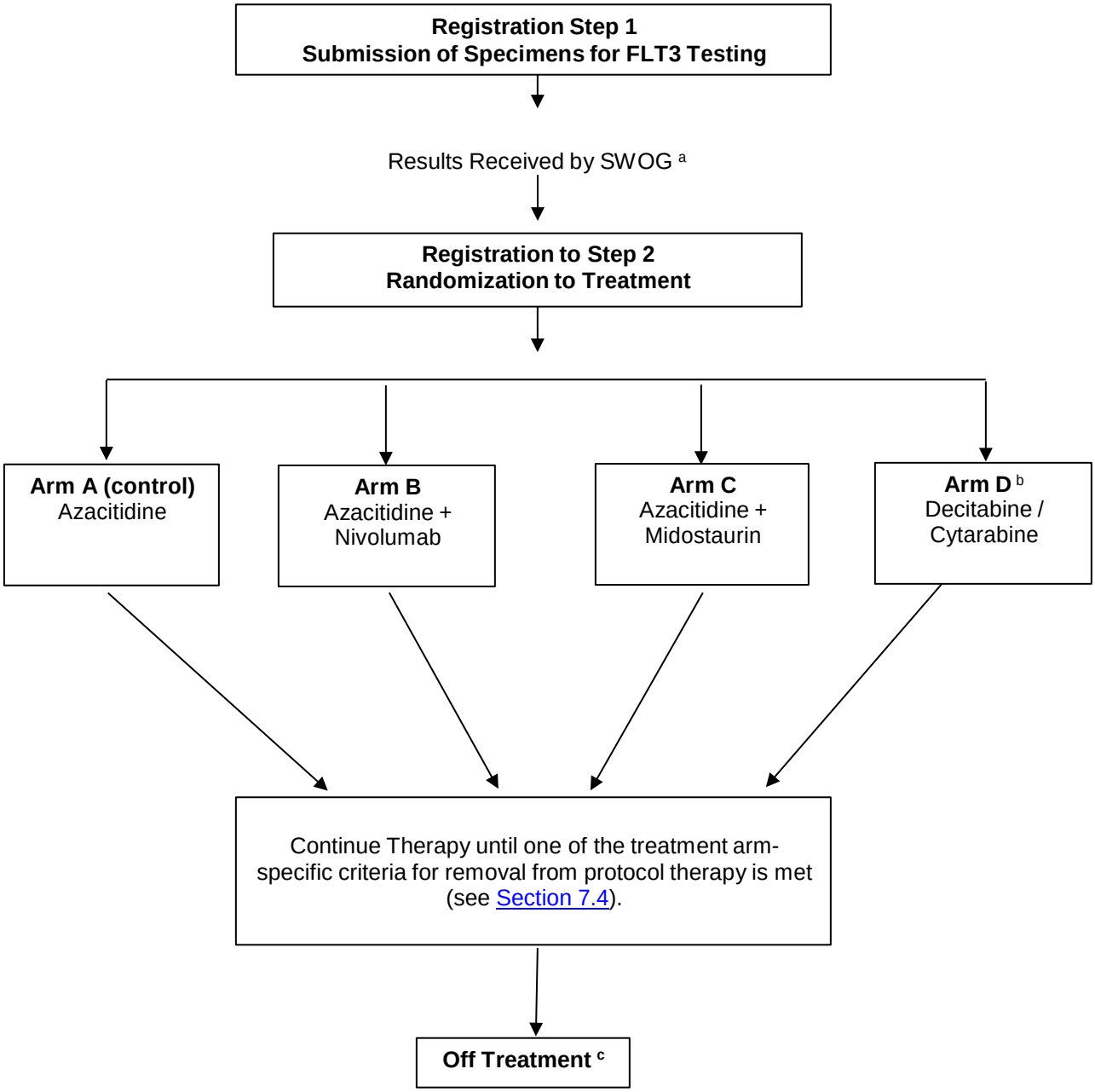
SCHEMA



a Notification that FLT3 specimens have been processed will be provided via e-mail when FLT3 results are available for stratification purposes; receipt of this e-mail is an eligibility requirement for Step 2 (randomization).
b Arm D will open to accrual when Arms B and C have met Phase II accrual and are temporarily closed for Phase II analysis.
c Patients will be followed for 5 years after randomization.

4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

For purposes of this study Acute Myeloid Leukemia (AML) is defined by ≥ 20% myeloblasts in the blood or marrow and MDS (EB-2) is defined by blast counts ≥ 10% and < 20% in marrow or 5%-19% blasts in peripheral blood (if marrow is not available). Please refer to the 2016 updated WHO Classification of Myeloid Neoplasms and Acute Leukemia for more detailed information. *(16)*

4.2 Staging Criteria

Staging criteria are not applicable to this protocol.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or leukemiaquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. **If Day 28, 42, or 56 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Registration Step 1 – Specimen Submission

Disease Related Criteria

a. Patients must be suspected to have previously untreated acute myelogenous leukemia (AML) or myelodysplastic syndrome with excess blasts-2 (MDS-EB-2).

b. Patients must be ≥ 60 years of age.

c. Patients must not be known to have AML in the CNS.

Specimen Submission Criteria

d. Patients must have specimens submitted for FLT3 testing for randomization stratification. Collection of pretreatment specimens must be completed within 1 day of registration to Step 1. Specimens must be submitted via the SWOG Specimen Tracking System as outlined in Section 15.2. FLT3 results will be used for stratification purposes at the time of randomization. E-mail notification of randomization assignment must be received prior to Step 2 registration.

e. Patients must be offered participation in specimen banking as outlined in Section 15.3. With patient consent, pretreatment specimens must be collected and submitted via the SWOG Specimen Tracking System as outlined in Section 15.3.

Prior/Concurrent Therapy Criteria

f. 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.

g. Patients must be able to swallow oral medications without crushing or chewing.

Clinical/Laboratory Criteria

h. Prior malignancy is allowed providing it does not require concurrent therapy. ***Exception***: Active hormonal therapy is allowed.

i. Patients must not be pregnant or nursing, due to the teratogenic potential of the drugs used on this study. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception also includes (but is not limited to) heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or vasectomy. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women must agree to avoid breast-feeding and women of child-bearing potential (WOCBP) must agree to use highly effective contraception while receiving study drug and for a period of 31 weeks after the last dose of study drug. Sexually-active men must agree to use a condom while receiving study drug and for 31 weeks after the last dose of study drug. Vasectomized men must also agree to use a condom to avoid delivering drug in the seminal fluid.

Regulatory Criteria

j. 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.

k. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 Registration Step 2 – Randomization

Patients 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.

Disease Related Criteria

a. Patients must have morphologically confirmed, previously untreated acute myeloid leukemia (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.

Patients must have disease present in the blood or bone marrow; patients with only extramedullary disease in the absence of bone marrow or blood involvement are not eligible.

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).

b. Patients must not be known to have AML in the CNS.

c. Patients must be deemed, in the judgment of the treating physician, to be ineligible for intensive induction therapy, or must have refused intensive induction therapy. Rationale for clinical determination or notation of patient decision must be made on the **S1612** Onstudy Form.

d. Pretreatment cytogenetics must be performed on all patients as outlined in Section 15.4. Collection of pretreatment specimens must be completed within 42 days prior to randomization (registration Step 2). Reports of the results must be submitted as outlined in Sections 14.4 and 15.4.

Specimen Submission Criteria

e. FLT3 results will be used for stratification purposes at the time of randomization. E-mail notification that FLT3 specimens have been processed must be received prior to randomization (registration Step 2).

Prior/Concurrent Therapy Criteria

f. Prior treatment with hydroxyurea is permitted (see Section 7.2 for information regarding use of hydroxyurea while on protocol therapy). Prior ATRA for suspected APL and prior intrathecal therapy are permitted, but must plan to be discontinued prior to initiating protocol therapy. Patients with signs/symptoms of hyperleukocytosis or WBC ≥ 50,000/mcL can be treated with leukapheresis prior to randomization (registration to Step 2).

g. Patients may have received non-intensive therapy for antecedent hematologic disorders, including lenalidomide. Patients may have received prior chemotherapy for prior cancers. These therapies must be discontinued at least 5 days prior to randomization (registration to Step 2).

h. Patients who are transfusion-dependent and patients receiving growth factor support are eligible. Patients must discontinue growth factor support prior to initiation of protocol therapy.

Clinical/Laboratory Criteria

i. The following tests must be performed within 14 days prior to randomization (registration to Step 2) to establish baseline values:

- Performance Status
- CBC/Differential/Platelets
- Creatinine Clearance (Cockcroft-Gault)*
- Total Bilirubin
- AST and ALT
- LDH
- Albumin
- Glucose
- Fibrinogen
- ECG (see Section 5.3b, Arm C)

$$*C_{CR} = \frac{(140\text{-age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

j. Patients must have complete history and physical examination within 28 days prior to randomization (registration to Step 2). History must include autoimmune disease status (to determine whether patient is eligible for Arm B, see Section 5.3a).

k. Patients must not have active infection (systemic bacterial, fungal, or viral infection) that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement despite appropriate antibiotics or other treatment).

Regulatory Criteria

l. Patients must be eligible for at least one of the currently active investigational treatment arms (**S1612B** or **S1612C**). If the patient does not meet eligibility criteria for at least one active investigational arm, then the patient is not eligible for **S1612**. See Section 5.3 for treatment arm specific eligibility criteria.

m. 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.

5.3 Treatment Arm Specific Eligibility Criteria for Active Treatment Arms

a. Arm B (Azacitidine + Nivolumab)

1. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

2. Additional Arm-Specific Laboratory/Treatment Criteria

- Patients must have AST and ALT ≤ 2.5 x IULN.
- Patients must have total bilirubin ≤ 1.5 x IULN.
- Patients must have baseline troponin test performed for eligibility; however, no associated values must be met in order for the patient to be eligible.

b. Arm C (Azacitidine + Midostaurin)

1. Additional Arm-Specific Laboratory/Treatment Criteria

- Patients must have total bilirubin ≤ 2.5 x IULN.
- Patients must have creatinine clearance ≤ 2.5 x IULN.
- Patients must have QTc interval < 500/msec (by Bazett's formula) on baseline ECG.
- Patients must not have any history of hypersensitivity to any drugs or metabolites of midostaurin.

c. All tests for establishing baseline values must be completed within 14 days prior to registration to Step 2 (randomization).