

**SWOG S0703: A Phase II Trial of Azacitidine (NSC-102816) Plus Gemtuzumab  
Ozogamicin as Induction and Post-Remission Therapy in Patients of Age 60 and Older with  
Previously Untreated Non-M3 Acute Myeloid Leukemia**

*Fast Facts*

ELIGIBILITY CRITERIA

Initial Registration (Step # 1):

1. Patients must have a morphologically confirmed diagnosis of acute myeloid leukemia (AML) with classification other than WHO Acute Promyelocytic Leukemia (FAB M3), based on bone marrow examination performed within 14 days prior to registration. Note: This protocol uses the WHO diagnostic criteria for AML, not the FAB criteria (see Section 4.1). Patients with WHO Acute Promyelocytic Leukemia (FAB M3) or blastic transformation of chronic myelogenous leukemia are not eligible.
2. Patients must have a Zubrod performance status of 0-3 (see Section 10.7).
3. Patients with known hypersensitivity to azacitidine, mannitol, hydroxyurea or gemtuzumab ozogamicin are not eligible.
4. Patients must have reached their 60<sup>th</sup> birthday.
5. Patients must not have received prior systemic chemotherapy for acute leukemia with the exception of hydroxyurea. Administration of hydroxyurea to control high WBC count prior to registration is permitted.
6. Patients with a history of prior myelodysplastic syndrome (MDS) are eligible. However, prior treatment of MDS with AML induction-type chemotherapy or high dose chemotherapy with hematopoietic stem cell support is not allowed. Patients may have received hematopoietic growth factors, thalidomide, lenalidomide, arsenic trioxide, signal transduction inhibitors and low dose cytarabine for treatment of myelodysplastic syndrome. However, the dose of cytarabine must be < 100 mg/m<sup>2</sup>/day. Patients with previous therapy with azacitidine, decitabine and gemtuzumab ozogamicin (Mylotarg®) are not eligible. Patients must be off prior therapy for MDS at least 30 days prior to study registration and all toxicities must have resolved.
7. Patients must have a bilirubin  $\leq 2.0 \times$  Institutional Upper Limit of Normal (IULN) within 14 days prior to registration, unless the elevation is believed to be due to hepatic infiltration by AML. Hyperbilirubinemia due primarily to elevated unconjugated hyperbilirubinemia secondary to Gilbert's syndrome or hemolysis is allowed.
8. Patients must have SGOT (AST)  $\leq 2.0 \times$  IULN, or SGPT (ALT)  $\leq 2.0 \times$  IULN, or both within 14 days prior to registration, unless the elevation is believed to be due to hepatic infiltration by AML. If both tests are performed, then both values must be within the specified limits.
9. Patients must have a serum creatinine  $\leq 1.5 \times$  IULN within 14 days prior to registration.
10. Patients must have an adequate cardiac function with left ventricular ejection fraction of  $\geq 40\%$  (as determined by either MUGA or echocardiogram) and no clinical evidence of congestive heart failure within 56 days of registration.
11. Patients must be registered on SWOG-9007 ("Cytogenetic Studies in Leukemia Patients"). Collection of pretreatment marrow (or peripheral blood if the marrow is a dry tap) must be completed within 14 days prior to registration. If a specimen of the diagnostic marrow was not submitted (e.g., because the marrow exam was done elsewhere or the patient's participation in this study was not anticipated), a repeat marrow aspirate and biopsy is recommended; if this cannot be done, peripheral blood collected within 14 days prior to registration must be submitted. The marrow or peripheral blood specimen must be submitted to an approved Southwest Oncology Group Cytogenetics Laboratory for cytogenetic analysis as described in SWOG-9007. (Specimen submission for SWOG-9007 is also required at additional time points as detailed in Section 15.2.)
12. Patients must be registered on S9910 ("Leukemia Centralized Reference Laboratories and Tissue Repositories, Ancillary"). Collection of pretreatment blood and/or marrow specimens must be completed within 14 days prior to registration. If a marrow specimen is available, either from the diagnostic marrow or a repeat pre-registration marrow (see Section 5.1k), then it must be submitted along with a peripheral blood specimen; otherwise peripheral blood alone must be submitted. Specimens of marrow and/or peripheral blood must be submitted to the Southwest Oncology Group Leukemia Repository at the University of New Mexico for cellular and molecular studies as described

in S9910. (Specimen submission for S9910 is also required at additional time points as detailed in Section 15.3.)

13. Patients with central nervous involvement are excluded. If central nervous involvement is clinically suspected, it must be ruled out by a lumbar puncture.
14. Women of reproductive potential must have a pregnancy test within 28 days prior to registration. Patients must not be pregnant or nursing because of the teratogenic potential of the drugs used in this study. Women/men of reproductive potential must have agreed to use an effective contraceptive method.
15. Patients not known to be HIV+ must be tested for HIV infection (the human immunodeficiency virus) within 14 days prior to registration (see Section 2.0 for justification). Patients who are HIV+ may be eligible providing they meet all of the following additional criteria:
  - a. Patient must have no history of AIDS defining events.
  - b. CD4 cells  $\geq 500/\text{mm}^3$ .
  - c. Viral load of  $< 50$  copies HIV mRNA/ $\text{mm}^3$  if on cART or  $< 25,000$  copies HIV mRNA if not on cART.
  - d. No zidovudine or stavudine as part of cART.

Patients who are HIV+ and do not meet all of these criteria will not be eligible for this study.
16. No other prior malignancy is allowed except for the following: (a) adequately treated basal cell or squamous cell skin cancer; or (b) any diagnosis of malignancy made at least 2 years earlier, of which there is no clinically evident cancer, and for which the patient has completed all chemotherapy and radiotherapy at least 6 months prior to study registration. Prior treatment with AML induction-type chemotherapy is not allowed. Concurrent hormonal therapy is allowed.
17. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
18. At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board for this study has been entered into the data base.

#### **Pre-Study Parameters**

1. History and physical including height, weight, performance status, baseline abnormalities, (oral surgery evaluation as part of GCP)
2. Labs including CBC with differential, serum bilirubin, serum creatinine, AST, ALT, (glucose, Na, K, Mg, Ca as part of GCP), HIV test if patient is not known to be HIV+, pregnancy test for women of childbearing potential
3. Bone marrow exams
4. MUGA or Echo, (ECG and CXR as part of GCP)

**Treatment – see section 7.0 for details**

May be administered in the outpatient setting unless there are complications related to AML or co-morbid conditions that would make outpatient treatment unsafe.

Pre-Treatment: Allopurinol 300 mg orally once daily from the time of diagnosis until Day 14 of the first induction treatment (unless allergic to Allopurinol).

**Induction**

<b>Agent</b>	<b>Dose</b>	<b>Route</b>	<b>Days</b>	<b>Notes</b>
Hydroxurea	1500 mg or more twice daily	Oral	Before starting azacitidine	
Azacitidine	75 mg/m <sup>2</sup>	Sub-Q	1-7	Do not begin until WBC < 10,000/mcL
Gemtuzumab Ozogamicin	3 mg/m <sup>2</sup>	IV	8	Administer proper pre-mediations

**See protocol for complete treatment details**

Bone marrow aspirate and biopsy will be performed on Day 14. Should patient need second induction cycle, the dose and schedule will be the same.

**Consolidation**

<b>Agent</b>	<b>Dose</b>	<b>Route</b>	<b>Days</b>
Azacitidine	75 mg/m <sup>2</sup>	Sub-Q	1-7
Gemtuzumab Ozogamicin	3 mg/m <sup>2</sup>	IV	8

**See protocol for complete treatment details**

Bone marrow biopsy between days 28 and 42 after consolidation therapy to confirm remission.

**Maintenance**

<b>Agent</b>	<b>Dose</b>	<b>Route</b>	<b>Days</b>	<b>Notes</b>
Azacitidine	75 mg/m <sup>2</sup>	Sub-Q	1-7	Repeat every 28 days for 4 cycles

**See protocol for complete treatment details**

Bone marrow will be performed approximately 28 days after completion of fourth cycles of maintenance therapy.

Azacitidine provided.