



Alliance A041701: A Randomized Phase II/III Study of Conventional Chemotherapy +/- Uproleselan (GMI-1271) in Older Adults with Acute Myeloid Leukemia Receiving Intensive Induction Chemotherapy

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For more than 40 years, 7+3 regimens (i.e., cytarabine infused for seven days with three days of an anthracycline) have been a standard for AML induction therapy [1]. Despite widespread use in older adults, 7+3 induction in these patients is associated with lower complete remission rates (50-60 percent), increased early mortality (up to 20 percent), and higher relapse rates compared with younger adults [2, 3]. Attempts at improving 7+3 through the addition of novel agents or intensification of post-remission therapy has largely failed to improve outcomes [4-6].

In Alliance A041701, investigators will test the addition of uproleselan to a standard daunorubicin/cytarabine regimen in older adults with previously untreated AML. Uproleselan blocks E-selectin, an adhesion molecule, which allows cells in the bone marrow to bind to and interact with leukemia cells and is important in protecting leukemia cells from the effects of chemotherapy. Blocking E-selectin with uproleselan is hypothesized to sensitize leukemia cells to the effect of chemotherapy. Furthermore, uproleselan may reduce the damage to mucosal lining of the gastrointestinal tract caused by chemotherapy by interfering with the binding of inflammatory cells to the gut. In a Phase 1/2 clinical trial, uproleselan was evaluated in both newly diagnosed elderly and relapsed/refractory patients with AML. In both populations, patients treated with uproleselan together with standard chemotherapy achieved better than expected remission rates and overall survival, as well as lower than expected induction-related mortality rates, as compared to historical controls.

The primary endpoint in the phase II portion of the study will be event-free survival (EFS) and in the phase III portion, overall survival.

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Primary

Phase II

- Compare the event-free survival (EFS) of daunorubicin, cytarabine plus uproleselan versus daunorubicin and cytarabine in subjects \geq age 60 with previously untreated acute myeloid leukemia.

Phase III

- Compare the overall survival (OS) of the daunorubicin, cytarabine plus uproleselan to daunorubicin and cytarabine in this patient population.

Secondary

- Determine the rates of complete remission (CR), complete remission with incomplete count recovery (CRi), complete remission with incomplete hematopoietic recovery (CRh) and cytogenetic complete remission (CCyR) for each chemotherapy regimen.
- Determine the overall survival (OS), and remission duration of patients for each chemotherapy regimen.
- Describe the frequency and severity of adverse events for patients for each chemotherapy regimen.
- Describe the interaction of pretreatment disease and patient characteristics including morphology, cytogenetics, molecular genetic features, WBC count and hemogram, and performance status on clinical outcomes.

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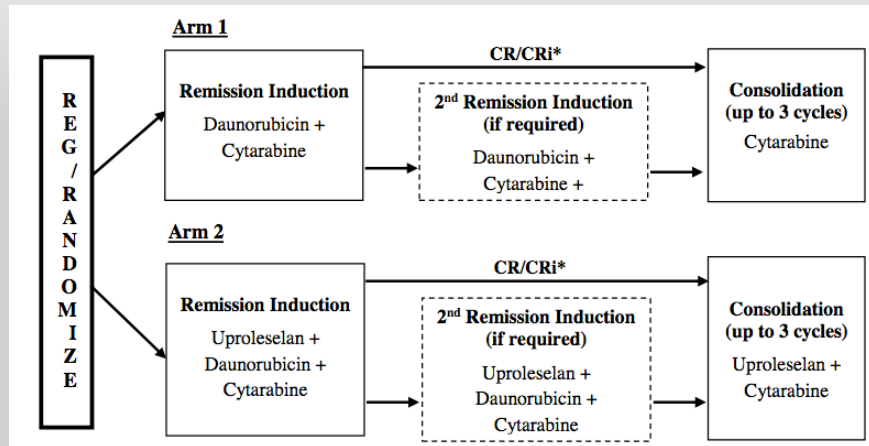
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*During Remission Induction, a bone marrow examination (aspirate and biopsy) on Day 14 (+3 days) is required in all patients. Patients with evidence of persistent leukemia on day 14 or a subsequent bone marrow biopsy will receive a second induction course. Patients who achieve either a CR or CRi are eligible to proceed to consolidation therapy.



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Treatment Plan

- Patients will be randomized into one of two groups.
- Those in Group 1 will receive the 7+3 regimen of cytarabine infused for seven days with three days of daunorubicin as part of remission induction. Patients with residual disease indicated by bone marrow examination receive a second induction. For consolidation, patients who achieve complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) will receive cytarabine intravenously for five days. Treatment will repeat every 28 days for up to 3 courses in the absence of disease progression or unacceptable toxicity.
- Those in Group 2 will receive the 7+3 regimen of cytarabine infused for seven days with three days of daunorubicin plus 10 days of uproleselan as part of remission induction. Patients with residual disease indicated by bone marrow examination receive a second induction. For consolidation, patients who achieve complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) will receive uproleselan for eight days. Treatment will repeat every 28 days for up to 3 courses in the absence of disease progression or unacceptable toxicity.
- There will be three sub-studies within the A041701 trial. Cytogenetics and Molecular Genetic Analysis are required for all patients. A041701-LC1 is an integrated substudy and patients are encouraged to participate.

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Eligibility Criteria

- Diagnosis of acute myeloid leukemia (AML) based on 2017 WHO criteria excluding acute promyelocytic leukemia with PML-RARA
- No activating mutation in Fms-like tyrosine kinase-3 (FLT3)
- No evidence of CNS involvement of AML
- No prior chemotherapy for myelodysplastic syndrome (MDS) or AML including hypomethylating agents or lenalidomide with the following exceptions:
 - Emergency leukapheresis
 - Hydroxyurea
 - Growth factor/cytokine support
 - All-trans retinoic acid (ATRA)
 - Single dose of intrathecal cytarabine and/or methotrexate for patients undergoing lumbar puncture to evaluate for CNS involvement
- Age \geq 60 years

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