensitize erythroid progenitors to erythropoietin.

**Objectives:** 1) To compare the rate of major erythroid response (MER) between lenalidomide monotherapy and combined treatment of lenalidomide and EPO in EPO non-responsive Low/Int-1 risk MDS patients or EPO-treatment naïve patients with low probability of EPO benefit; 2) To compare the time to MER by treatment; 3) To evaluate the duration of MER by treatment assignment; 4) To estimate the frequency of MER to salvage combination therapy in patients who fail to experience a MER with lenalidomide monotherapy; 5) To evaluate and compare the frequency of minor erythroid response and cytogenetic response by treatment assignment; 6) To evaluate the relationship between erythroid response and laboratory correlates including pretreatment endogenous EPO level, lenalidomide potentiation of EPO-induced STAT5 phosphorylation in pretreatment marrow specimen and in trephine biopsy specimens, the relationship between CD34 tyrosine phosphatase isoform profile and response, and ex vivo enhancement of trophic response (apoptosis reduction, colony-forming capacity) in MDS progenitors; 7) To investigate the mechanism and target of lenalidomide action in patients with chromosome 5q31.1 deletion.

**Statistical endpoints:** The major endpoint of this study is major erythroid response, defined as sustained transfusion independence in transfusion-dependent patients or a rise in hemoglobin ≥2g/dL in transfusion-independent patients with anemia of greater than 8 weeks duration. The objective major erythroid response will be assessed 16 weeks after start of therapy. Based on prior studies, it is hypothesized that the major erythroid response rate with lenalidomide alone will be 30% and we wish to test whether the rate with the addition of erythropoietin will increase to 50%. A sample size of 212 patients will provide approximately 80% power to detect such an improvement with an overall one-sided type 1 error rate of 0.025.

**E1905** A Randomized phase II Trial of Azacitidine with or without the Histone Deacetylase Inhibitor MS-275 for the Treatment of Myelodysplastic Syndrome, Chronic Myelomonocytic Leukemia (Dysplastic Type), and Acute Myeloid Leukemia with Multilineage Dysplasia. *(Activated 10/1/06; Currently accruing)*

**Schema:** Patients with myelodysplasia (IPSS Int-2 or higher), chronic myelomonocytic leukemia (dysplastic type) or acute myeloid leukemia with multilineage dysplasia are entered on study and randomized to Arm A, azacitidine QD subcutaneously Days 1-10 every 28 days for 6 cycles or Arm B, azacitidine as given in Arm A plus MS-275 orally on Days 3 and 10 of each cycle. Patients with hematologic improvement or a partial or complete response may continue on their treatment arm for 18 more cycles.

**Rationale:** Based on a prior randomized trial, azacitidine was approved for treatment of myelodysplasia. Complete and partial responses were seen in 7 and 10 percent of patients respectively, and another 37% had evidence for hematologic improvement using a regimen of 75 mg/m²/day for 7 days on a 28 day schedule. Azacitidine is a prodrug for decitabine, which also has been shown to have activity in myelodysplasia. Both of these agents are thought to act at least in part by inhibiting DNA methyltransferase. There is interest in the study of histone deacetylase inhibitors in myeloid malignancies in part because certain leukemia specific fusion gene products specifically recruit nuclear co-repressor complexes including histone deacetylases, resulting in transcriptional silencing of otherwise important active genes. The attraction of combining a DNA methyltransferase inhibitor with a histone deacetylase inhibitor is based on in vitro data showing that optimal expression of methylated genes require repeated exposure to a methyltransferase inhibitor followed by inhibition of histone deacetylase. In preparation for combination studies, attempts were made to optimize the dose and schedule of azacitidine and an unexpected finding was that longer subcutaneous dosing of azacitidine both led to histone acetylation and also appeared to have a higher hematologic response rate in a limited number of patients. MS-275 is a benzamide histone deacetylase inhibitor that has been evaluated as a
single agent in patients with relapsed or refractory acute myeloid leukemia. In a phase I trial, over 1/3 of patients showed hematologic improvement or partial response. A subsequent phase I trial of azacitidine plus MS-275 was conducted with 22 patients treated in 8 different cohorts. No dose limiting toxicities were seen and 11 of the first 15 patients had clinical responses.

Objectives: 1) To estimate the major response rate (complete and partial responses by the International Working Group (IWG) response criteria) to a 10-day regimen of azacitidine and to the same regimen of azacitidine in combination with MS-275 administered orally on Days 3 and 10 of each cycle in patients with MDS, CMMoL (dysplastic) and AML-TLD; 2) To evaluate the toxicity of azacitidine and MS-275 in this patient population; 3) To identify changes in gene promoter methylation and gene expression that may be associated with response to azacitidine and MS-275; 4) To identify other molecular mechanisms (such as DNA damage) that may be associated with response to azacitidine and MS-275.

Statistical endpoints: Prior studies of azacitidine showed a complete or partial response rate of 23% and a transfusion response of 23%. The primary objective of this study is to investigate whether a novel schedule of azacitidine alone or in combination with MS-275 will increase the combined complete, partial, and transfusion response rates from the previous 50% range to 70% in either arm. This was planned as a two-stage design with 21 eligible patients accrued to each arm. If fewer than 12 respond, accrual to that arm would be stopped. If 27 or more responses are seen in a total of 45 patients at the end of the second stage, that arm will be considered worthy of further study. Thus, overall accrual will be as high as 90 eligible patients assuming neither arm is stopped early. Accrual to the first stage was completed and the interim analysis completed. Both arms were sufficiently active to resume accrual to the second stage of the study.

VISION

The mission of the Southwest Oncology Group Leukemia Committee is to improve the outcome of treatment for leukemia and related diseases primarily through the conduct of phase II and phase III clinical trials of new therapeutic approaches, making use of advances in the understanding of the molecular biology of leukemia and the availability of new diagnostic tests and therapeutic agents. We are also committed to using these trials to conduct associated correlative laboratory sciences studies with the long term goal of helping us better understand the pathogenesis of leukemia, improve prognostic and monitoring techniques, and develop new insights that may lead to further therapeutic advances. The Leukemia Translational Medicine Subcommittee is an established and productive team of physicians and scientists that designs, integrates, and conducts correlative science studies in the context of SWOG leukemia trials. First founded in 1986 and competitively reviewed and funded in the 1987 U10 Cooperative Group Agreement, the Leukemia Translational Medicine program was competitively re-reviewed and renewed in 1992, 1997, and in 2003, each time receiving a merit score of “outstanding.” Using well-established ancillary biology protocols, reference laboratories, informatics systems, and tissue repositories, members of the Committee have made significant contributions to the fundamental understanding of leukemia cell and molecular biology and have been leaders in the translation of this science to clinical applications. The Translational Medicine Subcommittee has four established Leukemia Reference Laboratories and Repositories: 1) The SWOG AML/MDS Reference Laboratory & Tissue Repository at the University of New Mexico led by Cheryl L. Willman, MD and colleagues; 2) The SWOG ALL//CML Reference Laboratory & Tissue Repository at the FHCRC led by Jerald Radich, MD and colleagues; 2) The SWOG Flow Cytometric Minimal Residual Disease Laboratory at the University of Washington led by Brent Wood, MD; and 4) SWOG Leukemia Cytogenetics (focused primarily on cytogenetic review and correlative FISH studies) led by Ming Fan, MD, PhD of the Fred Hutchinson Cancer Center and Diane Roulston, PhD of the University of Michigan. Two companion protocols for SWOG Leukemia Translational Medicine Studies accompany each SWOG Leukemia Clinical Trial. These ancillary protocols include S9907: Cytogenetic Studies in Leukemia Patients (which facilitates review of submitted karyotypes and directs correlative cytogenetic and FISH studies and S9910: Leukemia Centralized Reference Laboratories and Tissue Repositories (which directs and facilitates sample submission for correlative science and translational
medicine studies integrated into the design of each SWOG Leukemia Trial and the banking of residual leukemia samples).

Great attention is given to the choice of clinical and laboratory questions to address, and to the development and conduct of these studies. As noted in the “Membership” section, a conference call attended by selected members of the Leukemia Committee is held monthly, and a half-day Southwest Oncology Group Leukemia Committee and Translational Medicine Subcommittee retreat is held twice each year. In addition, each month a conference call is held attended by the Leukemia Committee Chairs of SWOG, ECOG, CALGB, the NCIC, a representative of the BMT/CTN, and a CTEP representative. Further, SWOG representatives have played a major role in the conduct of national leukemia state of the sciences meetings (69-70). Our general philosophy for the development of our roster of studies is as follows: we periodically review phase I and II trials being conducted by our member institutions during our monthly calls and semi-annual retreats. We select from these the most promising trials for confirmation as group-wide phase II studies. Phase III studies may be the natural progression of these phase II trials, but every effort is made to develop intergroup trials whenever possible, and to consider the major questions identified by state of the science meetings. Biostatisticians, pathologists, cytogeneticists and laboratory scientists are included in discussions at all stages of trial development.

The full roster of studies that are active or are in active development is shown in Table 2. As noted, the large majority of phase III trials are intergroup studies, reflecting the outstanding collaborative spirit of the cooperative group committee chairs. It should be noted that these intergroup studies are truly cooperatively developed, and so a great deal of intellectual input comes from members of all groups in the development of each study, no matter the lead institution.
Currently, two major questions are being addressed in the treatment of patients with newly diagnosed APL. First, in patients with low or intermediate risk disease who are polymerase chain reaction negative for PML/RARα fusion transcripts after optimal induction and consolidation therapy, we are asking if one year of maintenance therapy is needed. Second, in patients with high risk disease, we will determine whether the incidence of early death and subsequent disease relapse can be diminished using a novel induction regimen employing three of the most active single agents followed by aggressive consolidation and maintenance therapy.

Prior studies in which the Southwest Oncology Group participated demonstrated a benefit of treatment with tretinoin during both induction and maintenance (71), and in addition, described the toxicities associated with tretinoin therapy (72), the association of different breakpoints in the t(15;17) with disease characteristics and outcome (73), and the potential to use semi-quantitative polymerase chain reaction measurements to monitor outcome (74). We also completed a study showing that proximate tretinoin selection pressure is not likely the main determinant for the emergence of strongly dominant PML-RARα mutant subclones (23). During the last grant period, we participated in the development and completion of C9710, an intergroup trial in which we found that the addition of arsenic trioxide as consolidation therapy improved the disease-free and overall survival.
survival of patients with previously untreated APL (1). Thus, this study has changed the standard of care for this disease. Among patients with intermediate and favorable risk disease, defined as those with a WBC of ≤10,000/mm³ at diagnosis, death during induction was 3% and the risk of relapse during the first year was <3%. These outstanding results, coupled with a recent report from the Japanese Adult Leukemia Study Group, (26) led us to ask in S0521 whether patients who, after intensive consolidation therapy, are polymerase chain negative for the PML/RARα fusion transcripts require a further year of potentially toxic maintenance treatment. The results of C9710 also demonstrated a less favorable outcome in high-risk patients (those with a white blood cell count >10,000/mm³ at diagnosis) who, consistent with European data (25), had a risk of death during induction of 20% and a risk of relapse during the first year in excess of 10%. Based on encouraging pilot data provided to us by Dr. Elihu Estey from MD Anderson (27 and personal communication), we will be testing in a phase II trial (S0535) a novel induction regimen combining retinoin, arsenic trioxide, and gemtuzumab ozogamicin, followed by consolidation and maintenance modeled on that used in C9710, to determine if this regimen results in an outcome sufficiently safe and encouraging to warrant further study in a phase III trial.

Previously Untreated Acute Myeloid Leukemia in Patients <Age 60

In younger patients with previously untreated acute myeloid leukemia, we are asking whether the addition of gemtuzumab ozogamicin to standard induction therapy improves complete response rates and whether the use of the drug as maintenance prolongs disease-free survival. The prognostic significance of detection of mutations of FLT3 and of minimal residual disease using flow-based assays are also being evaluated. Samples from patients entering this trial are also being analyzed using gene expression profiling to determine whether expression signatures predictive of early failure or persistence of residual disease can be found (supported by National Cancer Institute funding to the University of New Mexico, the Fred Hutchinson Cancer Research Center, and the Southwest Oncology Group under the Strategic Partnerships to Evaluate Cancer Gene Signatures (SPECS) Program (NCI U01 CA 114762)).

Standard induction therapy of acute myeloid leukemia consists of three days of an anthracycline and seven days of cytarabine at 100 or 200 mg/m² per day and has not changed in almost three decades. With such regimens, complete response rates in Cooperative Group trials have ranged around 65-70%, and attempts to improve upon these rates using, for example, high dose cytarabine as in S9500 (2) or the addition of etoposide have not yielded higher complete response rates. Gemtuzumab ozogamicin combines a humanized anti-CD33 antibody with the potent antitumor antibiotic calicheamicin and as a single agent induces complete remissions in approximately 30% of patients with acute myeloid leukemia in first untreated relapse, with similar activity in good, intermediate, and poor risk cytogenetic subgroups. Two phase II studies have tested regimens combining gemtuzumab ozogamicin with standard anthracycline and cytarabine induction and have reported complete response rates in 86% and 85% of patients respectfully and an acceptable toxicity profile.(29-30) Thus, in study S0106 we are testing in a randomized fashion whether the three-drug combination is more effective in inducing complete remission than standard induction.

Obtaining a complete response is a prerequisite for a cure, but improving complete response rates does not ensure improvement in disease-free or overall survival. Standard post-remission therapy for younger patients with acute myeloid leukemia remains unsettled, but for standard and good risk patients several cycles of therapy, including high dose cytarabine, are generally used. Gemtuzumab ozogamicin is well tolerated when given as a single agent to patients with leukemia in remission and appears to contribute to prolonged remission duration in acute promyelocytic leukemia.(27) Thus, in this study, patients completing consolidation therapy are re-randomized to receive gemtuzumab maintenance or observation.

While S0106 was being developed, the British Medical Research Council initiated a similar randomized trial testing the impact of the addition of gemtuzumab ozogamicin to standard induction chemotherapy. Preliminary results presented in abstract form involved 1113 randomized patients and suggested no difference in complete response rates, but a significant advantage in disease-free survival with the addition of gemtuzumab (31).
There was no significant difference in overall toxicities with the addition of gemtuzumab, and among those patients proceeding to transplantation, there was no increase in the incidence of liver disease. Further follow-up of the MRC trials demonstrates improvement in both disease-free and overall survival with the use of gemtuzumab in patients with unfavorable risk cytogenetics, but no improvement in those with unfavorable risk disease. As of August 12, 2008, 412 of the planned 684 patients had been randomized on S0106. With the current accrual rate of 15 patients per month, we estimate that accrual on S0106 will be completed by about the end of 2009.

As noted earlier, the leadership of the Leukemia Committees of SWOG, ECOG, CALGB and NCIC, along with representation from the BMT/CTN and CTEP met on November 3, 2008 to begin to jointly develop the successor of our current trials for younger patients with previously untreated AML, all of which will likely complete accrual around the same time. Preliminary plans are to perform a single North American Intergroup Trial which will test risk adapted therapy asking four major questions: 1) In patients with CBF AML, does inhibition of cKIT using a potent tyrosine kinase inhibitor prolong disease-free survival; 2) In patients with FLT3 mutations, does the use of a FLT3 inhibitor improve outcome; 3) In patients with unfavorable cytogenetics, what proportion can rapidly be brought to allogeneic transplantation, and what is the outcome of such transplants; and 4) In patients with intermediate risk disease, does maintenance with a demethylating agent prolong disease-free and overall survival.

Previously Untreated Acute Myeloid Leukemia in Patients Over Age 60 Who Are Candidates for Intensive Chemotherapy

In patients over age 60 with newly diagnosed AML, we are conducting a phase II trial of a combination of azacitidine 75 mg/m² subcutaneously days 1-7 combined with gemtuzumab ozogamicin 3 mg/m² intravenously on day 8.

Treatment of AML in patients over age 60 has generally been far less satisfactory than in younger patients due both to an inability of the patient to tolerate intensive therapy and increased intrinsic drug resistance in older AML patients. In previous studies conducted by our group, we demonstrated a high rate of p-glycoprotein expression and functional drug efflux in older patients with de novo AML and in younger patients with high risk AML (recurrent, refractory or secondary), and found that this was associated with a significantly lower complete response rate and a higher incidence of drug resistance with the use of conventional induction therapy. In an effort to reverse the effects of p-glycoprotein, we conducted a prospective randomized trial in younger patients with high risk AML testing a regimen of high dose cytarabine and continuous infusion daunomycin with or without continuous infusion cyclosporine (SWOG-9126). The hypothesis being tested in that study was that cyclosporine should be able to effectively block p-glycoprotein and that by giving the anthracycline by continuous infusion with cyclosporine, there should be only limited if any increased toxicity since acute toxicities with anthracycline appear to be related mostly to peak blood levels. The results of this randomized trial were consistent with our hypothesis in that with cyclosporine overall survival was significantly improved and the incidence of drug resistance as a reason for treatment failure was significantly reduced (34/0). This regimen was viewed as probably too intensive for patients over age 60, and so in an attempt to apply the lessons learned in SWOG-9126 to older individuals, we initiated two sequential phase II trials: S0112, which evaluated the efficacy of conventional dose cytarabine and daunomycin both given by continuous infusion, followed by S0301, which tested the same regimen but with cyclosporine. Although the final analyses are not yet completed, the results of these studies suggest that giving cytarabine and daunomycin by continuous infusion gives results similar to what we have previously obtained with bolus anthracycline (as expected), and that the addition of cyclosporine to this regimen may not have produced a marked improvement in CR rate, but may have led to an improvement in relapse-free and overall survival at 24 months. The lack of an apparent improvement in CR rates made us less enthusiastic about comparing the induction regimens in S0112 and S0301 in a prospective randomized trial. However, the possible improvement in relapse-free survival, similar to what was seen in SWOG-9126, suggests that cyclosporine inhibition of Pgp might be a strategy to pursue as consolidative therapy in the future.
During this same period, SWOG investigators at Loyola university initiated a trial testing the combination of azacitidine 75 mg/m²/d for 7 days followed by gemtuzumab ozogamicin 3mg/m² on day 8. This trial was based on the fact that both azacitidine and gemtuzumab have activity as single agents and both have relatively little non-hematopoietic toxicity. Further, in vitro studies conducted in Seattle and elsewhere show that exposure of leukemic blasts to azacitidine increased CD33 expression and sensitized AML blasts to killing by gemtuzumab. The results in the first 20 patients treated were promising. Among these patients, median age 77, there were no treatment related deaths and 75% achieved a CR (39). Thus, we are testing this regimen in S0703 in two groups of patients, those considered fit for standard chemotherapy, and those considered unfit. If the results appear encouraging in the fit population, we would then compare this regimen to standard chemotherapy. If the regimen appears encouraging in the less fit population, we would compare this regimen to low dose cytarabine (see the following discussion).

In single institution pilot studies, allogeneic hematopoietic cell transplantation using reduced intensity conditioning has yielded promising results. In 2001, we initiated S0125 in an attempt to confirm these results in a group wide phase II study. Unfortunately, the trial accrued poorly, in part due to co-morbidities in older patients with AML in first remission, in part due to a lack of donors healthy and able to serve, and in part because of reluctance of patients and physicians to consider this therapy at the time the trial was initiated. Similar slow accrual was experienced by the CALGB in a similar trial, but more recently, with the help of the BMTCTN, the CALGB trial may after a number of years reach its accrual goal. The leaders of the three cooperative groups and their transplant committees will be meeting with representatives from the BMTCTN and CTEP to review the results of the recently completed trial and determine whether the time is right for future studies pursuing the role of reduced intensity conditioning allogeneic HCT in older patients with AML.

**Previously Untreated Acute Myeloid Leukemia in Older Patients Not Considered Candidates for Aggressive Chemotherapy**

During the last grant period, we conducted a phase II study (S0432) testing two different schedules and two different doses of the farnesyl transferase inhibitor tipifarnib. Of the four dose schedules tested, arm 3 (300 mg/bid x 21 days q 28 days) showed activity of some interest, with a CR rate of 11% and an overall response rate (CR, CRi, and PR) of 20%. However, this degree of activity was not felt to be sufficient to take forward as a single agent. Thus, as described in the section above, we are now pursuing the combination of azacitidine plus gemtuzumab in this population in study S0703. Also in patients of age 60 and above with AML with 5q-, S0605 is asking whether lenalidomide is sufficiently active as a single agent to warrant further investigation. This study is based on the remarkable activity of this agent in patients with myelodysplasia with 5q31.1 deletions where a 70% response rate was seen, including a 44% complete cytogenetic response rate. Included in this group of patients were 8 with complex cytogenetic abnormalities in addition to 5q- where a complete cytogenetic response rate of 50% was observed.(36) S0605 was designed as a two-stage trial. Sufficient activity was seen in the first stage to continue to full accrual of 40 patients. If sufficient activity is seen after full accrual, we would follow this study with one combining lenalidomide with conventional chemotherapy. A pilot study of such a combination is currently underway at Cleveland Clinic.

**Recurrent Acute Myeloid Leukemia**

In patients with recurrent AML, S0804 is testing a combination of idarubicin, high dose cytarabine plus pravastatin. This trial is based on preclinical work from Southwest Oncology Group investigators (8,9,49) showing that cholesterol homeostasis is abnormal in AML blasts, and that inhibiting cholesterol synthesis specifically sensitizes AML blasts to cytotoxic agents. These findings formed the basis of a recently completed phase I trial conducted by investigators at MD Anderson and the Fred Hutchinson Cancer Research Center. (40) In that trial, we found that doses of pravastatin up to 1280 mg/day given directly before and during chemotherapy were well tolerated, effectively lowered plasma and blast cell cholesterol content and resulted in a highly encouraging response rate. Thus, we are testing this regimen in a group wide phase II study. We are
also considering the possibility of a trial in relapsed leukemia that involves blockade of VLA-4, again based on preclinical work conducted by Southwest Oncology Group investigators. (75)

**Previously Untreated Ph- Acute Lymphoblastic Leukemia (ALL)**

In adolescents and young adults, together with the Cancer and Acute Leukemia Group B, we are asking whether use of a pediatric-specific treatment regimen might result in improved outcome. This trial is based on several retrospective analyses showing that the outcome of adolescent patients (ages 15-21) with ALL appeared to be markedly better when treated on pediatric cooperative group studies rather than when treated on adult cooperative group trials. (50,76) For example, in one retrospective analysis, the results were 64% 6-year event free survival on the Children’s Cancer Study Group Trial compared to 39% on the Cancer and Acute Leukemia Group B study. (76) Whether these differing outcomes are the result of differences in the treatment regimens, in the patient population, or in how the protocols were applied is unclear, but will be addressed by adopting one specific arm of COG AALL0232 for our intergroup trial C10403.

For patients from 18 to 65 years of age with previously untreated Ph- ALL, we are asking in S0333 whether initial therapy with a double induction regimen is sufficiently effective to warrant further investigation, perhaps in comparison to standard approaches. We are, in addition, asking in this trial whether assays of minimal residual disease and gene expression can identify those patients likely to fail therapy who might therefore benefit from alternative approaches. The gene expression studies are supported by the previously mentioned SPECS U01 (CA 114762) and a Leukemia and Lymphoma Society Specialized Center Of Research (SCOR) grant to the University of New Mexico, the Fred Hutchinson Cancer Research Center, and the Southwest Oncology Group. This trial is based on the observation that with standard induction regimens of daunomycin, vincristine, prednisone, and pegylated asparaginase the large majority of adults with ALL achieve complete remission but the majority will recur with their disease. A regimen of mitoxantrone and high dose cytarabine is also highly active as induction therapy in this disease, (51) and therefore, we will address whether a double induction regimen is tolerable and sufficiently active to move forward to a phase III trial. Both the French Cooperative Group as well as the British Medical Research Council-Eastern Cooperative Oncology Group studies suggest that allogeneic hematopoietic cell transplantation improves long term disease free survival for patients with high risk lymphoblastic leukemia and so in our trial, patients with high risk disease with matched siblings are offered allogeneic transplantation. (57,77) Patients with intermediate risk disease also have a substantial chance of subsequent disease recurrence, but the risks of early allogeneic transplantation are also considerable. If by using detection of minimal residual disease, gene expression profiling, or other molecular studies, we were able to identify a group of patients at very high risk for recurrent disease, such patients would be appropriate candidates for a trial studying early allogeneic transplantation.

Accrual to S0333 should be completed by early 2009. Upon completion of S0333, our current plans are to join ECOG in their trial E2907, which is currently in development. E2907, as currently designed, will test the utility of the addition of a B-cell antibody during induction in patients with B-cell ALL, and test the utility of consolidation therapy with nelarabine in patients with T-cell ALL. During the conduct of E2907, we will be able to observe the long-term outcomes of S0333 and determine how to integrate these findings into future adult ALL trials.

**Previously Untreated Ph+ Acute Lymphoblastic Leukemia**

For patients age 50 or less with newly diagnosed Ph+ ALL, we are leading the intergroup trial S0805, a phase II study of a combination of hyper-CVAD and dasatinib with or without allogeneic hematopoietic cell transplantation. Because of the dismal prognosis of patients with Ph+ ALL, allogeneic transplantation has become the standard of care. However, recent pilot and phase II trials combining BCR-ABL specific tyrosine kinase inhibitors with conventional chemotherapy have reported encouraging results, although long-term follow-up is currently lacking. Accordingly, at a recent state-of-the-science meeting, the question of the comparative outcomes of contemporary chemotherapy regimens that include a tyrosine kinase inhibitor with
the outcome of allogeneic transplantation was given a very high priority (70). In S0805, a chemotherapy regimen of hyper-CVAD with dasatinib was chosen based on encouraging results from MD Anderson, which show that the regimen is very tolerable, and although the data are limited, appears to result in a deeper molecular remission than seen with hyper-CVAD plus imatinib. Patients with matched siblings and 10/10 matched unrelated donors will undergo transplantation and be treated post-transplant with dasatinib maintenance. This trial was developed in conjunction with ECOG, CALGB and the BMT/CTN, all of which will join in its conduct.

For patients over age 50 with newly diagnosed Ph+ ALL, we will be joining CALGB in the conduct of C10701. In this trial, remission induction consists of dasatinib plus dexamethasone. Patients who fail to clear marrow blasts with dasatinib plus dexamethasone alone subsequently receive additional therapy with vincristine, daunorubicin and cyclophosphamide. All patients who achieve a CR receive CNS prophylaxis and two years of maintenance therapy consisting of daily dasatinib along with monthly dexamethasone, vincristine, 6MP, and methotrexate and the addition every third month of daunomycin. The results of this phase II trial will be viewed as “interesting” if at least 40% of patients entered onto the study are alive and BCR-ABL negative at the completion of CNS prophylaxis. Like S0805, this trial was developed in conjunction with ECOG, SWOG and CALGB and all three groups are committed to participation.

Relapsed and Refractory Acute Lymphoblastic Leukemia

In patients with relapsed or refractory acute lymphoblastic leukemia we are testing the activity of newer agents in a series of phase II trials. The relative lack of progress in the treatment of ALL emphasizes the need for the identification and development of agents with activity in the disease. We completed an intergroup phase II study of 506u78 (nelarabine) in patients with relapsed refractory T cell disease (C19801) and found an encouraging 28% complete response rate in ALL and a 24% complete response rate in lymphoblastic lymphoma (13). Our current plans are to move this agent into the upfront treatment of patients with T-cell ALL as part of E2907. A study evaluating the efficacy of nelarabine in patients with relapsed refractory B cell ALL (S0010) was likewise completed but the results were less encouraging than seen with T cell disease. During the last grant period, we also completed accrual to S0530, a phase II trial of the combination of cytarabine and clofarabine in patients with relapse and refractory ALL. This study was based on encouraging results from the MD Anderson group combining cytarabine 1 gm/m²/day with clofarabine 40mg/m²/day both for 5 days, in patients with recurrent acute leukemia (both AML and ALL) (53). Although results of S0530, which closed August 1, 2008, are still pending, a preliminary analysis of currently evaluable patients suggests that the regimen may have sufficient activity to warrant further investigation. In an effort to further improve on the results of S0530, we will be conducting a second phase II trial (S0910) in a similar population of patients with recurrent B-cell ALL using the exact same regimen of cytarabine 1 gm/m²/day with clofarabine but with the addition of the anti-CD22 antibody epratuzumab. If these results appear encouraging, we would then consider a randomized trial comparing cytarabine and clofarabine +/- epratuzumab and also entertain strategies to bring this combination forward as consolidation therapy for patients with newly diagnosed disease.

Chronic Myeloid Leukemia

In patients with previously untreated chronic myeloid leukemia (CML) in chronic phase we are asking whether, when compared to standard imatinib therapy, treatment with a higher dose of imatinib or with the more potent tyrosine kinase inhibitor, dasatinib, increases the degree of tumor response measured by the decrease in BCR/ABL fusion transcripts measured by automated quantitative RT-PCR after 12 months of therapy.

A previously completed phase III trial comparing imatinib at 400mg/day to interferon plus cytarabine in newly diagnosed patients with chronic phase CML found a statistically significant improvement with imatinib in all parameters measured including complete hematologic response, major and complete cytogenetic response and freedom from disease progression (65). Based on these results, imatinib is now the non-transplant treatment of choice for patients with this disease. Despite these impressive results, only a rare patient treated
with imatinib in that trial achieved a molecular complete remission. When analyzed by reduction of BCR/ABL transcript levels using quantitative RT-PCR, 39% of patients achieved a 3-log reduction, but only 19% achieved a 4-log reduction, and 3% a 5-log reduction.\(^{(66)}\) Phase II data suggest that the rate of molecular response (>3-log reduction in BCR/ABL transcript level) may be higher for patients treated with imatinib at 800mg/qd than previously reported at 400mg/qd.\(^{(67)}\) Recently, a higher potency ABL inhibitor, dasatinib, has completed phase I and II trials in patients with imatinib resistant CML. Complete hematologic responses were seen in 87% of 40 evaluable patients with cytogenetic responses seen in 59%.\(^{(68)}\) Given the significant increase in potency seen with dasatinib and its activity in imatinib resistant cases, we are now evaluating dasatinib as upfront therapy for chronic phase CML. The long duration of response seen with standard dose imatinib makes the use of progression free survival as an endpoint for initial studies difficult. Published data suggest the rate of molecular response may serve as a surrogate likely to predict for clinical benefit.\(^{(66)}\) Thus, the endpoint of this three-armed study comparing standard dose imatinib to higher dose imatinib and to dasatinib, S0325, is the rate of molecular response measured by quantitative assessment of BCR/ABL transcripts after 12 months of therapy. In addition, in early 2008 the protocol was modified to extend study treatment and follow up to 5 years, which will provide valuable information regarding longer term outcomes.

**Chronic Lymphocytic Leukemia**

We plan to address three questions concerning the management of patients with previously untreated chronic lymphocytic leukemia (CLL). In patients with symptomatic disease, we are asking whether any of three novel regimens including fludarabine plus rituximab, fludarabine plus rituximab and cyclophosphamide, and fludarabine plus rituximab and lenalidomide are sufficiently active to warrant further study in a phase III randomized trial (C10404). In patients recently diagnosed with asymptomatic chronic lymphocytic leukemia, we will ask whether patients with high-risk disease benefit from immediate treatment or whether a watch and wait strategy is more appropriate (C10501). In elderly patients we will explore whether a regimen consisting only of monoclonal antibodies is sufficiently safe and effective to be studied further (E1908). And in patients with recurrent CLL, we will be testing the effectiveness of a combination of bendamustine plus rituximab (S0902). A previous intergroup trial, in which we participated, demonstrated that fludarabine is the most active single agent identified for the treatment of chronic lymphocytic leukemia, but results in relatively few complete remissions and essentially no cures.\(^{(78)}\) Two relatively limited phase II trials of concurrent or sequential fludarabine plus rituximab suggested improved response rates and improved duration of response compared to our previous experience with fludarabine alone.\(^{(17)}\) The intergroup study E2997 demonstrated in a prospective randomized trial that the combination of fludarabine plus cyclophosphamide resulted in significantly higher complete and overall response rates than seen with fludarabine alone.\(^{(19)}\) Uncontrolled studies from MD Anderson suggest even greater activity for a three drug combination of fludarabine, rituximab, and cyclophosphamide while very recent data suggest high activity of lenalidomide as a single agent in patients with fludarabine resistant disease.\(^{(58)}\) These findings have led us to design C10404, a randomized phase II trial with three arms: fludarabine plus rituximab, fludarabine plus rituximab and cyclophosphamide, and fludarabine plus rituximab and lenalidomide. The purpose of this study is to determine if any of these three novel regimens results in two-year progression free survival sufficiently superior to that previously seen with fludarabine alone to warrant further investigation. Each arm will be adequately sized to permit an estimate of the activity of the specific therapy in patients with low risk and high-risk disease, as determined by IgV\(_{H}\) gene status.

Prior to the availability of fludarabine, chlorambucil was the treatment of choice for CLL. Several trials of early intervention using chlorambucil versus treatment at the time of the development of symptoms were conducted based on the hypothesis that early intervention might diminish the total leukemic cell burden and thus delay the development of drug resistant, highly aggressive disease. Unfortunately, these studies failed to show a benefit for early intervention. The more recent availability of drug regimens with considerably higher response rates than chlorambucil, coupled with the ability to distinguish patients at high risk of disease progression versus those with low risk disease, leads us to readdress the question of whether early therapy with the active
combination of fludarabine plus rituximab might benefit patients at high risk for disease progression. A number of laboratory correlates will be examined in association with this trial (C10501).

The median age of patients with newly diagnosed CLL is about 70, and thus many patients with the disease present at an advanced age and with co-morbidities. While combined chemo-immunotherapy with fludarabine, rituximab and, perhaps, cyclophosphamide is highly active in younger patients, such regimens are poorly tolerated by many elderly patients. Thus, we plan to join ECOG in the further development and conduct of E1908, an intergroup study under development that will be testing two regimens consisting of antibodies only. The two regimens to be tested consist of alemtuzumab and rituximab, one with a standard dose of rituximab and one with a reduced dose. The rationale for testing a reduced dose of rituximab comes from a study by Williams et al. which suggests that when a threshold dose of rituximab is exceeded, recrudescent rituximab-opsonized cells are not cleared because of saturation of the mononuclear phagocytic system and instead the cells are shaved of the rituximab-CD20 complexes by other immune cells. (79) The hypothesis is that more frequent lower-dose rituximab may increase clearance of circulating CLL cells by preserving CD20 expression on CLL cells and thus improve the efficacy of treatment.

In patients with recurrent or refractory CLL, we will be testing the effectiveness of a combination of bendamustine plus rituximab. Bendamustine is an agent that appears to function both as an alkylator and as a purine analog. The drug has high activity as a single agent in the treatment of CLL, and in vitro the addition of rituximab and one with a reduced dose. The rationale for testing a reduced dose of rituximab comes from a study by Williams et al. which suggests that when a threshold dose of rituximab is exceeded, recrudescent rituximab-opsonized cells are not cleared because of saturation of the mononuclear phagocytic system and instead the cells are shaved of the rituximab-CD20 complexes by other immune cells. (79) The hypothesis is that more frequent lower-dose rituximab may increase clearance of circulating CLL cells by preserving CD20 expression on CLL cells and thus improve the efficacy of treatment.

Myelodysplasia (MDS)

For patients with low and intermediate risk MDS, we are asking in a randomized phase III trial whether erythropoietin improves the response rates seen with lenalidomide alone (E2905). In patients with higher risk disease, we will ask in a randomized phase II trial whether the addition of the histone deacetylase inhibitor MS275 to ten days of azacitidine appears sufficiently safe and effective to warrant further study (E1905).

Phase II trials have demonstrated that lenalidomide has activity in the treatment of myelodysplasia resulting in a 66% major erythroid response rate in patients with 5q31.1 deletions, and a 27% response rate in patients without the deletion. (36) Preclinical studies demonstrate that exposure of erythroid precursors to lenalidomide markedly increases their sensitivity to erythropoietin. In a 40 patient pilot study performed at the Moffitt Cancer Center, the addition of epoetin alpha to lenalidomide after failure to respond to the latter monotherapy, further increased the response to epoetin alpha by 28% in this population of previously erythropoietin refractory patients. Thus, E2905 will ask in a randomized manner whether, among patients with low and intermediate-1 risk myelodysplasia who are resistant to erythropoietin or unlikely to respond to erythropoietin alone, the combination of lenalidomide plus erythropoietin will result in a greater incidence of major erythroid responses than seen with lenalidomide alone. NCI RO1-funded translational laboratory investigations will investigate the integrity of the erythropoietin/STAT5 signaling pathway and ask whether lenalidomide’s capacity to relieve signal repression ex vivo in erythroid precursors or the isoform profile of the tyrosine phosphatase CD45 (a negative regulator of the erythropoietin receptor signal and target of lenalidomide) influence clinical response to treatment. MS-275 is a histone deacetylase inhibitor that, as a single agent has activity in recurrent myeloid leukemias. Based on the hypothesis that the combination of a histone deacetylase inhibitor with DNA methyltransferase inhibition should increase expression of previously methylated genes, a hypothesis based on in vitro studies, the combination of MS-275 with azacitidine has been explored in early phase I trials with encouraging results. Thus, we wish to further explore this combination of agents.

Problems and Solutions

At the time of the last competitive renewal, the major problem noted by the reviewers (and one which we were obviously aware of and directly discussed) was the lack of open studies and patient accrual. The lack of open
trials and patient accrual was due to a number of circumstances including premature closure of some trials and difficulty in activating others, but the result was that there were only 228 total accruals (86 to treatment protocols and 142 to cytogenetics and molecular biology protocols) in 2003. In contrast, in 2005 there were 843 accruals (407 treatment and 436 ancillary), and similarly high rates of accrual has been maintained every year since. This increased accrual is the result of having open studies asking important questions for the large majority of patients with leukemia. Thus, since the time of the last review we have successfully addressed this first major concern.

A second concern raised by the reviewers was the limited number of research themes being explored and the focus on themes developed at only a limited number of Southwest Oncology Group institutions, including that of the disease committee chair. As noted in the preceding narrative, research themes of the Leukemia Committee are now more diverse, and include ideas coming from a number of different academic laboratories and including a considerable number of novel therapeutic agents (clofarabine, tipifarnib, lenalidomide, MS-275, nelarabine, epratuzamab, pravastatin, bendamustine and others).

A final general concern raised by the reviewers was whether the structure of the Southwest Oncology Group Leukemia effort, with a small working group, and larger and separate Leukemia Translational Medicine Subcommittee and Leukemia Committee best served our goals. Particular concern was raised about whether non-working group members had an opportunity to present ideas and move them forward. In an effort to allow broader participation and avoid redundant efforts, beginning in the spring of 2005, we eliminated separate Leukemia Working Group, Leukemia Translational Medicine, and Leukemia Committee meetings and instead now have integrated half-day Leukemia/Leukemia Translational Medicine retreats associated with the Group Meetings every six months. In between meetings we have monthly leukemia committee conference calls. This allows full participation of all investigators and avoids undue duplication. One result of this is that Principal Investigators of many of the new protocols are in this role for the first time, including both experienced researchers such as Coutre, Druker, Lancet, and Erba, as well as more junior investigators such as Advani, Sekeres, Ravandi and Nand. Finally, we continue to work closely with the leadership of the other cooperative groups to ensure that the most important questions are being addressed in an efficient and timely manner.

PUBLICATIONS

SOUTHWEST ONCOLOGY GROUP

LEUKEMIA COMMITTEE
### LEUKEMIA MANUSCRIPTS PUBLISHED (2003)

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<td>Mevastatin can increase toxicity in primary AMLs exposed to standard therapeutic agents, but statin efficacy is not simply associated with ras hotspot mutations or overexpression. DL Stirewalt, FR Appelbaum, CL Willman, RA Zager, DE Banker. Leukemia Research 27:133-145, 2003. PMID: 12526919</td>
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### LEUKEMIA MANUSCRIPTS PUBLISHED (2004)


### LEUKEMIA ABSTRACTS PUBLISHED/PRESENTED (2004)

*9129  Microgranular variant (M3V) of acute promyelocytic leukemia (APL) does not have a worse prognosis than classical APL in the atra era: a report of 153 patients treated on Intergroup 0129 and pethema LPA96 and LPA99. MS Tallman, HT Kim, CA Schiffer, FR Appelbaum, JH Feusner, AK Ogden, L Shepherd, CL Willman, CD Bloomfield, JM Rowe, RA Larson, PH Wiemik, G Martin, C Rayon, J de la Serna, C Rivas, JD Gonzalez-San Miguel, G Deben, MA S anz. Blood 6/15/92 | 2/1/95
LEUKEMIA MANUSCRIPTS PUBLISHED (2005)


9108 Addition of rituximab to fludarabine may prolong progression free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated


LEUKEMIA ABSTRACTS PUBLISHED/PRESENTED (2005)


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LEUKEMIA ABSTRACTS PUBLISHED/PRESENTED (2006)


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<td>C19801</td>
<td>Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic lymphoblastic lymphoma: Cancer and Leukemia Group B study. 6/15/00 9/12/01</td>
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<td>Regularization strategies for hyperplane classifiers: application to cancer classification with gene</td>
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LEUKEMIA MANUSCRIPTS PUBLISHED (2008)


Multiple Very late antigen-4 (VLA-4) function of n/a n/a
myeloblasts correlates with improved overall survival for patients with acute myeloid leukemia. 
PS Becker, KJ Kopecky, AN Hanks, AN Wilks, JM Harlan, CL Willman, S Petersdorf, T Papayannopoulou, FR Appelbaum. 
Blood 2008 Oct 16 [Epub ahead of print] 
PMD: 18927435

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