Protocol Title: Randomized Phase II/III Trial of "Novel Therapeutics" Versus Azacitidine in Newly Diagnosed Patients with Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS), Age 60 or Older

LEAP: Intergroup Less-Intense AML Platform Trial

Target Population: Acute Myeloid Leukemia OR Adult Myelodysplastic Syndrome

Summary: This randomized phase II/III trial studies how well Azacitidine with or without Nivolumab or Midostaurin, or Decitabine and Cytarabine alone work in treating older patients with newly diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome.

REGISTRATION STEP 1-SPECIMEN SUBMISSION:
- Must be suspected to have previously untreated Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome with excess blasts-2 (MDS-EB-2).
- Must not be known to have AML in the central nervous system (CNS).
- Must have specimens submitted for FLT3 testing for randomization stratification.
- Patients who have received prior therapy with Midostaurin, any anti-PD-1 or anti-PD-L1 therapy, any DNA-methyltransferase inhibitor (including hypomethylating agents such as Azacitidine, Decitabine, or other investigational agent that acts by inhibiting DNA or RNA methylation) for any condition, or prior intensive cytotoxic therapy for MDS, are not eligible.
- Prior malignancy is allowed providing it does not require concurrent therapy.

REGISTRATION STEP 2-RANDOMIZATION:
- Must be registered to Step 2 no more than 42 Days after registration to Step 1 and no more than 42 Days after collection of specimens for FLT3 testing.
- Must have morphologically confirmed, previously untreated AML or MDS with excess blasts-2 (MDS-EB-2)
  - Patients with Acute Promyelocytic Leukemia (APL), Biphenotypic Leukemia, blastic transformation of Chronic Myelogenous Leukemia (CML or BCR/ABL), are not eligible
  - Must have disease present in the blood or bone marrow
  - All tests for establishing baseline disease status eligibility must be based on blood and/or bone marrow examination performed within 42 Days prior to randomization (registration Step 2)
- Must be deemed, in the judgment of the treating physician, to be ineligible for intensive induction therapy, or must have refused intensive induction therapy.
- Pretreatment cytogenetics must be performed on all patients.
- FLT3 results will be used for stratification purposes at the time of randomization.
- Prior treatment with hydroxyurea is permitted.
- Prior all-trans retinoic acid (ATRA) for suspected APL and prior intrathecal therapy are permitted, but must plan to be discontinued prior to initiating protocol therapy.
- Patients must be eligible for at least one of the currently active investigational treatment arms (S1612B or S1612C).

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For additional information: https://clinicaltrials.gov/ct2/show/NCT03092674