**CTSU E2906 - Phase III Randomized Trial of Clofarabine as Induction and Post- Remission Therapy vs. Standard Daunorubicin & Cytarabine Induction and Intermediate Dose Cytarabine Post-Remission Therapy, Followed by Decitabine Maintenance vs. Observation in Newly-Diagnosed Acute Myeloid Leukemia in Older Adults (Age ≥ 60 Years)**

***Fast Facts***

**Clofarabine & Decitabine Provided**
**CTCAE v4.0**

1. Age ≥ 60 years
2. Sexually active males must be strongly advised to use an accepted and effective method of contraception.
3. AST, ALT, total bilirubin ≤ Grade 1
   **NOTE:** If total bilirubin is 2 to 3 mg/dL, but direct bilirubin is normal, then the patient will be considered eligible.
4. Patient must not have a concurrent active malignancy for which they are receiving treatment (other than MDS).
5. Patient must not have an active, uncontrolled infection.

Additional Induction Eligibility Criteria

1. Newly-diagnosed acute myeloid leukemia patients according to WHO classificationwho are considered candidates for intensive chemotherapy based upon examination of peripheral blood or bone marrow aspirate specimens or touch preparations of the bone marrow biopsy obtained within two weeks prior to randomization. A bone marrow aspirate is required for enrollment. However, on occasion there is discordance between percentage of myeloblasts on the differential of the peripheral blood or aspirate. The peripheral blood criteria are sufficient for diagnosis. Confirmatory immunophenotyping will be performed centrally.
   **NOTE:** Patients must be registered to E3903 (Ancillary Laboratory Protocol for the Collection of Diagnostic Material on Patients Considered for ECOG Treatment Trials for Leukemia or Related Hematologic Disorders) and must undergo eligibility testing for the study by multiparameter flow cytometry.
   **NOTE:** SWOG/CTSU institutions: E3903 is not open
2. ECOG performance status 0-3 (restricted to ECOG PS 0-2 if age ≥70 years)
3. Patients with APL confirmed either by the presence of t(15:17)(q22:q21) or PML/RARα transcripts will be excluded.
4. Patients must not have blastic transformation of chronic myelogenous leukemia.
5. Patients with secondary acute myeloid leukemia are eligible for enrollment onto the trial. Secondary AML is defined as AML that has developed in a person with a history of antecedent blood count abnormalities, or myelodysplastic syndrome (MDS), or a myeloproliferative disorder (excluding Chronic Myeloid Leukemia); or a history of prior chemotherapy or radiation therapy for a disease other than AML. **NOTE:** Prior therapy of MDS with decitabine, low-dose cytarabine, or azacitidine is excluded
6. Patients may not have received prior chemotherapy for AML with the exception of hydroxyurea for increased blast count or leukapheresis for leukocytosis.
   Patients must have a total serum bilirubin ≤ 1.5 X ULN (grade ≤ 1) and a serum creatinine ≤ 1 mg/dL. If total bilirubin is 2 to 3 mg/dL, but direct bilirubin is normal, then the patient will be considered eligible. Patients with a serum creatinine >1 are eligible if they have a calculated GFR of ≥ 60 mL/min (i.e. class I or class II chronic kidney disease) using the MDRD formula. The values must be obtained within 48 hours prior to randomization (for MDRD extended version with defaults to SI units please refer to http://mdrd.com). **NOTE:** Daily creatinine and MDRD formula are only for the 1st induction cycle.
7. Patients must have a cardiac ejection fraction of ≥ 45% or within institutional normal limits. A nuclear medicine gated blood pool examination is preferred. A 2-D ECHO scan is acceptable if a calculated ejection fraction is obtained and follow-up measurement of the cardiac ejection fraction will also be performed by echocardiography. Measurement of cardiac ejection fraction should be within two weeks prior to receiving treatment. **NOTE:** When a MUGA or echocardiogram cannot be obtained due to weekend or holiday, then patients may be enrolled provided there is no history of significant cardiovascular disease and a measurement of cardiac ejection fraction will be performed within 5 days of study enrollment.
8. Patients with suspected CNS involvement should undergo lumbar puncture. Those with documented CNS involvement will be excluded.

9. [Omitted as GRCOP will not be participating in E3903 ancillary study.]
10. Patients who have received previous treatment for AHD with 5-azacitidine, decitabine, or low dose cytarabine will be excluded.
11. Patients with known HIV infection are excluded due to the potential immunosuppressive effects of clofarabine and allogeneic transplantation.
12. HLA typing must be performed at registration for patients 60-69 years, if possible
13. [Omitted as GRCOP will not be participating in E3903, ancillary study.]

See sections 3.7, 3.8 and 3.9 of the Eligibility Criteria prior to enrolling patients in the Maintenance, Consolidation, or Transplant portions of the study.

**Pre-study Parameters for Induction**

1. History and physical including height and weight
2. HLA Typing for patients who are 60-69 and siblings who are eligible donors
3. Labs including CBC, serum creatinine, uric acid, bilirubin, ALT, AST, Alk Phos, LDH, Mg,
4. Bone marrow aspirate, biopsy and cytogenetics
5. MUGA or Echo, EKG
6. QOL, Geriatric Assessment

**Treatment**

**Please refer to the protocol for complete details. Pre-Registration will occur followed by specimen submission for centralized immunophenotyping to LTSL.**

The following is for patients not receiving a stem cell transplant:

**Step 1 – Induction** – Patients are randomized to Arm A or B.

Arm A

| | | | | | |
|---|---|---|---|---|---|
| Daunorubicin | 60 mg/m2 | IV | Days 1-3 | 1-2 cycles | → Patients with CR continue on to Arm C |
| Cytarabine | 100 mg/m2 | IV | Day 1-7 | 1-2 cycles | |

Arm B

| | | | | | |
|---|---|---|---|---|---|
| Clofarabine | 30 mg/m2 | IV | Days 1-5 | 1-2 cycles | → Patients with CR continue on to Arm D |

**Step 2 – Consolidation**

Arm C

| | | | | |
|---|---|---|---|---|
| Cytarabine | 1500 mg/m2 | IV | Q 12 hrs (age 60-69)<br>Q 24 hrs (age 70+) | 2 cycles |

Arm D

| | | | | |
|---|---|---|---|---|
| Clofarabine | 20 mg/m2 | IV | Days 1-5 | 2 cycles |

→ Patients with CR will be randomized to Arms E or F

**Step 3 – Maintenance** – Patients will randomized to Arm E or F

Arm E – Observation

Arm F

| | | | | |
|---|---|---|---|---|
| Decitabine | 20 mg/m2 | IV | Days 1-3 | Q 4 weeks for 12 months |

The following is for patients receiving a stem cell transplant:

**Step 1 – Induction** – Patients are randomized to Arm A or B.

Arm A

| | | | | |
|---|---|---|---|---|
| Daunorubicin | 60 mg/m2 | IV | Days 1-3 | 1-2 cycles |
| Cytarabine | 100 mg/m2 | IV | Day 1-7 | 1-2 cycles |

→ Patients with CR continue on to Arm C

Arm B

| | | | | |
|---|---|---|---|---|
| Clofarabine | 30 mg/m2 | IV | Days 1-5 | 1-2 cycles |

→ Patients with CR continue on to Arm D

**Step 2 – Consolidation**

Arm C

| | | | | |
|---|---|---|---|---|
| Cytarabine | 1500 mg/m2 | IV | Q 12 hrs (age 60-69)<br>Q 24 hrs (age 70+) | 2 cycles |

Arm D

| | | | | |
|---|---|---|---|---|
| Clofarabine | 20 mg/m2 | IV | Days 1-5 | 2 cycles |

→ Patients with CR continue on to receive SCT.