SWOG CANCER RESEARCH NETWORK

Version Date: November 16, 2021

TO: ALL NATIONAL CANCER CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: **S1612**, "A 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"

REVISION #4

Study Chair: Laura C. Michaelis, M.D.
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IRB Review Requirements
(√) No review required

Protocol Changes
(√) Other: Addition of translational medicine objective

REVISION #4

The primary purpose of this revision is to add translational medicine related to the use of duplex sequencing to determine measurable residual disease (MRD) in AML patients through the use of retrospective specimens collected on **S1612**.This work is funded through an approved BIQSFP proposal.

Protocol Changes

1. The version date of the protocol has been updated.
2. Table of Contents: The Table of Contents has been updated.
3. Section 1.4: This section has been added to include the additional translational medicine objective related to the use of duplex sequencing to determine measurable residual disease. A reference to Appendix 18.5 has been added.
4. Section 18.0: The new section for the translational medicine study has been added to the appendix list. The corresponding pages have been added to the appendix section.

Model Consent Form Changes

1. The version date has been updated. No other changes have been made to the consent.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL AND INFORMATION OFFICE

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SWOG

TITLE

A 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: **LE**SS-INTENSE **A**ML **P**LATFORM TRIAL
NCT#TBD

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AGENTS:

Commercially Available Agents:
Azacitidine (Vidaza®) (NSC-102816)
Cytarabine (AraC, Cytosine Arabinoside) (NSC-63878)
Decitabine (NSC-127716)

NCI Supplied Investigational Agents:
Midostaurin (NSC-656576)
Nivolumab (BMS-936558, MDX1106, Optivo®) (NSC-748726)

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NRG/NRG Oncology
SWOG/SWOG

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. <u>Other Tools and Reports</u>: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctslogon.aspx

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

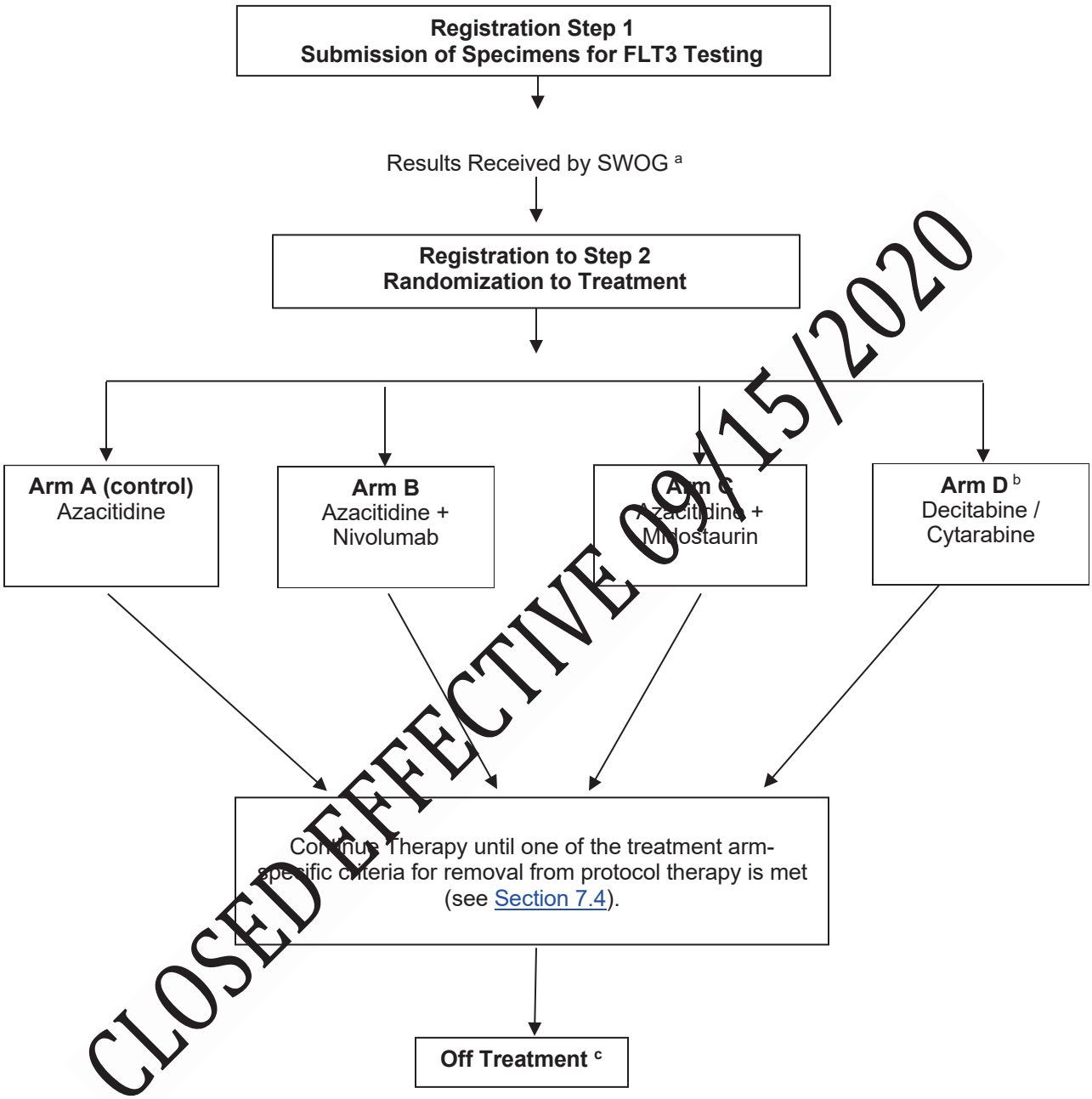
<u>For patient eligibility or data submission questions</u> contact the SWOG Data Operations Center by phone or e-mail:
206/652-2267
leukemiaquestion@crab.org

<u>For treatment or toxicity related questions</u> contact the appropriate Study Chair(s) by phone or e-mail. Study Chair information can be found on the title page.

<u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org.

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.

1.0 OBJECTIVES

1.1 Primary Objectives

a. Phase II Component: To select, based on overall survival, any or all of the "Novel Therapeutic" regimens for further testing against azacitidine in patients age 60 and older with newly diagnosed acute myeloid leukemia (AML) or myelodysplastic syndrome with excessive blasts-2 (MDS-EB-2).

b. Phase III Component: To compare overall survival of the "Novel Therapeutic" regimens selected in the Phase II portion of the trial to azacitidine in these patient populations.

1.2 Secondary Objectives

a. To estimate the frequency and severity of toxicities of the regimens in these patient populations.

b. To estimate response rates, event-free survival, and relapse-free survival for these regimens in these patient populations.

1.3 Additional Objectives

a. To investigate associations between cytogenetic and molecular abnormalities (including FLT3) and outcomes for each of the regimens in these patient populations.

b. To bank specimens for future correlative studies.

1.4 Additional Translational Medicine Objectives Related to Duplex Sequencing for Determining Measurable Residual Disease

a. To perform duplex sequencing (DS) and to test it against flow cytometry in patients treated under S0106 (see Appendix 18.5)

2.0 BACKGROUND

2.1 General

Acute myeloid leukemia (AML) primarily affects older adults, for whom outcomes have not substantially improved over the last several decades. Outside of clinical trials, this patient population commonly receives monotherapy with a DNA-methyltransferase inhibitor such as azacitidine or decitabine. However, this treatment option is associated with low response rates and only modest improvements in overall survival relative to supportive care alone. The need for new therapies is thus unquestioned. Since the modern era of drug development brings a rapidly increasing number of novel therapeutics into the clinic, timely identification of beneficial therapies has never been as important as today.

To this end, a randomized Phase II/III trial platform, similar to the United Kingdom's Medical Research Council/National Cancer Research Institute (MRC/NCRI) trial, will be conducted for this AML patient population. *(1)* The trial is not designed as a "pick-the-winner" trial, but is intended to serve as a versatile drug-testing study that allows a randomized comparison between a novel therapy and the control (but not between individual novel therapies), with a design allowing for accrual to one or more experimental arms at any given time, and the possibility of subsequent addition of new experimental arms and/or permanent closure of existing experimental arms based on interim results.

The initial control arm will be azacitidine monotherapy because of its widespread use and general acceptance in the United States as a treatment regimen for patients who are considered unfit for conventional intensive induction chemotherapy. If another regimen is determined to have improved overall survival (OS) compared to azacitidine, the study will be modified and the control arm replaced.

2.2 Arm A

The initial control arm will be azacitidine monotherapy. In a Phase II study of azacitidine (with or without valproic acid or all-transretinoic acid) in patients with AML (median age, 74 years), the rate of complete remission, CRi, and partial response was 33%, median response duration was 6.9 months, median OS was 9.4 months, and 2-year OS was 51%. *(2)*

In a study published in 2015, involving nearly 500 patients, azacitidine was compared with other conventional care regimens in a very similar population. Patients with AML older than age 65 years (median age, 75 years) with either de-novo or secondary AML (over 30% marrow blasts) were randomly assigned to receive either azacitidine 75 mg/m2/day for 7 days or one of three conventional care regimens: best supportive care, LDAC, or induction chemotherapy (i.e., daunorubicin and cytarabine). Of the 488 patients enrolled, 18% were assigned to the best supportive care, and 18% to the intensive chemotherapy arm. Thirty-five percent of patients had poor-risk cytogenetics and 32% had myelodysplasia-related changes. There was a trend for an improved median OS in the azacitidine-treated patients (10.4 vs. 6.5 months), but this did not achieve statistical significance. In a preplanned sensitivity analysis with censoring for any subsequent AML therapy, however, there did emerge a statistically significant improvement in OS (12.1 vs. 6.9 months) with a stratified HR 0.76 (log-rank P = 0.0190). *(3)*

Additional benefits of this regimen in the target population are a high-level of familiarity with administration and its ability to be given in the outpatient setting. If another regimen is determined to have improved OS compared to azacitidine, the study will be modified and the control arm replaced.

2.3 Arm B

Experimental Arm B will test the combination of nivolumab and azacitidine. There is increased expression of programmed death (PD)-1 receptor in approximately 40% of patients with AML, a finding that has been correlated with poor response to azacitidine (2). Its ligand, PD-L1, is also overexpressed in AML as it is in many solid tumor and other hematologic malignancies, allowing tumor immune evasion and growth (3). Nivolumab is a blocking anti-PD antibody that has been widely used in both solid tumors and lymphoid hematologic malignancies. Therefore, utilizing nivolumab may be a rational strategy to improving AML cells' sensitivity to azacitidine. The dosing scheme for the proposed trial is derived from an ongoing Phase I study of azacitidine 75 mg/m^2 daily for 7 days combined with nivolumab 3 mg/kg every 2 weeks (NCT02397720) that is being conducted at the MD Anderson Cancer Center (MDACC). Among approximately 20 patients treated to date, no unanticipated adverse events or dose-limiting toxicities have been observed. Autoimmune phenomena including pneumonitis, nephritis and skin rash have occurred – typically about three weeks after treatment initiation – but have responded to steroid therapy, and patients have been successfully re-challenged with nivolumab while remaining on a low dose of steroids. *(4)*

2.4 Arm C

Proposed (Experimental) Arm C will test the combination of azacitidine and midostaurin, a multi-targeted FMS-like tyrosine kinase 3 receptor (FLT3) kinase inhibitor. Mutations in the FLT3, either presenting as an internal tandem duplication (ITD) in the juxtamembrane domain or a point mutation in the activation loop of FLT3, are among the most common molecular abnormalities found in AML. In particular, for FLT3 ITD abnormalities, numerous studies have demonstrated adverse prognostic significance. In addition, approximately 80% of AML samples overexpress either FLT3 receptor or FLT3 ligand proteins, which can confer a proliferative growth signal and aggressive behavior even in the absence of FLT3 ITD mutations. *(5)* The FLT3 signaling pathway has therefore gained major attention as

target for small molecule inhibitors. Stone et al. recently reported the final results of a large, international, randomized study investigating the addition of midostaurin to conventional induction and post-remission chemotherapy and, subsequently, as maintenance in patients with newly diagnosed FLT3-mutated AML and found statistically significantly improved event-free and overall survival in the experimental arm (abstract #6 [plenary session], 2015 annual meeting of the American Society of Hematology). Of note, the magnitude in outcome improvement with midostaurin was similar in patients with FLT3 point mutations or ITD and independent of the ITD allelic burden, suggesting that at least part of the observed benefit was due to effects on kinases other than FLT3. This possibility is supported by recent studies demonstrating that kinase inhibitors targeting FLT3 can have efficacy in patients with wildtype FLT3. (*6,7)* Together, these observations provide the rationale for the inclusion of patients into this experimental arm regardless of the FLT3 mutational status. Of note, the combination of azacitidine and midostaurin has been tested in two small, single agent phase I studies. *(8,9)* Safety has been documented with azacitidine given in standard dosing combined with midostaurin administered at a dose of 50mg BID beginning on day 8 and continuing until day 21 for a 28-day cycle.

2.5 Arm D

Experimental Arm D is based on a study designed by Dr. Annie Im at the University of Pittsburgh. Preclinical studies suggest that "epigenetic priming" using decitabine followed by cytarabine increases the cytotoxicity of cytarabine, possibly due to the reactivation of genes that have been silenced in AML cells. The treatment scheme will include decitabine 20 mg/m^2 intravenously (IV) x 5 days followed by cytarabine 100 mg/m^2 continuous IV infusion x 5 days for 1-2 cycles of induction therapy. This is followed by maintenance with decitabine monotherapy in patients who achieve a complete or partial remission. Results from the pilot study of this trial show a 12-month overall survival of 48% (65% 1 year survival for those achieving CR/CRi, which was 67% of all the patients) with encouraging responses and minimal toxicities in patients over the age of 70 years and patients with secondary disease *(10)*.

Strict Biologic Rationale:

In attempts to improve the efficacy of hypomethylating agents in AML, combination strategies based on potential synergistic mechanisms of action have been explored. The combination of decitabine and cytarabine administered both concurrently and sequentially has been studied in experiments using human leukemic cell lines. It was shown that the sequential administration led to synergistic induction of cell death. *(11)*. Specifically, the cytotoxicity of cytarabine was increased when given after decitabine, and cytarabine preferentially killed hypomethylated cells. The conclusion was that decitabine-induced hypomethylation sensitizes leukemia cells to the cytotoxicity of cytarabine, with the hypothesis that this was likely due to reactivation of genes involved in the mechanism. There have been small case series and a Phase 1 study evaluating this strategy of "epigenetic priming" in AML, MDS, and ALL, showing promising efficacy without a signal of increased toxicity. *(12;13;14;15)*

There is rationale for sequential as opposed to concurrent administration with this combination. First, both agents are activated by the same enzyme (deoxycytidine kinase), and thus competition is avoided with sequential use. In addition, both agents are incorporated into DNA during the S-phase, again with potential for competition if administered concurrently. Also, cytarabine leads to cell cycle arrest, and decitabine is only active during the cell cycle, again limiting availability of the drug with concurrent administration. Finally, it is well understood that adequate hypomethylation and gene re-expression require time for multiple DNA replication cycles, and thus sequential administration allows for more time for adequate epigenetic priming.

NOTE: Experimental Arm D is planned for activation when experimental Arms B and C have met Phase II accrual and Arms B and C are temporarily closed while the data matures

for the Phase II analyses. This will allow for the trial to continue to register and randomize patients even while some arms are temporarily closed.

2.6 Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

2.7 Accrual Targets

The tables below present anticipated accrual based on prior SWOG studies **S0432**, **S0703**, and **S1117**. The tables present anticipated accrual for treatment arms A, B, and C, based on the Phase III total sample size (334 patients per treatment arm). Due to the dynamic nature of this trial, investigators expect to accrue more than 334 patients to the control arm, because only concurrently randomized eligible patients will be used in analyses.

DOMESTIC PLANNED ENROLLMENT REPORT (per treatment arm)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	15	25	5	0	45
Native Hawaiian or Other Pacific Islander	5	0	0	0	5
Black or African American	25	10	0	0	35
White	480	880	5	20	1385
More Than One Race	0	0	0	0	0
Total	525	915	10	20	1470

INTERNATIONAL (Including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	5	0	0	5
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	0	0	0	5
White	65	120	0	5	190
More Than One Race	0	0	0	0	0
Total	70	125	0	5	200

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study azacitidine, cytarabine, and decitabine are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, midostaurin and nivolumab are being provided by and IND held by the National Cancer Institute. The current versions of the Investigator Brochures for these agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via e-mail.

3.1 Azacitidine (Vidaza®) (NSC-102816)

a. PHARMACOLOGY

Mechanism of Action: Azacitidine is a pyrimidine nucleoside analog of cytidine. Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation *in vitro* does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

b. PHARMACOKINETICS

1. Absorption: The absorption of azacitidine after subcutaneous injection is rapid with the peak plasma concentration occurring in 0.5 hour. The bioavailability of subcutaneous azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve.

2. Distribution: Mean volume of distribution following IV dosing is 76 ± 26 L.

3. Metabolism: Multiple metabolites have been found with unspecified activity.

4. Elimination: Primary route of excretion is through the kidney at 85% of the total dose. The mean elimination half-life of both IV and subcutanous dosing is 4 hours. Less than 1% of drug is excreted through the feces.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific

exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

Frequency is provided based on 1470 patients. Below is the CAEPR for azacitidine.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, July 27, 2017[1]

Adverse Events with Possible Relationship to Azacitidine (CTCAE 4.0 Term) [n= 1470]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
	Heart failure		***Heart failure (Gr 2)***
	Pericardial effusion		***Pericardial effusion (Gr 2)***
	Sinus tachycardia		***Sinus tachycardia (Gr 2)***
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr 2)***
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 32)***
	Colitis		***Colitis (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Esophagitis		***Esophagitis (Gr 2)***
	Gastrointestinal hemorrhage[2]		
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
Fever			***Fever (Gr 3)***

Adverse Events with Possible Relationship to Azacitidine (CTCAE 4.0 Term) [n= 1470]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Injection site reaction			***Injection site reaction (Gr 2)***
	Malaise		
	Non-cardiac chest pain		
	Pain		
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
Infection[3]			***Infection[3] (Gr 4)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		***Bruising (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 4)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 4)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		***Acidosis (Gr 2)***
Anorexia			***Anorexia (Gr 2)***
	Hypokalemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***

Adverse Events with Possible Relationship to Azacitidine (CTCAE 4.0 Term) [n= 1470]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Generalized muscle weakness		***Generalized muscle weakness (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
	Somnolence		***Somnolence (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		
	Confusion		***Confusion (Gr 2)***
	Depression		
	Insomnia		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 4)***
	Epistaxis		***Epistaxis (Gr 2)***
	Pharyngolaryngeal pain		
	Postnasal drip		***Postnasal drip (Gr 2)***
	Respiratory, thoracic and mediastinal disorders - Other (abnormal breath sounds)[4]		***Respiratory, thoracic and mediastinal disorders - Other (abnormal breath sounds)[4] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Purpura		***Purpura (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***

Adverse Events with Possible Relationship to Azacitidine (CTCAE 4.0 Term) [n= 1470]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders - Other (skin lesion)		
VASCULAR DISORDERS			
	Hematoma		***Hematoma (Gr 2)***
	Hypotension		***Hypotension (Gr 3)***
	Vascular disorders - Other (pallor)		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3] Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[4] Abnormal breath sounds includes rales and rhonchi.

Adverse events reported on azacitidine trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that azacitidine caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (agranulocytosis); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (splenomegaly); Blood and lymphatic system disorders - Other (transfusion: platelets); Bone marrow hypocellular; Leukocytosis

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac disorders - Other (cardiac valve vegetation); Chest pain - cardiac; Myocardial infarction; Palpitations; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Ventricular fibrillation; Wolff-Parkinson-White syndrome

EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus

EYE DISORDERS - Eye disorders - Other (eye/conjunctival hemorrhage); Eye disorders - Other (retina hemorrhage); Papilledema; Uveitis

GASTROINTESTINAL DISORDERS - Abdominal distension; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal pain; Esophageal ulcer; Flatulence; Gastritis; Gastrointestinal disorders - Other (diverticulitis);

Gastrointestinal disorders - Other (inguinal hernia, obstructive); Gastrointestinal disorders - Other (intestinal ischemia); Gastrointestinal disorders - Other (intussusception); Hemorrhoids; Pancreatitis; Periodontal disease; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (general weakness); General disorders and administration site conditions - Other (Sweet's Syndrome); General disorders and administration site conditions - Other (systemic inflammatory response syndrome); Multi-organ failure; Sudden death NOS

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (bile duct stone); Hepatobiliary disorders - Other (hepatic cirrhosis)

IMMUNE SYSTEM DISORDERS - Autoimmune disorder

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Burn; Fall; Hip fracture; Injury, poisoning and procedural complications - Other (excoriation); Postoperative hemorrhage; Injury, poisoning and procedural complications - Other (transfusion reaction); Wound dehiscence

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (blood LDH increased); Investigations - Other (blood urea increased); Investigations - Other (cardiac murmur); Investigations - Other (coagulopathy); Investigations - Other (protein total decreased); Lipase increased; Serum amylase increased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (fluid overload); Metabolism and nutrition disorders - Other (hypovolemia); Metabolism and nutrition disorders - Other (low carbon dioxide); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (chondritis); Musculoskeletal and connective tissue disorder - Other (intervertebral disc protrusion); Musculoskeletal and connective tissue disorder - Other (muscle cramps); Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (colonic polyp, vaginal polyp); Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Dysesthesia; Dysgeusia; Hydrocephalus; Intracranial hemorrhage; Lethargy; Memory impairment; Nervous system disorders - Other (head injury); Paresthesia; Peripheral sensory neuropathy; Seizure; Sinus pain; Syncope

PSYCHIATRIC DISORDERS - Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Renal and urinary disorders - Other (calculus urinary); Renal calculi; Urinary frequency; Urinary retention; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Reproductive system and breast disorders - Other (benign prostatic hyperplasia); Uterine hemorrhage; Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Atelectasis; Hypoxia; Nasal congestion; Pleural effusion; Pleuritic pain;

Pneumonitis; Pneumothorax; Productive cough; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Respiratory, thoracic and mediastinal disorders - Other (pharyngeal erythema); Respiratory, thoracic and mediastinal disorders - Other (pneumonia legionella); Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (ecthyma gangrenosum); Skin and subcutaneous tissue disorders - Other (skin laceration); Skin and subcutaneous tissue disorders - Other (skin nodule); Skin induration; Urticaria

VASCULAR DISORDERS - Flushing; Hypertension; Thromboembolic event; Vascular disorders - Other (poor venous access); Vasculitis; Visceral arterial ischemia

Note: Azacitidine in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether azacitidine or its metabolites are excreted in human milk and administration of azacitidine is not recommended.

3. Drug Interactions: No formal clinical assessments of drug-drug interactions between azacitidine and other agents have been conducted. Refer to the current FDA-approved package insert.

d. DOSING & ADMINISTRATION

See Section 7.1a, Treatment Plan.

e. HOW SUPPLIED

Azacitidine is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.2 Cytarabine (AraC, Cytosine Arabinoside) (NSC-63878)

a. DESCRIPTION

AraC is chemically 4-amino-1-S-D-arabino-furanosyl-2(1H)-primidinone. AraC is metabolized to its active form, ara-CTP. The ara-CTP functions as an inhibitor of DNA polymerase. Ara-C exhibits cell phase specificity, killing cells undergoing DNA synthesis (S phase) and may also block cells from progressing to S phase from G1. Extensive chromosomal damage, including chromatid breaks, occurs. AraC appears to be most effective in tumors with high growth fraction.

b. TOXICOLOGY

Human Toxicology: Side effects of AraC include myelosuppression, nausea, vomiting, diarrhea, anorexia, anal ulceration, stomatitis, rash, headache, fever, myalgia, malaise, bone pain, chest pain, hepatic and renal dysfunction, and

alopecia. Central nervous system toxicity, i.e., significant cerebral and cerebellar dysfunction, progression to coma, has been seen with high doses. Severe cardiomyopathy has been reported with high dose AraC in combination with cyclophosphamide. Progressive ascending paralysis has occurred in two patients receiving IV and intrathecal AraC. Marked keratoconjunctivitis has also occurred with high doses.

The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever. Paraplegia and meningitis have been reported with intrathecal administration. AraC given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. If used intrathecally or if high dose therapy is used, do not use a diluent containing benzyl alcohol. AraC can cause fetal harm when administered to a pregnant woman, however, there are no adequate and well controlled studies in pregnant women.

c. PHARMACOLOGY

Kinetics: AraC is metabolized by deoxycytidine kinase and related kinases to nucleotide triphosphate, which is an active inhibitor of DNA polymerase. Deoxycytidine prevents or delays cytotoxic activity. The active form is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. The balance of kinase and deaminase levels appears to be an important factor in sensitivity/resistance of the cell to AraC. After IV injection, plasma disappearance of ara-C is biphasic. Initial half-life is 10 minutes, delayed half-life is 1 - 3 hours. After 24 hours, 80% is excreted in the urine as its inactive metabolite, AraI. After a single IV administration of AraC, levels in CSF are low. With intrathecal administration, half-life is 2 hours. There is little conversion to AraU because of low CSF levels of deaminase. Drug interaction of AraC has been reported with digoxin, gentamycin and fluorocytocine.

Formulation: AraC is supplied as a sterile powder in 100 mg and 500 mg vials for injection. AraC is also available in 1 and 2 gram vials. The drug should be reconstituted with sterile water for injection.

Storage and Stability: The sterile powder should be stored at room temperature 15° - 30°C (59° - 86°). The resulting solution has a stability of 48 hours if stored at ROOM TEMPERATURE. Do not use if even a slight haze develops. The reconstituted solution may be further diluted in 5% Dextrose or sodium chloride injection.

d. DOSING & ADMINISTRATION

See Section 7.1d, Treatment Plan.

e. HOW SUPPLIED

Supplier: AraC is commercially available and therefore should be purchased by a third party. This drug will NOT be supplied by the NCI.

Please refer to the package insert for complete information.

3.3 Decitabine (Dacogen®, 5-aza-2'-deoxycitidine) (NSC-)

a. PHARMACOLOGY

Mechanism of Action: After phosphorylation, decitabine is incorporated into DNA and inhibits DNA methyltransferase. Decitabine causes hypomethylation of DNA and subsequent cell death. The formation of covalent adducts between DNA

methyltransferase and decitabine may also contribute to cytotoxicity in rapidly dividing cells. Decitabine-induced hypomethylation may restore normal function of genes needed for cell growth.

b. PHARMACOKINETICS

1. Absorption: N/A

1. Distribution: Plasma protein binding of decitabine is less than 1%

2. Metabolism: The metabolism and route of elimination is unknown. One possible pathway appears to be deamination by cytidine deaminase, primarily found in the liver, granulocytes, intestinal epithelium, and whole blood.

3. Elimination: The mean half life was 0.62 hr in patients who received 15 mg/m^2 of decitabine IV over 3 hr and 0.54 hr in patients who received 20 mg/m^2 of decitabine IV over 1 hr.

c. ADVERSE EFFECTS

1. Possible Side Effects of Decitabine: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. *Frequency is provided based on 1832 patients.* Below is the CAEPR for Decitabine (5-aza-2'-deoxycytidine).
NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, January 4, 2017

Adverse Events with Possible Relationship to Decitabine (5-aza-2'-deoxycytidine) (CTCAE 4.0 Term) [n= 1832]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	Febrile neutropenia	
GASTROINTESTINAL DISORDERS		
Nausea	Abdominal pain	
	Anal mucositis	
	Constipation	
	Diarrhea	
	Mucositis oral	
	Rectal mucositis	
	Small intestinal mucositis	

Adverse Events with Possible Relationship to Decitabine (5-aza-2'-deoxycytidine) (CTCAE 4.0 Term) [n= 1832]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	Chills	
Fever	Edema limbs	
	Non-cardiac chest pain	
	Pain	
IMMUNE SYSTEM DISORDERS		
	Autoimmune disorder	
INFECTIONS AND INFESTATIONS		
Infection[2]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
INVESTIGATIONS		
Neutrophil count decreased	Alanine aminotransferase increased	
Platelet count decreased	Aspartate aminotransferase increased	
White blood cell decreased	Blood bilirubin increased	
	Creatinine increased	
	Lymphocyte count decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperglycemia	
	Hyperuricemia	
	Hypoalbuminemia	
	Hypocalcemia	
	Hypokalemia	
	Hypomagnesemia	
	Hyponatremia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	Intracranial hemorrhage
	Headache	
	Somnolence	

Adverse Events with Possible Relationship to Decitabine (5-aza-2'-deoxycytidine) (CTCAE 4.0 Term) [n= 1832]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
PSYCHIATRIC DISORDERS		
	Anxiety Insomnia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough Dyspnea Laryngeal mucositis Pharyngeal mucositis Pharyngolaryngeal pain Respiratory hemorrhage[3] Tracheal mucositis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia Pruritus Purpura Rash maculo-papular	
VASCULAR DISORDERS		
	Hematoma Phlebitis Vascular disorders - Other (hemorrhage with decreased platelets)	

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

2 Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

3 Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

4 Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

5 Gastrointestinal obstruction includes Colonic obstruction, Duodenal

obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

Adverse events reported on decitabine (5-aza-2'-deoxycytidine) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that decitabine (5-aza-2'-deoxycytidine) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (coagulaopathy); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (pancytopenia); Bone marrow hypocellular; Hemolysis; Leukocytosis; Spleen disorder
CARDIAC DISORDERS - Acute coronary syndromes; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac murmur); Cardiac disorders - Other (dilation atrial); Chest pain - cardiac; Heart failure; Myocardial infarction; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Ear pain; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (eye hemorrhage); Eye disorders - Other (eye swelling); Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal disorders - Other (oral mucosal blistering); Gastrointestinal hemorrhage[4]; Gastrointestinal obstruction[5]; Gastrointestinal pain; Hemorrhoids; Ileus; Oral pain; Periodontal disease; Proctitis; Rectal pain; Toothache; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; Infusion related reaction; Injection site reaction; Localized edema; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholethiasis); Hepatobiliary disorders - Other (hepatomegaly)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture; Injury, poisoning and procedural complications - Other (catheter site pain); Injury, poisoning and procedural complications - Other (hernia); Injury, poisoning and procedural complications - Other (procedural pain); Injury, poisoning and procedural complications - Other (stent occlusion)
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alkaline phosphatase increased; CPK increased; Cardiac troponin I increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Fibrinogen decreased; GGT increased; INR increased; Investigations - Other (blood bicarbonate decreased); Investigations - Other (blood bicarbonate increased); Investigations - Other (blood bilrubin decreased); Investigations - Other (blood chloride decreased); Investigations - Other (blood chloride increased); Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (blood urea increased); Investigations - Other (elevated ammonia); Investigations - Other (eosinophilia); Investigations - Other (platelet count increase); Investigations - Other (protein total decreased); Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration;

Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypoglycemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hyperphosphatemia); Metabolism and nutrition disorders - Other (malnutrition)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Aphonia; Ataxia; Cognitive disturbance; Dysesthesia; Dysgeusia; Ischemia cerebrovascular; Lethargy; Paresthesia; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Hematuria; Urinary fistula; Urinary frequency; Urinary retention; Urinary tract pain; Urinary urgency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchospasm; Hypoxia; Nasal congestion; Pleural effusion; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (breath sounds abnormal/decreased); Respiratory, thoracic and mediastinal disorders - Other (crepitations); Respiratory, thoracic and mediastinal disorders - Other (pulmonary congestion); Sinus disorder; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Erythema multiforme; Hyperhidrosis; Skin and subcutaneous tissue disorders - Other (hyperkeratosis); Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Skin hyperpigmentation; Skin hypopigmentation; Skin ulceration; Stevens-Johnson syndrome; Urticaria
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension ;Thromboembolic event; Vascular disorders - Other (aortic anyeurism); Vascular disorders - Other (catheter site hemorrhage); Vascular disorders - Other (circulatory collapse); Vascular disorders - Other (hemorrhage); Vascular disorders - Other (splenic infarct vs hemorrhage/rupture); Vascular disorders - Other (veno-occlusive disease); Vasculitis

Note: Decitabine (5-aza-2'-deoxycytidine) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Pregnancy and Lactation: Pregnancy category D. Decitabine can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of decitabine use in pregnant women. Adverse events were observed in animal reproduction studies. Based on the mechanism of action, decitabine may cause fetal harm if administered during pregnancy. Women of childbearing potential should be advised to use effective contraception to avoid pregnancy during treatment and for 1 month after treatment. In addition, males should be advised to avoid fathering a child while on decitabine therapy and for 2 months after treatment. Because of the potential for serious adverse reactions in the nursing infant, a decision should be made to discontinue nursing or the drug, taking into account the importance of treatment to the

mother.

2. Drug Interactions: Drug interaction studies with decitabine have not been conducted. According to in vitro studies, decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. In vitro studies also suggested that decitabine is not a substrate for cytochrome P450 enzymes.

d. DOSING & ADMINISTRATION

See Section 7.1d, Treatment Plan.

e. HOW SUPPLIED

Decitabine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.4 Midostaurin (NSC-656576)

a. PHARMACOLOGY

Mechanism of Action: Midostaurin is an inhibitor of several PKC isoforms of the tyrosine kinase of the VEGF receptor, and most importantly of the Class III tyrosine kinase FLT3 and KIT which are involved in hematopoiesis and play a key role in certain hematopoietic disorders. Midostaurin binds to the catalytic domain of these kinases and inhibits the mitogenic signaling of the respective growth factors in cells and results in growth arrest. The FLT3 signaling pathway is frequently ligand-independently activated in AML cells through point mutation in the catalytic domain of the receptor or through insertions in the juxta-membrane (JM) domain. Similarly, the KIT signaling pathway is frequently ligand-independently activated in neoplastic diseases including GIST and mast-cell disease.

b. PHARMACOKINETICS

1. Absorption: Midostaurin maximum concentrations (Tmax) occurred between 1-3 hours post dose in a fasted state. Midostaurin exposure increased 1.2-fold when co-administered with a standard meal and increased 1.6-fold when co-administered with a high-fat meal compared to when administered in a fasted state.

2. Distribution: The estimated mean volume of distribution (% coefficient of variation) is 95.2 L (31%). Midostaurin and its metabolites are distributed mostly in plasma in vitro. Midostaurin, CGP62221, and CGP52421 are greater than 99.8% bound to plasma protein in vitro.

3. Metabolism: Midostaurin is primarily metabolized by CYP3A4. CGP62221 and CPG52424 (mean +/- standard deviation) account for 28 +/- 2.7% and 38 +/- 6.6% of the total circulating radioactivity.

4. Elimination: Fecal excretion accounts for 95% of the recovered dose, with 91% of the recovered dose excreted as metabolites and 4% as unchanged midostaurin. 5% of the recovered dose was found in the urine. The geometric mean terminal half-life (% coefficient of variation) is 21 hours (19%) for midostaurin, 32 hours (31%) for CGP62221, and 482 hours (25%) for CGP52421.

c. ADVERSE EFFECTS

1. Adverse Effects:

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Midostaurin (NSC 656576)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 684 patients.* Below is the CAEPR for Midostaurin (NSC 656576).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, June 28, 2018[1]

Adverse Events with Possible Relationship to Midostaurin (CTCAE 5.0 Term) [n= 684]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		***Fatigue (Gr 3)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			

	Alanine aminotransferase increased	
	Lipase increased	
	Neutrophil count decreased	
	Platelet count decreased	***Platelet count decreased (Gr 4)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Back pain	
NERVOUS SYSTEM DISORDERS		
	Headache	***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATION SOC.

Adverse events reported on midostaurin trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that midostaurin caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiomegaly); Cardiac disorders - Other (ventricular dysfunction); Heart failure; Left ventricular systolic dysfunction; Mitral valve disease; Myocardial infarction; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Ear pain; Vertigo
ENDOCRINE DISORDERS – Endocrine disorders – Other (diabetes mellitus); Hyperthyroidism
EYE DISORDERS - Blurred vision; Dry eye; Keratitis; Periorbital edema
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Belching; Bloating; Colitis; Colonic hemorrhage; Dyspepsia; Dysphagia; Enterocolitis; Flatulence; Gastric hemorrhage; Gastric ulcer; Gastrointestinal disorders - Other (anorectal discomfort); Gastrointestinal disorders - Other (cramping); Gastrointestinal disorders - Other (salivary hypersecretion); Gingival pain; Ileus; Lower gastrointestinal hemorrhage; Mucositis oral; Oral hemorrhage; Oral pain; Pancreatitis; Rectal hemorrhage; Rectal pain; Small intestinal obstruction; Stomach pain; Typhlitis; Upper gastrointestinal hemorrhage; Visceral arterial ischemia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Disease progression; Edema face; Flu like symptoms; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders – Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatotoxicity)

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS – Fall
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Hemoglobin increased; Investigations - Other (blast cell count increased); Lymphocyte count decreased; Serum amylase increased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypercalcemia; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (osteomylitis and tenosynovitis L hand); Myalgia; Neck pain; Pain in extremity; Trismus
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Concentration impairment; Dizziness; Intracranial hemorrhage; Lethargy; Memory impairment; Nervous system disorders - Other (possible neuroleptic malignant syndrome); Peripheral sensory neuropathy; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC ISORDERS – Agitation; Anxiety; Confusion; Insomnia; Psychiatric disorders – Other (altered mental status)
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Hematuria; Renal and urinary disorders - Other (urinary bladder hemorrhage); Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS – Dysmenorrhea; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Cough; Epistaxis; Hiccups; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (bronchitis); Respiratory, thoracic and mediastinal disorders - Other (pulmonary nodules); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Sinus disorder
SKIN AND SUBCUTANEOUS TISSUE DISORDERS – Dry skin; Erythroderma; Hyperhidrosis; Purpura; Rash maculo-papular; Skin and subcutaneous tissue disorders – Other (toxic skin eruption); Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Midostaurin in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Midostaurin may cause fetal harm when administered to pregnant women. Women must avoid breast-feeding, and all women of childbearing potential will be required to employ a highly effective method of birth control, which is defined as a birth control which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. This has to be employed for the duration of the

study and for three months post study for women because of the long half-life (T1/2) of the metabolite, CGP52421 (>1 month). Acceptable methods of birth control include implants, injectables, and hormonal contraceptives, some IUDs (Intrauterine Devices), sexual abstinence or vasectomized partner.

Sexually active males must use a condom during intercourse while taking drug and for 5 months after stopping midostaurin medication to cover the half-life of the compound metabolites and spermatogenesis. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

3. Drug Interactions

Midostaurin is a substrate of CYP3A4. Midostaurin and its metabolites inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. Avoid concomitant administration of strong or moderate CYP3A4 inhibitors when possible. Midostaurin and its metabolites induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A in vitro. Avoid concomitant use as strong CYP3A4 inducers decrease exposure to midostaurin and its active metabolites. Midostaurin inhibits organic anion transporter polypeptide (OATP) 1A1 and induces multidrug resistant protein (MRP) 1 in vitro.

Due to potential drug interactions, a complete patient medication list, including midostaurin, should be screened prior to initiation of and during treatment with midostaurin. See Section 8.0 Toxicities to be Monitored and Dosage Modifications. In addition, refer to the current FDA-approved package insert.

d. DOSING & ADMINISTRATION

See Section 7.1c, Treatment Plan.

e. HOW SUPPLIED

1. Appearance: Midostaurin is currently prepared as 25 mg soft gelatin capsule.

Midostaurin will be supplied as soft gelatin capsules to be taken orally. The study drug will be packed in child resistant blisters. The drug should be stored in the blister pack until use and no further preparation of the study drug is needed. Upon opening a blister pack, patients may notice a pungent odor. The odor is due to ethyl thioglycolate that forms when ethanol in the capsules interacts with the thermostabilizer in the foil. The capsules are not affected, and the odor will dissipate. Each capsule contains 25 mg of midostaurin.

2. Distributor: Midostaurin is supplied by Novartis and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 25 mg soft gelatin capsules individually sealed in a blister card. Each blister card contains 8 capsules and each box contains 8 blister cards for a total of 64 capsules.

f. STORAGE, PREPARATION & STABILITY

Storage condition: Soft gelatin capsule: Do not store above 25°C.

g. DRUG ORDERING & ACCOUNTABILITY

See Section 3.6.

3.5 Nivolumab (BMS-936558, MDX1106, Optivo®) (NSC-748726)

a. PHARMACOLOGY

Mechanism of Action: Nivolumab is human monoclonal antibody which targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

b. PHARMACOKINETICS

1. Distribution: Nivolumab has linear pharmacokinetics after single and multiple dosing within the range 0.1 mg/kg to 10 mg/kg. The volume distribution (Vd) is 8L.

2. Elimination: Clearance is independent of dose in the range 0.1 mg/kg to 10 mg/kg. The total body clearance is 9.5 mL/hr, and the elimination half-life of is approximately 26.7 days. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2069 patients. Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, June 18, 2018[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hypophysitis[3]		
	Hyperthyroidism[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Autoimmune disorder[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased [3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased [3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased [3]		***Blood bilirubin increased[3] (Gr 2)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Rhabdomyolysis	
		Myositis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradi-culitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous disorders -Other (bullous pemphigoid)	
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3] BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4] Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5] Cytokine release syndrome may manifest as hemophagocytic lymphohistocytosis with accompanying fever and pancytopenia.

[6] Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell trancplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT.

[7] Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia;

Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation:

Pregnancy: Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of reproductive potential should use highly-effective contraception during therapy and for at least 23 weeks after treatment has been discontinued. Men receiving nivolumab and who are sexually active with women of child bearing potential should adhere to contraception for a period of 31 weeks after the last dose of nivolumab.

Lactation: It is not known if nivolumab is excreted into breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends women to discontinue breastfeeding during treatment with nivolumab.

3. Drug Interactions: Nivolumab is not expected to have any effect on cytochrome P450 or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions.

d. DOSING & ADMINISTRATION

See Section 7.1b, Treatment Plan

Nivolumab is to be administered as a 30-60-minute IV infusion through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter. DO NOT administer as IV push or bolus injection.

e. HOW SUPPLIED

1. Nivolumab is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), pH 6.0.

2. Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with butyl rubber stoppers and aluminum seals.

f. STORAGE, PREPARATION & STABILITY

1. Vials of Nivolumab must be stored at 2°-8°C (36°-46°F) and protected from light, freezing and shaking. If a storage temperature excursion is identified, promptly return nivolumab to 2°-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

2. Nivolumab can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP to drug concentrations no less than 0.35 mg/mL. Note: Mix gently. Do not shake.

3. Compatibility: Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

4. Stability: Shelf life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

g. DRUG ORDERING & ACCOUNTABILITY

See Section 3.6.

3.6 Drug Ordering and Accountability for NCI-Supplied Agents

a. Drug Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (S1612) must be used for ordering all CTEP

supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or e-mail PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Patients must be randomized to a treatment arm in OPEN prior to ordering agent. Agent orders may be expedited overnight Monday-Thursday when sites provide expedited courier information. Initiation of treatment must occur no more than seven working days after patient randomization.

b. Drug Handling and Accountability

1. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

2. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

c. Drug return and/or disposition instruction

1. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

2. Drug Expiration: Shelf life stability studies of the intact vials of nivolumab are on-going. Shelf life stability studies of the midostaurin capsules are on-going.

3. Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

d. Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account:

https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB IB Coordinator: IBCoordinator@mail.nih.gov
- PMB e-mail: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

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).

6.1 STRATIFICATION FACTORS

A dynamic allocation scheme will be used to balance the randomization (registration Step 2) on the following stratification factors within arms between which a patient is eligible to be randomized *(17)*:

1. PS (PS 0-1 versus PS 2-4).

2. FLT3-ITD status (wild type FLT3 versus mutated FLT3-ITD versus non-evaluable) based on central laboratory results.

   Baseline blast percentage (MDS-EB-2 [< 20%] versus AML [20% or higher]).

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact the Study Chairs listed for the specific treatment arm in which the patient is enrolled. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

Treatment may be administered on an inpatient or outpatient basis, at the discretion of the treating physician.

7.1 Treatment

a. Arm A: Azacitidine (Control)

For treatment or dose modification questions, please contact Dr. Laura Michaelis and Dr. Roland Walter (**S1612A@swog.org**).

Azacitidine may be administered on either a 7-day continuous schedule or a 7-day interrupted schedule (e.g. 5-2-2: azacitidine administered Days 1-5 followed by 2 days of no treatment followed by 2 days of azacitidine administration). Any interrupted schedule is allowable, providing the entire 7-day dose is given within a total of no more than 12 calendar days. The Study Chair(s) should be contacted if there are questions regarding the dosing schedule.

Patients should continue treatment on protocol as long as they are deriving clinical benefit in the opinion of the treating physician for up to 5 years from randomization, or until one of the criteria in Section 7.4 has been met.

Agent	Dose	Route	Day	Schedule*
Azacitidine	75 mg/m^2/day	SC or IV	1-7#	Every 28 days

* One cycle = 28 days.
# Azacitidine may be administered continuously for 7 days (e.g., Days 1-7) or with breaks (e.g., Days 1-5 and 8-9) within no more than 12 calendar days.

Patients receiving intravenous azacitidine may be switched to subcutaneous administration if venous access becomes difficult. Patients receiving subcutaneous azacitidine may be switched to intravenous, at the discretion of the treating physician. Treatment interruptions should be documented on the appropriate treatment summary form.

For dose delays > 45 days, the Study Chairs should be contacted to discuss whether treatment should be continued.

b. Arm B: Azacitidine + Nivolumab

For treatment or dose modification questions, please contact Dr. Sarit Assouline and Dr. Annette Hay (**S1612B@swog.org**).

Patients should continue treatment on protocol as long as they are deriving clinical benefit in the opinion of the treating physician for up to 5 years from randomization, or until one of the criteria in Section 7.4 has been met.

Before starting treatment, patients should receive baseline ECHO, if clinically indicated.

Agent	Dose	Route	Day	Schedule*
Azacitidine	75 mg/m^2/day	SC or IV	1-7#	Every 28 days
Nivolumab	3 mg/kg	IV over 30-60 mins	1 and 15	Every 28 days

* One cycle = 28 days.
# Azacitidine may be administered continuously for 7 days (e.g., Days 1-7) or with breaks (e.g., Days 1-5 and 8-9) within no more than 12 calendar days.

Patients receiving intravenous azacitidine may be switched to subcutaneous administration if venous access becomes difficult. Patients receiving subcutaneous azacitidine may be switched to intravenous, at the discretion of the treating physician. Treatment interruptions should be documented on the appropriate treatment summary form.

c. Arm C: Azacitidine + Midostaurin

For treatment or dose modification questions, please contact Dr. Laura Michaelis and Dr. Roland Walter (**S1612C@swog.org**).

Patients should continue treatment on protocol as long as they are deriving clinical benefit in the opinion of the treating physician for up to 5 years from randomization, or until one of the criteria in Section 7.4 has been met.

Agent	Dose	Route	Day	Schedule*
Azacitidine	75 mg/m^2/day	SC or IV	1-7#	Every 28 days
Midostaurin	50 mg (twice/day)^	orally	8-21	Every 28 days

* One cycle = 28 days.
# Azacitidine may be administered continuously for 7 days (e.g., Days 1-7) or with breaks (e.g., Days 1-5 and 8-9) within 12 calendar days.
^ Administered with water following meals. Doses are to be separated by 12 hours. Total daily intake will be 4 capsules (2 capsules of 25 mg each every 12 hours).

Patients receiving intravenous azacitidine may be switched to subcutaneous administration if venous access becomes difficult. Patients receiving subcutaneous azacitidine may be switched to intravenous, at the discretion of the treating physician. Treatment interruptions should be documented on the appropriate treatment summary form.

d. Arm D: Decitabine + Cytarabine

For treatment or dose modification questions, please contact Dr. Annie Im and Dr. James Foran (**S1612D@swog.org**).

1. Pre-Medication

Patients will receive ondansetron 8 mg PO 30 minutes prior to each dose of decitabine and 30 minutes prior to start of administration of each 24-hour bag of cytarabine.

Patients may receive dexamethasone 4 mg PO prior to cytarabine administration.

2. Treatment

a. Induction

Agent	Dose	Route	Day	Schedule*
Decitabine	20mg/m^2/day	IV (over 2 hrs)	1-5	Every 28 days
Cytarabine	100 mg/m^2	IV (cont)	6-11	Every 28 days

* One cycle = 28 days.

Patients may receive up to 2 cycles of Induction treatment. Patients will continue to Maintenance treatment if the patient is deemed stable, at the discretion of the treating physician. Patients not deriving clinical benefit in the opinion of the treating physician within 2 cycles of Induction treatment will be removed from protocol therapy (see Section 7.4).

b. Maintenance

Agent	Dose	Route	Day	Schedule*
Decitabine	20mg/m^2/day	IV (over 2 hrs)	1-5	Every 28 days

* One cycle = 28 days.

During Maintenance, patients experiencing treatment delay > 8 weeks with delay in count recovery should be assessed for relapse, with bone marrow examination at the discretion of the treating physician. Patients should continue Maintenance therapy as long as they are deriving clinical benefit in the opinion of the treating physician for up to 5 years from randomization, or until one of the criteria in Section 7.4 is met.

7.2 Concomitant Therapies

a. Supportive Therapies

1. Antiemetic and antidiarrheal medications will be used per standard practices. It is recommended that serotonin (5-HT3) receptor antagonists should be administered approximately 30 minutes prior to subcutaneous administration of azacitidine.

2. Antibiotic prophylaxis: Patients may receive prophylaxis directed against gram-negative gastrointestinal infections, candidiasis, and/or herpes simplex virus, per individual institutional practices.

3. See Section 7.3c regarding use of growth factors.

4. Blood product transfusions and related supportive care should be administered per local institutional standards.

b. Prohibited Therapies

Prohibited concomitant therapies include investigational agents, androgens, supraphysiologic doses of corticosteroids, erythropoietin, or chemotherapeutic agents active against MDS.

c. Concomitant Therapy

1. Concomitant Anti-Infective Prophylaxis and Treatment

It is highly recommended to avoid concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, posaconazole). The suggested antifungal regimens from a drug metabolism perspective are described below:

Prophylaxis
a. Fluconazole (moderate CYP3A4 inhibitor)
b. Micafungin

If a patient requires active treatment for a fungal or mold infection and the only treatment options is an azole that is a strong CYP3A4 inhibitor, then the suggested agents from a drug metabolism and safety perspective include:

Treatment

c. Isavuconazole
or
d. Voriconazole
e. Posaconazole

2. CYP Metabolization

a. General

Isavuconazole is a moderate inhibitor of CYP34A. The other two are both strong CYP3A4 inhibitors and will likely increase midostaurin concentrations. With intra-patient variability with regard to CYP3A4 inhibition and midostaurin pharmacokinetics, the suggested approach is to avoid strong CYP3A4 inhibitors unless there are no treatment alternatives. If CYP24A inhibitors are used, monitor patients closely for toxicity. Elderly patients may be particularly prone to toxicities. See Appendix 18.2, Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4.)

b. Arm C (Azacitidine + Midostaurin)

Patients in Arm C should have non-essential medications that are strong CYP3A inhibitors discontinued (see Appendix 18.4). If these medications must be continued, then Patients in Arm C should be monitored for adverse reactions with medications that are strong CYP3A inhibitors, especially during the first week of midostaurin treatment, according to the package insert. Information regarding concurrent administration of midostaurin and CYP3A inhibitors must be documented (dates of administration, the specific CYP3A inhibitor(s), duration of concurrent administration) and the adverse event (onset of event, severity, duration, and details regarding PK [as available]) must be captured in the comments section of the **S1612** Adverse Events Form.

7.3 General Supportive Care Guidelines

a. Patients receiving hydroxyurea prior to randomization must discontinue hydroxyurea within 14 days of initiation of protocol therapy. It is recommended that leukocytosis be controlled, in the judgment of the treating physician, prior to initiation of protocol therapy.

b. Supportive care will be given to each patient per local institutional guidelines, unless otherwise specified for a specific treatment arm.

c. White Blood Cell Growth Factors

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines (http://jco.ascopubs.org/content/24/19/3187.full) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

7.4 Criteria for Removal from Protocol Treatment

a. Unacceptable toxicity.

b. The patients may withdraw from the study at any time for any reason.

c. The treating physician may remove the patient for treatment failure, progressive disease, or relapse, at their discretion; however, it is not required that patients be removed from protocol therapy for disease progression or relapse, if, in the opinion of the treating physician, remaining on protocol therapy is in the patient's best interest. Information regarding disease progression and relapse will be reported in the **S1612** Disease Assessment Form, per the requirements in Section 14.0.

d. Patient becomes pregnant.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.6 Follow-Up Period

All patients will be followed until death or 5 years after randomization (registration to Step 2), whichever occurs first. Patients not registered to Step 2 will not be followed beyond documentation of reason for not being randomized (see Section 14.4b)

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Toxicity Monitoring and Dose Modification Information

a. General Considerations

1. Dose modifications will be based on the toxicity requiring the largest dose reduction.

2. Dose modifications may be made for individual drugs if, in the judgment of the treating physician, the toxicity is attributable to one drug.

3. For Arm C (azacitidine + midostaurin), if patients must permanently discontinue treatment with azacitidine, the patient must be removed from protocol therapy; continued monotherapy with midostaurin will not be permitted. For all other arms with multiple drugs, if either drug must be permanently discontinued, the patient may remain on protocol treatment with the remaining drug, at the discretion of the treating physician.

b. Azacitidine (Arm A, Arm B, and Arm C)

1. General Considerations

a. Both subcutaneous and IV administered azacitidine will follow the same dose reduction schema.

b. Each treatment cycle will be 28 calendar days, regardless of whether treatment is held during a cycle. As needed, delays are allowed between the end of one treatment cycle and the start of the next treatment cycle.

c. Dose Re-Escalation

If a patient has undergone dose reduction because of an adverse event, and the adverse event does not recur during the subsequent cycle, the dose may be re-escalated to the dose administered when the event occurred. Patients may have their dose re-escalated because initial adverse events commonly associated with azacitidine may not occur as patients begin to respond to therapy, and continued dose reduction may impact long-term efficacy. However, if the dose of azacitidine is modified during the course of the study and the investigator believes benefit is demonstrated at a dose lower than 75 mg/m2, that dose may be maintained during subsequent cycles that are given (unless toxicity develops).

2. Toxicity Monitoring and Dose Modification Information

a. Dose Adjustments: General

Both subcutaneous and IV administered azacitidine will follow the same dose reduction schema.

No dose adjustments will be allowed during Cycle 1.

After Cycle 1, azacitidine dose should be adjusted per the guidelines below for non-hematologic toxicities. After cycle 2, azacitidine dose should be adjusted per the guidelines below for hematologic toxicities

b. Dose Adjustment Based on Hematology Laboratory Values

Hematologic toxicity, including anemia, neutropenia, and thrombocytopenia, can occur with azacitidine therapy, particularly during the first 2 cycles. Complete blood counts should be performed per local institutional standards.

If a patient, prior to protocol treatment, does not have reduced blood counts, (i.e. WBC is > 3.0 x 109, ANC > 1.5 x 109/L, and platelets > 75.0 x 109/L), then the platelet count and ANC should recover prior to the next cycle. Recovery is defined as an increase of cell line(s) where hematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (i.e., blood count at recovery ≥ nadir count + (0.5 x [baseline count – nadir count]). If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been

achieved within 14 days, the dose should be reduced per the table below. Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops).

	Nadir Counts	**% Dose in the next Cycle if recovery[1] is not achieved in next 14 days**
ANC (x 10^9/L)	Platelets (x 10^9/L)	
≤ 1.0	≤ 50.0	50%
> 1.0	> 50.0	100%

1 Recovery = counts ≥ Nadir Count + (0.5 x [baseline count – nadir count]).

For subjects with reduced baseline blood counts (i.e., WBC count < 3.0 x 109/L or ANC < 1.5 x 109/L or platelets < 75.0 x 109/L) prior to treatment, if the decrease in WBC/ANC/platelets from that prior to treatment is < 50%, or > 50% but with an improvement in a different cell line, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC/ANC/platelets is > 50% from that prior to treatment, with no improvement in cell line differentiation, the next cycle of azacitidine therapy should be delayed until the platelet count and the ANC have recovered, as defined above. If recovery is achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced per the following table:

Bone Marrow Cellularity	**% Dose in the next Cycle if recovery[1] is not achieved in next 14 days**	
	Recovery ≤ 21 days	Recovery > 21 days
15-50%	100%	50%
< 15%	100%	33%

1 Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count]).

Following dose modifications, the cycle duration should return to 28 days. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops).

c. Dose Adjustment Based on Renal Function:

If creatinine clearance is > 1.5 x IULN, the azacitidine dose may be reduced by up to 50%. Renal abnormalities ranging from elevated creatinine clearance to renal failure and death were reported rarely in subjects treated with intravenous azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalemia (serum potassium < 3 mmol/L) developed in 5 subjects with

chronic myelogenous leukemia (CML) treated with azacitidine and etoposide.

If unexplained reductions in serum bicarbonate (< 20 mmol/L) occur, the dose should be reduced by 50% on the next course. Similarly, if unexplained elevations in creatinine clearance or blood urea nitrogen (BUN) to ≥ 2-fold above baseline values and above ULN occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle. The reduced dose should be maintained during subsequent cycles that are given (unless toxicity develops).

d. Additional Azacitidine Dose Modification

Toxicity	Modification
Grade 3 or 4 Non-Hematologic Toxicity (possibly, probably, or definitely related to azacitidine)	Hold azacitidine until toxicity resolves to ≤ Grade 2 (or baseline). If toxicity does not resolve within 3 weeks, remove patient from protocol treatment.
Creatinine Clearance > 1.5 x IULN	Reduce azacitidine dose by 50% until resolved to ≤ 1.5 x IULN, then resume full dose.

c. Nivolumab (Arm B)

1. General Considerations

c. Patients experiencing ≤ Grade 2 adverse event related to nivolumab may receive pre-medications at the discretion of the treating investigator, per local institutional guidelines.

d. No dose modifications of nivolumab will be allowed, except as outlined below. Adverse events will be managed per the guidelines below. See Section 8.2c.4c for dose modification and management for cardiomyopathy myocarditis.

e. Dose interruptions will be based on adverse event severity on the day of planned therapy.

f. Treatment with nivolumab may be delayed for up to 56 days. During this time, patients may continue to receive azacitidine at the discretion of the treating physician/local investigator.

2. Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents such as nivolumab are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno- oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: (I-O).

See Section 8.2g for toxicity management and follow-up algorithms for endocrinopathy, gastrointestinal, hepatic, neurological, pulmonary, renal,

and skin adverse events. Note: Per the link below, Prednisone PO, or other equipotent steroid, may be utilized in place of methylprednisolone IV.

3. Concomitant Corticosteroid Treatment for Management of Immune-Related Reactions

For guidance on allowable concomitant corticosteroid treatment and tapering of steroids, please see:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_Full.pdf.

4. Dose Delays

a. In addition to the AEs identified in the tables below, nivolumab dose should be delayed for any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

b. Patients requiring a delay of > 8 weeks, or who experience immune-related toxicity with inability to decrease with prednisone < 10mg PO daily, must permanently discontinue nivolumab.

Patients who received systemic corticosteroids for management of any drug-related immunologic toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone 10 mg/day

1. Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed.

Assessments should continue as per protocol even if dosing is delayed.

d. Dose Modification and Management

1. Dose Modification and Management for Cardiomyopathy Myocarditis

- Drug will be held for Grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for Grade 3 or 4 cardiac dysfunction and Grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

Cardiac *	Management/Next Dose for BMS-936558 (Nivolumab) Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider

Cardiac *	Management/Next Dose for BMS-936558 (Nivolumab) Cardiac Toxicities
	cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit, if appropriate). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
* *Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin.* ** *Patients with evidence of myositis without myocarditis may be treated according as "other event".* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

2. Dose Modification and Management for Other Adverse Events

Treatment-related Adverse Event	Grade of Event	Management/Next Dose for *Nivolumab*
Nephritis	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 2.
	Grade 3	Hold nivolumab until < Grade 2.
	Grade 4	Off protocol therapy.
Diarrhea (immune-related enterocolitis)	≤ Grade 1	No change.
	Grade 2	Hold until < Grade 2
	Grade 3	Hold nivolumab until < Grade 2.
	Grade 4	Off protocol therapy.
Endocrinopathy (hypophysitis, adrenal insufficiency, Type 1 diabetes	≤ Grade 1	No change.
	Grade 2	Hold until < Grade 2.
	Grade 3	Hold until < Grade 2.
	Grade 4	Off protocol therapy.
	(Note: Asymptomatic hypothyroidism does not require dose modification.)	
Neuropathy (new, motor, sensory, encephalitis)	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 2.
	Grade 3	Off protocol therapy.
	Grade 4	Off protocol therapy.
Drug-related uveitis, eye pain, or blurred vision	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 1. If Grade 2 event does not respond to topical therapy and does not improved to Grade 1 within the re-treatment period, patient must go off protocol therapy.
	Grade 3	Off protocol therapy.
	Grade 4	Off protocol therapy.
	≤ Grade 1	No change.

Treatment-related Adverse Event	Grade of Event	Management/Next Dose for *Nivolumab*
Skin drug-related AE	Grade 2	No change.
	Grade 3	Hold nivolumab until < Grade 3.
	Grade 4	Off protocol therapy.
Pneumo-nitis, broncho-spasm, pulmonary toxicity or interstitial lung disease	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until event resolves to baseline.
	Grade 3	Off protocol therapy.
	Grade 4	Off protocol therapy.
	Above does not include infusion reactions. See also: Appendix 18.3.	
Other, Non-skin, drug-related adverse events	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 2.
	Grade 3	Hold nivolumab until < Grade 2.
	Grade 4	Off protocol therapy.
	Above does not include infusion/ hypersensitivity reactions, laboratory abnormalities or AEs otherwise indicated in this table. [1] In event of recurrence of same Grade 3 adverse reaction, patient should be removed from protocol therapy.	
Infusion / hypersen-sitivity reactions (manifestation may include: fever, chills, rigors, headache, rash, pruritus, arthralgia, hypoten-sion, hyperten-sion, broncho-spasm)	≤ Grade 1	Remain at bedside and monitor subject until recovery from symptoms. Following prophylactic premedication is recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/ paracetamol 325 to 1000 mg at least 30 minutes before additional administration. No change in dose for future administration.
	Grade 2	• Stop infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid (e.g. hydrocortisone 50-100mg) and/or bronchodilator therapy may also be administered as appropriate if reaction is severe or patient not responding to diphenhydramine or acetaminophen.

Treatment-related Adverse Event	Grade of Event	Management/Next Dose for *Nivolumab*
		• If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. • Monitor subject closely. If symptoms recur, then no further drug will be administered at that visit. • Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). • For future infusions, following prophylactic pre-medications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen /paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used if premedication with diphenhydramine and acetaminophen is not sufficient to prevent infusion reactions.
Infusion / hypersen-sitivity reactions (manifest-ation may include: fever, chills, rigors, headache, rash, pruritus, arthralgia, hypoten-sion, hypertension, broncho-spasm)	Grade 3 or Grade 4	• Immediately discontinue infusion. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV

Treatment-related Adverse Event	Grade of Event	Management/Next Dose for *Nivolumab*
		with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. • Permanently discontinue drug. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms. • In case of late-occurring hypersensitivity symptoms, symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).
	All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Arm B Study Chairs at: S1612B@swog.org AND reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines. Note: Treatment guidelines may be modified based upon local SOPs, as appropriate.	
Thrombocytopenia*	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 2.
	Grade 3	Hold nivolumab until < Grade 2. Grade 3 drug-related thrombocytopenia > 7 days and associated with bleeding requires discontinuation from protocol.
	Grade 4	Off protocol therapy.
Neutropenia*	≤ Grade 1	No change.
	Grade 2	Hold nivolumab until < Grade 2.
	Grade 3	Hold nivolumab until < Grade 2.
	Grade 4	Off protocol therapy.
Abnormal liver function (AST/ALT, Total bilirubin, immune-related hepatitis)	≤ Grade 1	No change.
	Grade 2	No change
	Grade 3	Hold nivolumab until < Grade 3. If AST/ALT>8x ULN or bilirubin >5x ULN, off protocol therapy
	Grade 4	Off protocol therapy.
Amylase or lipase, associated with GI symptoms	≤ Grade 1	No change.
	Grade 2	No change.
	Grade 3	No change if asymptomatic. If GI symptoms, hold nivolumab

Treatment-related Adverse Event	Grade of Event	Management/Next Dose for *Nivolumab*
		until asymptomatic and < Grade 3.
	Grade 4	Off protocol therapy. Note: Isolated Grade 4 abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset, do **not** require permanent discontinuation. [1]
	[1] Contact the Arm B Study Chairs at: S1612B@swog.org for consultation on Grade 4 amylase or lipase abnormalities.	

* If due to nivolumab toxicity; if due to leukemia infiltration, discuss with Study Chair before reducing/holding drug.

e. Midostaurin (Arm C)

Missed doses of midostaurin will not be made up.

Toxicity	Modification
Hematologic Toxicity	
Grade 4 Neutropenia	Cycle 1: No modifications Subsequent cycles: Hold midostaurin until ANC ≥ 1,000/mcL, then resume midostaurin at full dose. If neutropenia persists for more than 2 weeks, discontinue midostaurin.
Pulmonary Toxicity	
≥ Grade 3 pulmonary infiltrate	Hold midostaurin until infiltrates resolve to ≤ Grade 1, then resume midostaurin at full dose.
Cardiac Toxicity	
QTc interval > 450 msec and ≤ 470 msec (by Bazett's formula)	Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication which may prolong QTc interval. No dose reduction.
QTc interval > 470 msec and ≤ 500 msec (by Bazett's formula)	Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication which may prolong QTc interval. Decrease midostaurin to 50 mg once daily until QTc improves to ≤ 470 msec, then resume midostaurin at full dose.
QTc interval > 500 msec (by Bazett's formula)	Immediately hold midostaurin. Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication which may prolong QTc interval. If QTc interval improves to between > 470 msec and ≤ 500 msec, restart midostaurin at 50 mg once daily Once QTc interval improves to ≤ 470 msec, resume midostaurin at full dose.

Toxicity	Modification
Hematologic Toxicity	
	If QTc remains > 470 for more than 3 weeks, hold midostaurin until QTc interval improves to ≤ 470, then resume midostaurin at full dose.
Other Non-Hematologic Toxicity	
Grade 3 or Grade 4 non-hematologic toxicity, at least possibly related to midostaurin	Hold midostaurin until toxicity resumes to ≤ Grade 1, then resume midostaurin at full dose.

f. Cytarabine and Decitabine (Arm D)

Dose Modifications and Delays

INDUCTION	
Creatinine increase > 2.0 x baseline or ULN (whichever is higher) (unless there is a reversible etiology, e.g., no count recovery)	Delay treatment until resolved to baseline or IULN (whichever is higher), then restart treatment; no dose reduction required
ALT, AST, or total bilirubin > 5 x ULN	Delay treatment until resolved to IULN, then restart treatment; no dose reduction required
MAINTENANCE	
At the start of a new cycle, any Grade 3 or 4 non-hematologic toxicity that is possibly, probably, or definitely related to decitabine	Delay treatment until resolved to ≤ Grade 2 or baseline (whichever is higher), then restart treatment; no dose reduction is required

Dose modifications outside of those outlined above will be allowed, but should first be discussed with and approved by the Study Chairs.

g. Management Algorithms for Immuno-Oncology Agents

Immuno-oncology agents such as nivolumab are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: (I-O):

1. Pulmonary Adverse Event Management

Toxicity	Toxicity Management and Follow-up
Pulmonary (i.e., Pneumonitis)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Evaluate with imaging and pulmonary consultation.
Grade 1	– Monitor for symptoms every 2-3 days – Consider Pulmonary and Infectious Disease (ID) consults – Re-image at least every 3 weeks If worsens: – Treat as Grade 2 or 3-4

Toxicity	Toxicity Management and Follow-up
Pulmonary (i.e., Pneumonitis)	
Grade 2	– Consider Pulmonary and ID consults – Monitor symptoms daily, consider hospitalization – 1.0 mg/kg/day methylprednisolone IV or oral equivalent – Consider bronchoscopy, lung biopsy – Re-image every 1-3 days If improves: – When symptoms return to near baseline, taper steroids over at least 1 month, consider prophylactic antibiotics If not improving after 2 weeks or worsening: – Treat as Grade 3-4
≥ Grade 3	– Hospitalize – Pulmonary and ID consults – 2-4 mg/kg/day methylprednisolone IV or oral equivalent – Add prophylactic antibiotics for opportunistic infections – Consider bronchoscopy, lung biopsy If improves to baseline: – Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: – Add additional immunosuppression (e.g., infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

2. Gastrointestinal Adverse Event Management

Toxicity	Toxicity Management and Follow-up
Gastrointestinal (i.e., Diarrhea/Colitis)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.
Grade 1	– Close monitoring for worsening symptoms. – Educate patient to report worsening immediately – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. If worsens: – Treat as Grade 2 or 3/4
Grade 2	– Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. If persists > 5-7 days or recurs: – 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent – When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic

Toxicity	Toxicity Management and Follow-up
Gastrointestinal (i.e., Diarrhea/Colitis)	
	antibiotics for opportunistic infections If worsens or persists > 3-5 days with oral steroids: – Treat as Grade 3/4
≥ Grade 3	– 1.0 to 2.0 mg/kg/day methylprednisolone IV or oral equivalent – Add prophylactic antibiotics for opportunistic infections – Consider lower endoscopy If improves: – Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: – Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

3. Hepatic Adverse Event Management

Toxicity	Toxicity Management
Hepatic (Elevated LFTs – ALT, AST, Total Bilirubin)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Consider imaging for obstruction.
Grade 1	– Continue liver function tests (LFT) monitoring per protocol If worsens: – Treat as Grade 2 or 3/4
Grade 2	– Increase frequency of LFT monitoring to every 3 days until resolution to baseline. Resume routine monitoring If elevations persist > 5-7 days or worsen: – 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections
≥ Grade 3	– Increase frequency of LFT monitoring to every 1-2 days – 1.0 to 2.0 mg/kg/day methylprednisolone IV or oral equivalent. The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV. – Add prophylactic antibiotics for opportunistic infections – Consult gastroenterologist If returns to Grade 2: – Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: – Add mycophenolate mofetil 1 gram (g) twice daily

Toxicity	Toxicity Management
	(BID) – If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

4. Renal Adverse Event Management

Toxicity	Toxicity Management
Renal (i.e., Creatinine Increased)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly.
Grade 1	– Monitor creatinine weekly until resolution to baseline; resume routine creatinine monitoring per protocol If worsens: – Treat as Grade 2 or 3/4
Grade 2-3	– Monitor creatinine every 2-3 days – 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent – Consider renal biopsy If returns to Grade 1: – Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: – Treat as Grade 4
≥ Grade 4	– Monitor creatinine daily – 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent – Consult nephrologist – Consider renal biopsy If returns to Grade 1: – Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

5. Skin Adverse Event Management

Toxicity	Toxicity Management
Skin (i.e., Rash, Macula-papular)	
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly.
Grade 1	Consider symptomatic treatment including oral antiprurities (e.g., diphenhydramine or hydrolyzine) and topical therapy (e.g., urea cream).

Toxicity	Toxicity Management
Skin (i.e., Rash, Macula-papular)	
Grade 2	Consider symptomatic treatment including oral antiprurities (e.g., diphenhydramine or hydrolyzine) and topical therapy (e.g., urea cream). If persists > 1-2 weeks or recurs: – Consider skin biopsy – Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections If worsens: – Treat as Grade 3/4
Grade 3	– Consider skin biopsy – Dermatology Consult – 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent If improves to Grade 1: – Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
Grade 4	– Consider skin biopsy – Dermatology Consult – 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

6. Endocrinopathy Adverse Event Management

Toxicity	Toxicity Management
Endocrinopathy (Endocrine Disorders - adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance)	
Any Grade	– Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly. Consider visual field testing, endocrinology consultation, and imaging. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
Grade 1	(including those with asymptomatic TSH elevation) Monitor patient with appropriate endocrine function test – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider Endocrinology Consult.

Toxicity	Toxicity Management
Grade 2	(including those with symptomatic endocrinopathy) – Discuss with Study Chair – Initiate hormone replacement as needed for management – Evaluate endocrine function, and as clinically indicated, consider pituitary scan – For patients with abnormal lab/pituitary scan work up, consider short-term,1-2 mg/kg/day methylprednisolone IV or oral equivalent with relevant hormone therapy – For patients with normal endocrine work up (lab or MRI scans), repeat labs in 1-3 week/MRI in 1 month. – If improves (with or without hormone replacement): – Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections – Patients with adrenal insufficiency may need to continue steroids with mineral corticoid component – Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness) – Discuss with Study Chair – Rule out sepsis – Administer stress dose of IV steroids with mineral corticoid activity – Administer IV fluids – Consult endocrinologist – If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy
Grade 3	–Discuss with Study Chair –Initiate empiric IV corticosteroids (e.g., methylprednisolone IV or oral equivalent) at 1 to 2 mg/kg/day –Administer hormone replacement therapy as necessary –For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity –Consult endocrinologist – Once improving, gradually taper immunosuppressive steroids over ≥4 weeks
Grade 4	

7: Neurological Adverse Event Management

Toxicity	Dose Modification	Toxicity Management
Neurological Toxicity (Nervous System Disorders)		
Any Grade	Patients should be thoroughly evaluated to rule out non-inflammatory causes. If non-inflammatory cause treat accordingly.	
Grade 1	–Continue to monitor the patient. <u>If worsens</u>: –Treat as Grade 2 or 3/4	
Grade 2	–Treat symptoms per local guidelines –Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent <u>If worsens</u>: –Treat as Grade 3/4	
≥ Grade 3	–Obtain Neurology Consult	

Toxicity	Dose Modification Toxicity Management
	−Treat symptoms per local guidelines −1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent −Add prophylactic antibiotics for opportunistic infections If improves to Grade 2: −Taper steroids over at least 1 month If worsens or atypical presentation: −Consider IVIG or other immunosuppressive therapies per local guidelines

Glucocorticosteroids should be used for the management of autoimmune complications related to nivolumab. Treatment with prednisone 1 mg/kg equivalent daily (minimum 40 mg daily) with a taper when symptoms and signs have resolved is recommended. Please refer to the product monograph for further details, or Appendix 3 from the Investigator Brochure.

8.3 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

All adverse events, regardless of grade or suspected relationship to study drug, should be collected and analyzed per the standard adverse event reporting mechanism (see Section 14.0).

9.0 STUDY CALENDARS

9.1 STUDY CALENDAR – ARM A: AZACITIDINE (CONTROL)

REQUIRED STUDIES	Pre-Reg	Cycle 1				C2	C3	C4	C5	Subsequent Cycles	Off Tx	Follow Up[5]
		W1	W2	W3	W4							
History and Physical Exam	X	X				X	X	X	X	X	X	X
Weight and Performance Status [6]	X	X				X	X	X	X	X	X	X
Toxicity Notation	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY STUDIES												
Bone Marrow Aspirate/Biopsy[1]	X						X		X	X[8]	X[8]	
CBC, Diff, Platelets	X	X[7]				X	X	X	X	X	X	X
Direct Bilirubin	X[6]											
Creatinine Clearance	X[6]	X[7]				X	X	X	X	X	X	X
Total bilirubin	X[6]	X[7]				X	X	X	X	X	X	X
AST and ALT	X[6]	X[7]				X	X	X	X	X		
LDH	X[6]											
Albumin	X[6]											
Glucose	X[6]											
Fibrinogen	X[6]											
Troponin	X[6]											
Autoimmune Status Clinical Assessment	X[6]											
SCANS												
ECG	X[6]											
SPECIMEN SUBMISSION												
FLT3 [2]	X											
Cytogenetics and FISH [3]	X											
Translational Medicine and Banking [4]	X						X		X			
TREATMENT												
Azacitidine		X				X	X	X	X	X		

1 Bone marrow biopsy will be performed at diagnosis, and after Cycles 2 and 4. Note that the Cycle 2 bone marrow biopsy does not affect protocol treatment decisions. Additional biopsies may be performed as clinically indicated.
2 See Section 15.2.
3 See Section 15.4.
4 See Section 15.3.
5 After discontinuation of protocol therapy, patients will be followed every 3 months for the first year, every 6 months for the second and third years, and then annually until 5 years after randomization.
6 Results of these tests do not determine eligibility but are performed prior to randomization in order to obtain baseline measurements.
7 If the pre-registration test is performed within 7 days prior to starting treatment, the test need NOT be repeated on Cycle 1, Day 1.
8 As clinically indicated.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20update.pdf.

9.2 STUDY CALENDAR – ARM B: AZACITIDINE + NIVOLUMAB

REQUIRED STUDIES	Pre-Reg	Cycle 1				C2	C3	C4	C5	Subsequent Cycles	Off Tx	Follow Up[5]
		W1	W2	W3	W4							
History and Physical Exam	X	X				X	X	X	X	X	X	X
Weight and Performance Status [6]	X	X				X	X	X	X	X	X	X
Toxicity Notation	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY STUDIES												
Bone Marrow Aspirate/Biopsy[1]	X						X		X	X[8]	X[8]	
CBC, Diff, Platelets	X	X[7]				X	X	X	X	X	X	X
Direct Bilirubin	X	X[7]				X	X	X	X	X		
Creatinine Clearance	X[6]	X[7]				X	X	X	X	X	X	X
Total bilirubin	X[6]	X[7]				X	X	X	X	X	X	X
AST and ALT	X	X[7]				X	X	X	X	X		
LDH	X[6]											
Albumin	X[6]											
Glucose	X[6]											
Fibrinogen	X[6]											
Amylase and Lipase	X[6]	X[7]				X	X	X	X			
Troponin	X[6]											
Autoimmune Status Clinical Assessment	X[6]											
SCANS												
ECG	X[6]											
ECHO	X											
SPECIMEN SUBMISSION												
FLT3 [2]	X											
Cytogenetics and FISH [3*]	X											
Translational Medicine and Banking [4]	X						X		X			
TREATMENT												
Azacitidine		X				X	X	X	X	X		
Nivolumab		X		X		X	X	X	X	X		

1 Bone marrow biopsy will be performed at diagnosis, and after Cycles 2 and 4. Note that the Cycle 2 bone marrow biopsy does not affect protocol treatment decisions. Additional biopsies may be performed as clinically indicated.
2 See Section 15.2.
3 See Section 15.4.
4 See Section 15.3.
5 After discontinuation of protocol therapy, patients will be followed every 3 months for the first year, every 6 months for the second and third years, and then annually until 5 years after randomization.
6 Results of these tests do not determine eligibility but are performed prior to randomization in order to obtain baseline measurements.
7 If the pre-registration test is performed within 7 days prior to starting treatment, the test need NOT be repeated on Cycle 1, Day 1.
8 As clinically indicated.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20update.pdf.

9.3 STUDY CALENDAR – ARM C – AZACITIDINE + MIDOSTAURIN

REQUIRED STUDIES	Pre-Reg	Cycle 1				C2	C3	C4	C5	Subsequent Cycles	Off Tx	Follow Up[5]
		W1	W2	W3	W4							
History and Physical Exam	X	X				X	X	X	X	X	X	X
Weight and Performance Status[6]	X	X				X	X	X	X	X	X	X
Toxicity Notation	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY STUDIES												
Bone Marrow Aspirate/Biopsy[1]	X						X		X	X[8]	X[8]	
CBC, Diff, Platelets	X	X[7]				X	X	X	X	X	X	X
Direct Bilirubin	X	X[7]				X	X	X	X	X	X	X
Creatinine Clearance	X	X[7]				X	X	X	X	X	X	X
Total bilirubin	X	X[7]				X	X	X	X	X	X	X
AST and ALT	X[6]	X[7]				X	X	X	X	X		
LDH	X[6]											
Albumin	X[6]											
Glucose	X[6]											
Fibrinogen	X[6]											
Troponin	X[6]											
Autoimmune Status Clinical Assessment[6]	X[6]											
SCANS												
ECG	X	X[9]	X[9]			X[9]	X[9]	X[9]	X[9]	X[9]		
SPECIMEN SUBMISSION												
FLT3 [2]	X											
Cytogenetics and FISH [3]	X											
Translational Medicine and Banking [4]	X						X		X			
TREATMENT												
Azacitidine		X				X	X	X	X	X		
Midostaurin			X	X		X	X	X	X	X		

1 Bone marrow biopsy will be performed at diagnosis and after Cycles 2 and 4. Note that the Cycle 2 bone marrow biopsy does not affect protocol treatment decisions. Additional biopsies may be performed as clinically indicated.
2 See Section 15.2.
3 See Section 15.4.
4 See Section 15.3.
5 After discontinuation of protocol therapy, patients will be followed every 3 months for the first year, every 6 months for the second and third years, and then annually until 5 years after randomization.
6 Results of these tests do not determine eligibility but are performed prior to randomization in order to obtain baseline measurements.
7 If the pre-registration test is performed within 7 days prior to starting treatment, the test need NOT be repeated on Cycle 1, Day 1.
8 As clinically indicated.
9 To be performed on Days 1 and 8 of Cycle 1 (prior to initiation of treatment) and on Day 1 of each subsequent cycle (prior to initiation of treatment).

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swgo.org/Visitors/Download/QA/Best%20Practices%20update.pdf.

9.4 STUDY CALENDAR – ARM D: DECITABINE + CYTARABINE

		INDUCTION[8]					MAINTENANCE								
REQUIRED STUDIES	Pre-Reg[7]	Cycle 1				C2	Cycle 1				C2	C3	Subsequent Cycles	Off Tx	Follow Up[5]
		W 1[7]	W 2	W 3	W 4		W 1	W 2	W 3	W 4					
History and Physical Exam	X	X				X					X		X	X	X
Weight and Performance Status [6]	X	X				X					X		X	X	X
Toxicity Notation	X	X	X	X	X	X					X		X	X	X
LABORATORY STUDIES															
Bone Marrow Aspirate/Biopsy[1]	X						X					X	X[9]	X[9]	
CBC, Diff, Platelets	X	X				X	X				X	X	X	X	X
Creatinine Clearance	X[6]	X				X	X				X	X	X	X	X
Direct Bilirubin	X[6]						X				X				
Total bilirubin	X[6]	X				X	X				X	X	X	X	X
AST and ALT	X[6]						X				X	X	X		
LDH	X[6]						X				X	X	X		
Albumin	X[6]						X				X	X	X		
Glucose	X[6]						X				X	X	X		
Fibrinogen	X[6]						X				X	X	X		
Troponin	X[6]														
Autoimmune Status Clinical Assessment	X[6]														
SCANS															
ECG	X														
SPECIMEN SUBMISSION															
FLT3 [2]	X														
Cytogenetics and FISH [3]	X														
Translational Medicine and Banking [4]	X						X					X			
TREATMENT															
Decitabine		X				X	X				X		X		
Cytarabine			X			X									

1 Bone marrow biopsy will be performed at diagnosis and after Cycles 2 and 4. Note that the Cycle 2 bone marrow biopsy does not affect protocol treatment decisions. Additional biopsies may be performed as clinically indicated.
2 See Section 15.2.
3 See Section 15.4.
4 See Section 15.3.
5 After discontinuation of protocol therapy, patients will be followed every 3 months for the first year, every 6 months for the second and third years, and then annually until 5 years after randomization.
6 Results of these tests do not determine eligibility but are performed prior to randomization in order to obtain baseline measurements.
7 If the pre-registration test is performed within 7 days prior to starting treatment, the test need NOT be repeated prior on Cycle 1, Day 1.
8 Patients may receive up to 2 cycles of Induction treatment. Patients deriving clinical benefit within 2 cycles will continue to Maintenance treatment. Patients not deriving clinical benefit within 2 cycles of Induction treatment will be removed from protocol therapy (see Section 7.1d).
9 As clinically indicated.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swgo.org/Visitors/Download/QA/Best%20Practices%20update.pdf.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Remission Definitions *(18)*

a. Morphologic complete remission (CR): Bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥ 1.0 x 10^9/L (1,000/mcL); platelet count ≥ 100 x 10^9/L (100,000/mcL).

b. Morphologic complete remission with incomplete blood count recovery (CRi): All CR criteria except for residual neutropenia [< 1.0 x 10^9/L (1,000/mcL)] OR thrombocytopenia [< 100 x 10^9/L (100,000/mcL)].

c. Partial Remission (PR): All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease from pretreatment bone marrow blast percentage by at least 50%.

d. Morphologic leukemia-free state (MLFS): Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required

e. Marrow CR (CRm): The patient must satisfy the definition of CR for the bone marrow examination (≤ 5% myeloblasts) and the marrow myeloblasts must have decreased by ≥ 50% from pretreatment. NOTE: CRm may be achieved with or without improved blood counts, with any hematologic improvement (see Section 10.3) noted separately.

f. Stable disease (SD): Failure to achieve at least a PR, but with no evidence of progression as defined in Section 10.3 for at least 8 weeks.

g. Refractory disease: failure to achieve CR, CRi, PR, MLFS, or SD, excluding patients with death in aplasia or death due to indeterminate cause.

h. Death in aplasia: Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic, with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia.

i. Death from indeterminate cause: Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available.

10.2 Assessment of Transfusion Dependency, Hemoglobin, and Platelet Counts

a. Accurate counts of RBC units and platelet transfusions received before and after starting protocol treatment are necessary to determine patients' responses to therapy. The numbers of RBC units and platelet transfusions during the 8 weeks before randomization will be recorded for use as baselines. Only RBC transfusions given for hemoglobin ≤ 9 g/dL or platelet transfusions for platelets < 50,000/mm^3 before randomization will be considered in the RBC/platelet transfusion response evaluation.

1. Transfusion dependence: Patients who receive one or more RBC or platelet transfusions will be considered RBC or platelet transfusion dependent, respectively, in the absence of another explanation such as gastrointestinal bleeding, hemolysis, etc.

2. Relevant reduction in RBC transfusion requirement: This is defined for patients who were RBC transfusion dependent and received ≥ 4 units during the 8 weeks before randomization. If, during the 8-week period after randomization, the total number of RBC units transfused has decreased by at least 4 units compared to the number transfused during the 8 weeks before randomization, then the patient will have a relevant reduction in RBC transfusion requirement.

3. Transfusion independence: For assessment of response, RBC or platelet transfusion independence requires that the patient receive no RBC or platelet transfusions, respectively, for a period of at least 8 weeks.

b. Accurate measurements of hemoglobin (Hgb), platelet (PLT), and ANC counts before and after starting protocol treatment are also necessary to determine patients' responses to therapy. Whenever patients are transfusion dependent, Hgb, PLT, and ANC counts must be measured immediately before transfusions, to ensure that they reflect the patient's true hematologic status.

10.3 Hematologic Improvement (HI)

Hematologic Improvement (HI) is assessed separately for erythroid cells, platelets, and neutrophils. For each type of response, the criteria must be satisfied for all blood examinations performed during a period of at least 8 weeks.

a. *Erythroid response (HI-E)*: is defined only for patients with hemoglobin < 11 g/dL prior to treatment.

1. *Response*: At least a 1.5 g/dL increase in hemoglobin from pretreatment; and, for RBC transfusion-dependent patients, achievement of transfusion independence or a relevant reduction in the RBC transfusion requirement.

2. *Progression/relapse following HI-E:* Reduction in hemoglobin concentration by at least 1.5 g/dL from maximum level during HI-E, or becoming RBC transfusion dependent, in the absence of another explanation such as gastrointestinal bleeding or hemolysis.

b. *Platelet response (HI-P)*: is defined only for patients with platelet count < 100,000/mm^3 prior to treatment.

1. Response: An absolute increase of ≥ 30,000/mm^3 from pretreatment for patients with a platelet count > 20,000/mm^3 at pretreatment. For patients with a platelet count ≤ 20,000/mm^3 at pretreatment, an increase of at least 100% from pretreatment counts to a platelet count > 20,000/mm^3. For platelet transfusion-dependent patients, platelet transfusion independence is also required.

2. Progression/relapse following HI-P: 50% or greater decrement from maximum platelet count achieved while HI-P, in the absence of another explanation such as gastrointestinal bleeding or hemolysis.

c. *Neutrophil response (HI-N)*: is defined only for patients with ANC < 1,000/mm^3 prior to treatment.

d. Response: ANC increase from pretreatment of at least 100%, and an absolute increase of > 500/mm^3 from pretreatment.

e. Progression/relapse following HI-N: 50% or greater decrement from maximum ANC achieved while HI-N, in the absence of another explanation such as acute infection.

10.4 Cytogenetic Response

Cytogenetic response is based on cytogenetic studies performed at local CLIA-approved laboratories

a. *Complete cytogenetic response:* is defined only for patients with preexisting clonal cytogenetic abnormalities, and requires (1) no detection of any preexisting clonal or nonclonal abnormality(ies) and (2) no cytogenetic evidence of any additional clonal populations, based on a study of at least 20 metaphases. FISH may be used as a supplement to follow a specifically defined cytogenetic abnormality.

b. *Partial cytogenetic response*: is defined as a 50% reduction of preexisting clonal cytogenetic abnormalities without evidence of any new clonal abnormalities.

c. *Cytogenetic relapse*: is defined as the detection of any clonal abnormality in a patient who previously achieved a complete cytogenetic response.

10.5 Disease Progression:

a. Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

1. > 50% increase in marrow blasts over baseline (a minimum 15% increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [> 0.5 x 109/L (500/mcL), and/or platelet count to >50 x 109/L (50,000/mcL) non-transfused]; or

2. > 50% increase in peripheral blasts (WBC x % blasts) to >25 x 109/L (>25,000/mcL) (in the absence of differentiation syndrome)

b. New extramedullary disease

Note: Transient cytopenias during chemotherapy courses should not be considered disease progression, as long as they recover to the previous levels. Progression based on blood values should not be considered at all until after the post-Cycle 4 marrow draw.

10.6 Time-to-Event Outcomes

a. Overall survival: Defined for all patients; measured from day of randomization on study until death from any cause with observations censored on the day of last contact for patients not known to have died.

b. Relapse-free survival: Defined only for patients achieving complete remission (CR), or CR with incomplete hematologic recovery (CRi); measured from the date of achievement of a remission until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date of last contact.

c. Event-free survival: Defined for all patients; measured from the date of randomization to the first of: date of primary refractory disease; date of progressive disease; date off protocol therapy without CR or CRi; date of relapse from CR or

CRi, or death from any cause; patients not known to have any of these events are censored on the date of last contact.

d. Cumulative incidence of relapse: Defined for all patients achieving CR or CRi; measured from the date of achievement of a remission until the date of relapse or death; patients not known to have relapsed or died are censored on the date of last contact; patients who died without relapse have death considered a competing cause of failure.

10.7 Performance Status

Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chai.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size and Accrual

Based on **S0432**, **S0703**, and **S1117**, the anticipated accrual is approximately 40 patients/month.

Only contemporaneously randomized and eligible patients will be evaluated for each comparison.

The design detailed below requires up to 300 eligible patients per arm. The earliest possibility of stopping an arm is at 100 patients per arm (33% accrual, expected approximately one year into a three-arm study). If 10% of patients are not eligible, the maximum accrual for an experimental arm is 334 patients. Because of staggered entry experimental arms, the control arm is expected to accrue more than 300 eligible patients. In addition, it is expected that up to 5% of patients registered to Step 1 (specimen submission for FLT3 testing) will not be randomized (Step 2 registration).

11.2 Design and Analyses Assumptions and Parameters

The primary objective of the Phase II study is to determine based on OS which if any of the experimental regimens should be tested further against the control regimen (azacitidine). Any regimen that passes the Phase II threshold will be taken forward for Phase III testing. The Phase II analysis will not select among experimental regimens.

The primary objective of the Phase III study is to compare OS between the control arm and experimental arm(s) selected in the Phase II study. Patients accrued during the Phase II portion of the trial will be used in the Phase III analysis. For all analyses, only concurrently randomized, eligible patients will be compared.

Based on data from the French study of azacitidine in older patients with hyper-proliferative AML, the study assumes that OS with azacitidine follows an exponential distribution with a median OS of 10.4 months (null hypothesis). *(19)* The study is powered for exponential OS in the experimental arms with a median OS of 15.6 months (corresponds to hazard ratio = 0.67, alternative hypothesis).

All testing will be stratified by the randomization stratification factors: age ≥ 70 AND PS 2-4 versus age < 70 OR PS 0-1; wild type FLT3-ITD versus mutated FLT3-ITD versus indeterminate FLT3-ITD; baseline blasts percentage (< 20% versus ≥ 20%).

For each experimental arm comparison versus the control arm, the study assumes equal randomization across arms, three years of accrual, and one year of follow-up after accrual completes. Analysis timing is event-based, so timing will adapt appropriately as the study progresses. For each experimental arm comparison versus the control arm, the study assumes a two-sided alpha of 5% or less.

11.3 Phase II Analyses

Up to 100 eligible patients will be enrolled to each arm for Phase II analysis. The Phase II analysis will be done at 104 pooled-arm deaths (deaths on both control + experimental arms). Accrual to experimental arms is expected to temporarily close to allow the OS data to mature. The length of the temporary closure will depend on accrual; it is expected an arm may need to be closed for up to 10 months while OS data mature. A stratified log-rank test of the null hypothesis (HR=1) with a one-sided alpha of 15% will be used to test an experimental arm versus azacitidine for further Phase III testing. This corresponds to continuing to Phase III testing arms with HRs < 0.87 favoring the experimental arm. A Phase II interim analysis for futility is scheduled for when there are 52 pooled-arm deaths. An experimental arm that has a hazard ratio (HR) favoring an experimental arm versus azacitidine will continue accrual. Accrual will not be held for the interim analysis.

11.4 Phase III Analyses

Up to 200 additional eligible patients will be enrolled to each arm for Phase III analysis (for a total of 300 eligible patients per arm). 100% of expected pooled-arm events for Phase III analysis is 414 deaths. The final Phase II analysis at 104 pooled-arm deaths corresponds to 25% of the full Phase III control arm OS events. For arms carried forward for Phase III testing, two additional interim analyses will be performed at 50% and 75% pooled-arm OS deaths (at 207 and 311 deaths). At each interim analysis an efficacy test will be done (test of the null hypothesis HR=1) using a stratified log-rank test with a one-sided alpha of 0.5%. At each interim analysis a futility test (test of the alternative hypothesis HR=0.67) will be done using a stratified log-rank test (modified to test the alternative HR) with a one-sided alpha of 2.5% at the first interim analysis and a one-sided alpha of 1.0% at the second interim analysis. The final analysis will occur at 100% pooled-arm OS deaths (414 deaths, expected at 6 months after accrual completes), or 1.5 years after accrual to an experimental arm completes, whichever occurs first. In order to account for interim analyses, each final test (stratified log-rank test of the null hypothesis HR=1) of an experimental arm versus azacitidine will be done with a two-sided alpha of 4.5%. This design has a power of 83% for each experimental arm. The table below summarizes properties of the design. If the event rate in the control arm is much slower than anticipated and the final analysis occurs at 1.5 years after completion of the accrual to an experimental arm, the power to detect the same effect size might be slightly different among the experimental arms, as the accrual duration may differ (depending on the accrual dynamics and how many arms are open at the same time).

If at any point an experimental arm has a positive interim or final analysis, accrual to the study will be terminated. Pending approval by the SWOG DSMC and CTEP, all study data will be released to the investigators.

Table 1. Characteristics of Analysis Plan (for each experimental regimen comparison versus azacitidine)

OS Scenario	Probability Under Alternative	Probability Under Null
Probability stop for futility at Phase II interim analysis	7%	50%
Probability continue to Phase III accrual based on Phase II analysis	84%	15%
Probability stop for futility at first Phase III interim analysis	3%	4%
Probability stop for efficacy at first Phase III interim analysis	40%	< 1%
Probability stop for futility at second Phase III interim analysis	≤ 1%	5%
Probability stop for efficacy at second Phase III interim analysis	25%	< 1%
Probability stop early for futility	19%	94%
Probability stop early for efficacy	64%	< 1%
Probability of positive result	83%	1%
Probability of positive result ignoring futility monitoring	98%	5%

Table 2. Additional Characteristics of Interim and Final Analyses

Analysis	N Deaths across Pooled Arms	Alpha Level	HR Threshold	Absolute Difference in 12-Month OS (Aza vs. Experimental Arm)
Phase II Analyses				
Interim futility	52	N/A	1.00	45% v. 45%
Final Phase II	104	One-sided 15%	0.84	45% v. 51%
Phase III Analyses				
First interim efficacy	207	One-sided 0.5%	0.64	45% v. 60%
First interim futility	207	One-sided 2.5%	0.90	45% v. 49%
Second interim efficacy	311	One-sided 0.5%	0.65	45% v. 60%
Second interim futility	311	One-sided 1.0%	0.90	45% v. 49%
Final efficacy	414	Two-sided 4.5%	0.82	45% v. 52%

11.5 Analysis of Other Endpoints

Toxicities: For each arm, three hundred eligible patients will be sufficient to estimate toxicity rates to within ± 6% (95% confidence interval). Any toxicity occurring with at least 1.5% probability is likely to be seen at least once (99% probability).

The study team (Study Chairs, Study Statisticians, and Committee Chair) will review the Cycle 1 and Cycle 2 toxicity data on the first 10 patients enrolled on the study (to any arm) with Performance Status 4. If the study team has concerns about excess toxicity among these patients, they will decide to continue to intensively monitor additional patients, or, in conjunction with the NCI, whether to modify the eligibility criteria.

Response and time-to-event endpoints: Remission rates will be tabulated. Time-to-event endpoints will be estimated using the Kaplan-Meier method or cumulative incident endpoints and associations with time-to-event outcomes will be assessed using Cox regression models (for cause-specific hazards as appropriate). Landmark analyses of different response categories will be evaluated based on dates at which 75% and 90% of patients have achieved a response (with other quantiles analyzed as needed.)

Analyses of FLT3-ITD and overall survival:
The prognostic effect of FLT3-ITD (positive versus negative or non-evaluable) with respect to the outcome OS will be evaluated using Cox regression models. We assume accrual

and follow-up as indicated above. Under the null hypothesis assumptions (OS following an exponential distribution with a median of 10.4 months), if 20% of patients are FLT3-ITD positive, each Phase 3 arm (300 patients) will have 87% power to detect a hazard ratio of 1.6 (corresponds to median OS among FLT3-ITD positive patients of 7 months and median OS among FLT3-ITD negative/non-evaluable patients of 11.2 months) with a two-sided alpha of 5%. The prognostic association will also be evaluable across all the arms and will have increased power with the increased sample size.

The predictive effect of FLT3-ITD (positive versus negative/non-evaluable) with respect to the outcome of OS and the treatments of azacitdine+midostaurin versus azacitidine will be evaluated using a Cox regression model with treatment arm and FLT3-ITD as covariates and including the interaction between the two covariates. If 20% of patients are FLT3-ITD positive on each arm and OS follows an exponential distribution, 600 patients (300/arm) will have 84% power to detect an interaction hazard ratio of 2 (corresponding to median OS of 7 months among FLT3-ITD positive patients treated with azacitidine, median OS of 14 months among FLT3-ITD positive patients treated with azacitidine+midostaurin, median OS of 11.2 months among FLT3-ITD negative patients on both arms) with a two-sided alpha of 5%.

As a sensitivity analysis, the same analyses as above will be done but excluding patients who were non-evaluable for FLT3-ITD (expected to be < 5% of patients).

As additional sensitivity analyses, the investigators will evaluate regression models with treatment arm, FLT3-ITD allelic ratio, and FLT3-TKD mutation status.

Associations between outcomes and cytogenetic abnormalities and risk categories and mutations: Univariate and multivariable regression models will be used assess potential associations between outcomes (CR, OS, EFS, and RFS) and cytogenetic abnormalities and mutation status (including FLT3-ITD). Regression models including interaction terms with treatment arm will be fit. In addition to analyzing FLT3-ITD as categorical variable used in randomization stratification, we will analyze FLT3-TKD also and evaluate FLT3-ITD allelic ratio as a quantitative variable and as a binary variable using the threshold of 0.50.

Potential control arm drift: Given the dynamic nature of the trial design it is possible that the prognostic factors of randomized patients will change over time. To control for this potential issue, only concurrently randomized patients will be evaluated in comparisons between arms. In addition, the patient characteristics table provided for the Data and Safety Monitoring Committee twice a year will summarize by 6-month or 12-month intervals based on randomization date.

11.6 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, three SWOG members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every six months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Discipline review is not necessary for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Specimens for FLT3 testing must be submitted at the time of registration to Step 1 using the SWOG Specimen Tracking System (see Section 15.2) (within 1 day of Step 1 registration and within 42 days prior to randomization [Step 2]). FLT3 results will be used for stratification purposes at the time of randomization. Upon receipt of e-mail notification of randomization assignment, the patient must be registered to Step 2 prior to initiation of treatment (no more than seven working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by e-mail at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by e-mail at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

1. Downloading Site Registration Documents:

Site registration forms may be downloaded from the S1612 protocol page located on the CTSU members' website. Add if a restricted access protocol: Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the SWOG link to expand, then select **S1612**. Click on the Site Registration Documents link.

2. Requirements for **S1612** Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 in order to receive further instruction and support.

4. Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: the status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol specific requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave® database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3 for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave® is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave® via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave® role (Rave® CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave® roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave® until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/ Rave® account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave® tab under the Rave® resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/ Rave® is available on the CTSU members' website under the Rave® tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please e-mail technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAY AFTER REGISTRATION TO STEP 1:

Submit specimens for FLT3 testing as outlined in Section 15.2.

b. WITHIN 7 DAYS OF DECISION NOT TO RANDOMIZE PATIENT:

Submit the **S1612** Notice of intention Not to Randomize

c. WITHIN 7 DAYS AFTER RANDOMIZATION (STEP 2 REGISTRATION):

Submit the following:

S1612 Onstudy Form

S1612 Transfusion Log

Pathology Report (upload reports via the Source Documentation: Baseline form in Rave®

d. WITHIN 28 DAYS AFTER RANDOMIZATION (STEP 2 REGISTRATION):

Submit the following:

S1612 Mutational Analysis and Cytogenetics Report Form

Pretreatment cytogenetics mutational analysis, FISH, and flow cytometry reports (whichever are performed). Upload reports via the Source Documentation: Baseline form in Rave®.

e. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT:

Submit the following:

S1612 Arm-Specific Treatment Form

S1612 Adverse Event Form*

S1612 Disease Assessment Form

If applicable, **S1612** Fungal Infections Form

If applicable, **S1612** Mutational Analysis and Cytogenetics Report Form

If applicable, **S1612** Transfusion Log

Bone marrow exam, pathology, cytogenetics and mutational analysis, FISH, and flow cytometry reports (whichever are performed). Upload reports via the Source Documentation: Follow-up form in Rave®.

f. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

S1612 Off Treatment Notice

Final **S1612** Arm-Specific Treatment Form

Final **S1612** Adverse Event Form*

Final **S1612** Disease Assessment Form

If applicable, **S1612** Mutational Analysis and Cytogenetics Report Form

If applicable, **S1612** Transfusion Log

Bone marrow exam, pathology, cytogenetics and mutational analysis, FISH, and flow cytometry reports (whichever are performed). Upload reports via the Source Documentation: Follow-up form in Rave®.

*All adverse events, regardless of grade or suspected relationship to study drug, should be collected and analyzed on the study.

g. AFTER THE PATIENT IS OFF TREATMENT, EVERY 3 MONTHS FOR THE FIRST YEAR, EVERY 6 MONTHS FOR THE SECOND AND THIRD YEARS, THEN ANNUALLY UNTIL FIVE YEARS FROM RANDOMIZATION (STEP 2 REGISTRATION) AND WITHIN 28 DAYS OF KNOWLEDGE OF RELAPSE, PROGRESSION, OR DEATH:

Submit the following:

S1612 Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported)

h. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the following:

Notice of Death

Forms listed in Section 14.4e (if the patient was still on protocol treatment) or **S1612** Follow Up Form (if the patient was off protocol treatment).

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

Patients must be registered to Step 1 before their specimens are entered into the SWOG Specimen Tracking System.

All specimen submissions for this study must be entered and tracked using the online SWOG Specimen Tracking System (STS). SWOG members may log on to STS via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and login to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for the CRA Workbench website. Non-SWOG members may access SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://crawb.crab.org/SpecTrack/Logon.aspx (select the option "SWOG - SWOG - CTSU").

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. STS laboratory IDs are used to identify laboratories to which specimens are shipped.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.
To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an e-mail to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://crawb.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

15.2 FLT3 Testing (REQUIRED)

Specimens for FLT3 screening testing **(submitted to the Radich Laboratory [Lab #93])**:

Note: Previous FLT3 testing performed outside of this study must be repeated for study stratification.

a. Specimen Collection and Submission Timepoints:

Specimens for FLT3 testing must be collected and submitted within 1 day of registration to Step 1 and within 42 days prior to randomization (registration to Step 2). FLT3 results will be used for stratification purposes at the time of randomization. E-mail notification of randomization assignment must be received by the site prior to patient randomization (see Section 5.2e). E-mail notification of randomization assignment is expected within 2-3 business days from the date of specimen receipt.

3 mL of bone marrow aspirate and 10 mL of peripheral blood must be collected per local institutional procedures into EDTA/purple top tubes. No onsite processing is required.

If marrow is inaspirable (dry tap), the peripheral blood submission is sufficient, regardless of peripheral blast count. If bone marrow aspiration is not obtainable for other logistical reasons, **and** the patient's peripheral blood demonstrates at least 25% circulating blasts, the peripheral blood submission will complete the requirement for FLT3 specimen submission.

b. Specimen Submission Instructions

Specimens must be submitted within 24 hours of collection. Note that Lab #93 does not accept Sunday deliveries. Arrangements should be made to ensure that specimens will be delivered Monday-Saturday.

Specimen collection and submission instructions can be accessed on the SWOG specimen submission webpage (https://swog.org/members/clinicaltrials/specimens/LeuSpecimens.asp).

Please ensure that specimens are labeled correctly per the online instructions, and that information in the sample submission form exactly matches the specimen label. **Specimens with incorrect labeling or with discrepancies between labels and submission forms will not be accepted by the laboratory.**

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

d. Laboratory Controls and Results

The laboratory will use 4 controls in every FLT3-ITD run: 2 positive (high and low), 1 wt and 1 ntc. The positive controls are previously validated patient samples. Both controls must be within the laboratory's established acceptability range before a patient's allelic ratio will be reported.

Interpreting FLT3 Results:

- FLT3 wt band at 328 bp = NEGATIVE
- FLT3 wt band at 328 AND one or more FLT3 ITD bands > 328 bp = POSITIVE
- Allelic ratio calculation: total ITD peak height/wt peak height

- Duplicate samples must have allelic ratios agreeing within 10%.
- The laboratory can detect and report any ITDs will an allelic ratio down to 0.01.

15.3 Translational Medicine and Banking (Optional for Patient – Required if Patient Consents)

Specimens for translational medicine and banking **(submitted to the SWOG Specimen Repository – Leukemia Division, Lab #200)**:

a. With patient's consent, specimens must be submitted as follows:

1. 3 mL of bone marrow aspirate and 10 mL of peripheral blood must be collected per local institutional procedures into EDTA/purple top tubes. No onsite processing is required.

   If marrow is inaspirable (dry tap), submission of the peripheral blood will suffice.

2. Specimens must be submitted at the following time points:

   - Prior to randomization (within 42 days prior to registration to Step 2) – required
   - After Cycle 2 (prior to treatment on Cycle 3)
   - After Cycle 4 (prior to treatment on Cycle 5)

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://swog.org/members/clinicaltrials/specimens/LeuSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

Banked specimens will be used for future, currently unspecified translational medicine studies, as new and important biologic markers and assays are identified. Future research will undergo the appropriate NCI/CTEP review process before specimens are released and used for testing. Specimen banking is an important component of the clinical trial to ensure that appropriate specimens are available for future research.

15.4 Cytogenetics and FISH (REQUIRED)

Specimens for cytogenetic and FISH analysis must be performed at each institution's preferred CLIA-approved laboratory as outlined below. If FISH analysis is not possible, patient may still be eligible based on cytogenetics; the reason for not performing FISH must be noted on the **S1612** Cytogenetics and FISH Analysis Form.

a. Specimen Collection and Submission Timepoints

- Prior to randomization (within 42 days prior to registration to Step 2) – required
- Any other time bone marrow exam is performed cytogenetic and FISH testing are encouraged, but not mandatory. However, if cytogenetics/FISH are performed, then results must be submitted as outlined below.

b. Result Reporting

The **S1612** Cytogenetics Lab Report Form must be submitted to the laboratory along with the specimen. The laboratory will then return the completed form with the results. E-mail contact information for the Data

Manager at the site must be provided to the lab performing cytogenetic studies. The institution will complete the **S1612** Cytogenetics and FISH Analysis Form in Medidata Rave® using the information provided by the lab.

16.1 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs per procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study.

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

3. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed

combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

a. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

b. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

4. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator. (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

5. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

6. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

7. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

8. The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in this study are midostaurin and nivolumab. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or e-mail the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report

For this study, ALL study arms will utilize the SAE reporting rules for investigational agents outlined in Table 16.1.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Midostaurin or Nivolumab

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:**

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Any supporting documentation should be submitted to CTEP per NCI guideline s for AE reporting located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions** SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.
The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

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18.0 APPENDIX

18.1 Midostaurin Patient Drug Information Handout and Wallet Card

18.2 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

18.3 Management Algorithms for Immuno-Oncology (I-O) Therapy for Endocrinopathy, Gastrointestinal, Hepatic, Neurological, Pulmonary, Renal and Skin Adverse Events for Nivolumab (Arm B) Adverse Event Management

18.4 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

18.5 Translational Medicine – Duplex Sequencing for Determining Measurable Residual Disease

18.1 Midostaurin Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient_____is enrolled on a clinical trial using the experimental study drug, midostaurin. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Midostaurin may interact with certain specific enzymes in your liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4/5, 1A2, 2C8, 2C9, 2C19, 2D6 and UGT1A1. Midostaurin is a substrate for CYP3A4/5 and may be affected by other drugs that are moderate or strong inhibitors or inducers of this enzyme. Midostaurin is an inhibitor of CYP 3A4/5, 1A2, 2C9 and an inducer of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4/5 and UGT1A1 and may affect the clearance of other drugs that are sensitive substrates for these enzyme pathways.
- The proteins in question are P-gp, OATP1B1, OATP1B3, MATE1, MATE2K, BCRP and MRP2. Midostaurin is an inhibitor of P-gp, OATP1B1, OATP1B3, MATE1, MATE2K, BCRP and an inducer of MRP2. Midostaurin has the potential to affect transport of other drugs that are moved in and out of cells by these transporters.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Midostaurin may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Midostaurin must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP3A4/5." Midostaurin inhibits CYP 3A4/5, 1A2, 2C9, P-glycoprotein (P-gp), OATP1B1, OATP1B3, MATE1, MATE2K and BCRP and induces CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4/5, UGT1A1 and MRP2. These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking midostaurin.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is_____and he or she can be contacted at_____.

March 2017

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **midostaurin.** This clinical trial is sponsored by the NCI. **Midostaurin** may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement. **Midostaurin** interacts with CYP 3A4/5, 1A2, 2B6, 2C8, 2C9, 2C19, UGT1A1, P-gp, MRP2, OATP1B1, OATP1B3, MATE1, MATE2K and BCRP and must be used very carefully with other medicines that interact with these enzymes and transporters.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP3A4/5." Midostaurin inhibits CYP 3A4/5, 1A2, 2C9, P-gp, OATP1B1, OATP1B3, MATE1, MATE2K and BCRP and induces CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4/5, UGT1A1 and MRP2. It may change how other medicine works in your body.
- Before prescribing new medicines, your regular health care providers should go to a frequently updated medical reference for a list of drugs to avoid or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

18.2 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information.

CYP2D6 Substrates	
Amitriptyline (hydroxylation)	Methamphetamine
Amphetamine	Metoclopramide
Betaxolol	Metoprolol
Bisoprolol	Mexitetine
Brofaromine	Mianserin
Buturolol	Mirtazapine (hydroxylation)
Bupropion	Molindone
Captopril	Morphine
Carvedilol	Nortriptyline (hydroxylation)
Cevimeline	Olanzapine (minor, hydroxymethylation)
Chlorpheniramine	Ondansetron
Chlorpromazine	Orphenadrine
Cinnarizine	Oxycodone
Clomipramine (hydroxylation)	Papaverine
Clozapine (minor pathway)	Paroxetine (minor pathway)
Codeine (hydroxylation, o-demelhylation)	Penbutolol
Cyclobenzaprine (hydroxylation)	Pentazocine
Cyclophosphamide	Perhexiline
Debrisoquin	Perphenazine
Delavirdine	Phenformin
Desipramine	Pindolol
Dexfenfluramine	Promethazine
Dextromethorphan (o-demethylation)	Propafenone
Dihydrocodeine	Propranolol
Diphenhydramine	Quetiapine
Dolasetron	Remoxipride
Donepezil	Risperidone
Doxepin	Ritonavir (minor)
Encainide	Ropivacaine
Fenlluramine	Selegiline
Flecainide	Sertindole
Fluosetine (minor pathway)	Sertratine (minor pathway)
Fluphenazine	Sparteine
Halofantrine	Tamoxifen
Haloperidol (minor pathway)	Thioridazine
Hydrocodone	Tiagabine
Hydrocortisone	Timolol
Hydroxyamphetamine	Tolterodine
Imipramine (hydroxylation)	Tramadol
Labetalol	Trazodone
Loratadine	Trimipramine
Maprotiline	Tropisetron
m-Chlorophenylpiperazine (m-CPP)	Venlafaxine (o-desmethylation)
Meperidine	Yohimbine
Methadone	

CYP2D6 Inhibitors	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxeline
Cimelidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Deiavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diitiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Vaiprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine

CYP3A3/4 Substrates	
Acetaminophen	Ketoconazole
Aifentanil	Lansoprazole (minor)
Alosetron	Letrozole
Alprazolam	Levobupivicaine
Amiodarone	Lidocaine
Amitriptyline (minor)	Loratadine
Amlodipine	Losartan
Anastrozole	Lovastatin
Androsterone	Methadone
Antipyrine	Mibefradil
Astemizole	Miconazole
Atorvastatin	Midazolam
Benzphetamine	Mifepristone
Bepridil	Mirtazapine (N-demethylation)
Bexarotene	Montelukast
Bromazepam	Navelbine
Bromocriptine	Nefazodone
Budesonide	Nelfinavir
Bupropion (minor)	Nevirapine
Buspirone	Nicardipine
Busutfan	Nifedipine
Caffeine	Niludipine
Cannabinoids	Nimodipine
Carbamazepine	Nisoldipine
Cevimeline	Nitrendipine
Cerivastatin	Omeprazole (sulfonation)
Chlorpromazine	Ondansetron
Cimetidine	Oral contraceptives
Cisapride	Orphenadrine
Citałopram	Paclitaxel

Clarithromycin	Pantoprazole
Clindamycin	Pimozide
Clomipramine	Pioglitazone
Clonazepam	Pravastatin
Clozapine	Prednisone
Cocaine	Progesterone
Codeine (demethylation)	Proguanil
Cortisol	Propafenone
Cortisone	Quercetin
Cyclobenzaprine (demethylation)	Quetiapine
Cyclophosphamide	Quinidine
Cyclosporine	Quinine
Dapsone	Repaglinide
Dehydroepiandrostendione	Retinoic acid
Delavirdine	Rifampin
Desmethyldiazepam	Risperidone
Dexamethasone	Ritonavir
Dextromethorphan (minor, N-demethylation)	Salmeterol
Diazepam (minor; hydroxylation, N-demethylation)	Saquinavir
	Sertindole
Digitoxin	Sertraline
Diltiazem	Sibutramine
Disopyramide	Sildenafil citrate
Docetaxel	Simvastatin
Dolasetron	Sirolimus
Donepezil	Sufentanil
Doxorubicin	Tacrolimus
Doxycycline	Tamoxifen
Dronabinol	Temazepam
Enalapril	Teniposide
Erylhromycin	Terfenadine
Estradiol	Testosterone
Ethinyl estradiol	Tetrahydrocannabinol
Ethosuximide	Theophylline
Etoposide	Tiagabine
Exemestene	Tolterodine
Dofetilide (minor)	Toremifene
Felodipine	Trazodone
Fentanyl	Tretinoin
Fexotenadine	Triazolam
Finaxteride	Troglitazone
Fluoxetine	Troleandomycin
Flutabmide	Venlafaxine (N-demethylation)
Glyburide	Verapamil
Granisetron	Vinblastine
Halofantrine	Vincristine
Hydrocortixone	Warfarin (R-warfarin)
Hydroxyarginine	Yohimbine
Ifosfamide	Zaleplon (minor pathway)
Imipramine	Zatoestron
Indinavir	Zileuton
Isradipine	Ziprasidone
Itraconazole	Zolpidem
	Zonisamide

CYP3A3/4 Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	

CYP3A3/4 Inhibitors	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Azithromycin	Mibefradil
Cannabinoids	Miconazole (moderate)
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole	Nevirapine
Cyclosporine	Norfloxacin
Danazol	Norfluoxetine
Delavirdine	Omeprazole (weak)
Dexamethasone	Oxiconazole
Diethyldithiocarbamate	Paroxetine (weak)
Diltiazem Dirithromycin	Propoxyphene
Disulfiram	Quinidine
Entacapone (high dose)	Quinine
Erythromycin	Quinupristin and dalfopristin
Ethinyl estradiol	Ranitidine
Fluconazole (weak)	Ritonavir
Fluoxetine	Saquinavir
Fluvoxamine	Sertindole
Gestodene	Sertraline
Grapefruit juice	Troglitazone
Indinavir	Troleandomycin
Isoniazid	Valproic acid (weak)
Itraconazole	Verapamil
	Zafirlukast
	Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371)

18.3 Management Algorithms for Immuno-Oncology (I-O) Therapy for Endocrinopathy, Gastrointestinal, Hepatic, Neurological, Pulmonary, Renal and Skin Adverse Events for Nivolumab (Arm B) Adverse Event Management

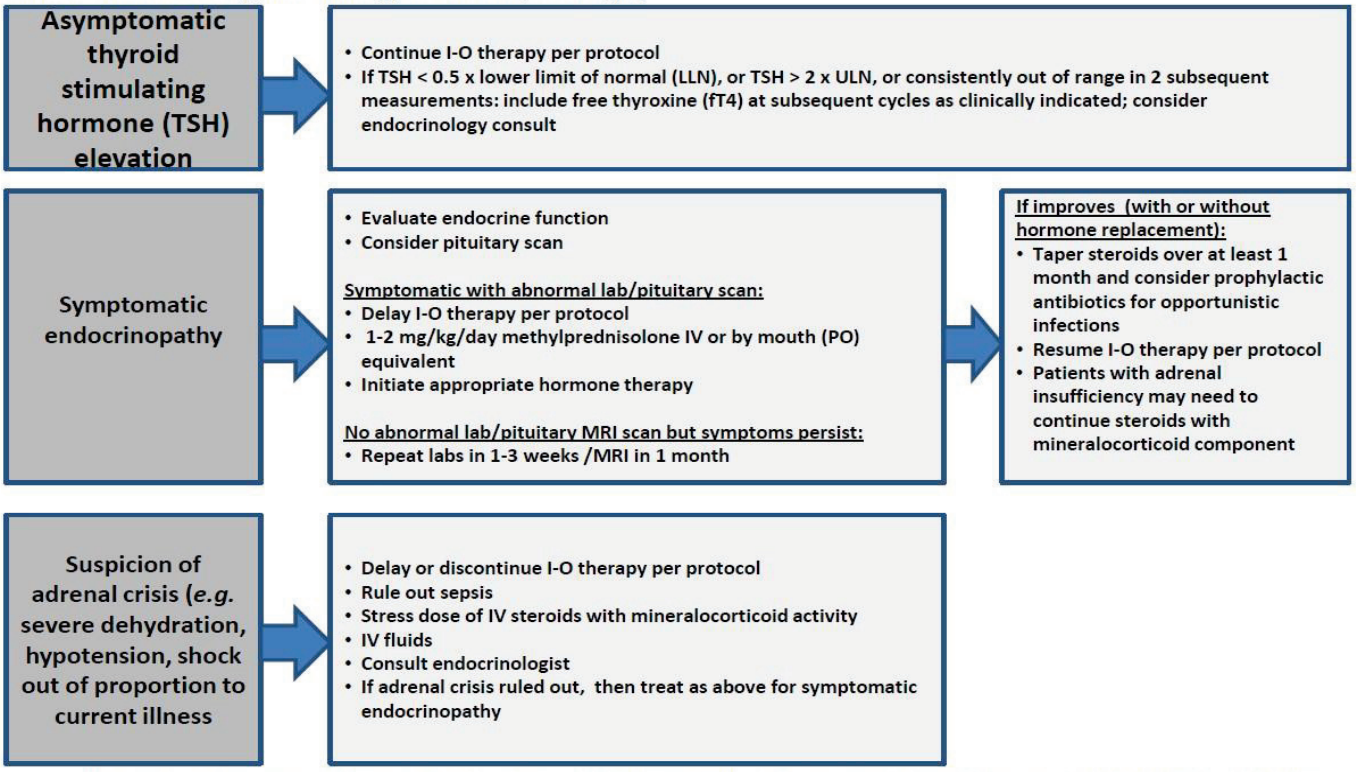
Note: For the following algorithms, prednisone PO may be utilized in place of methylprednisone IV.

Please see below.

a. Endocrinopathy Management Algorithm

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

b. GI Adverse Event Management Algorithm

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

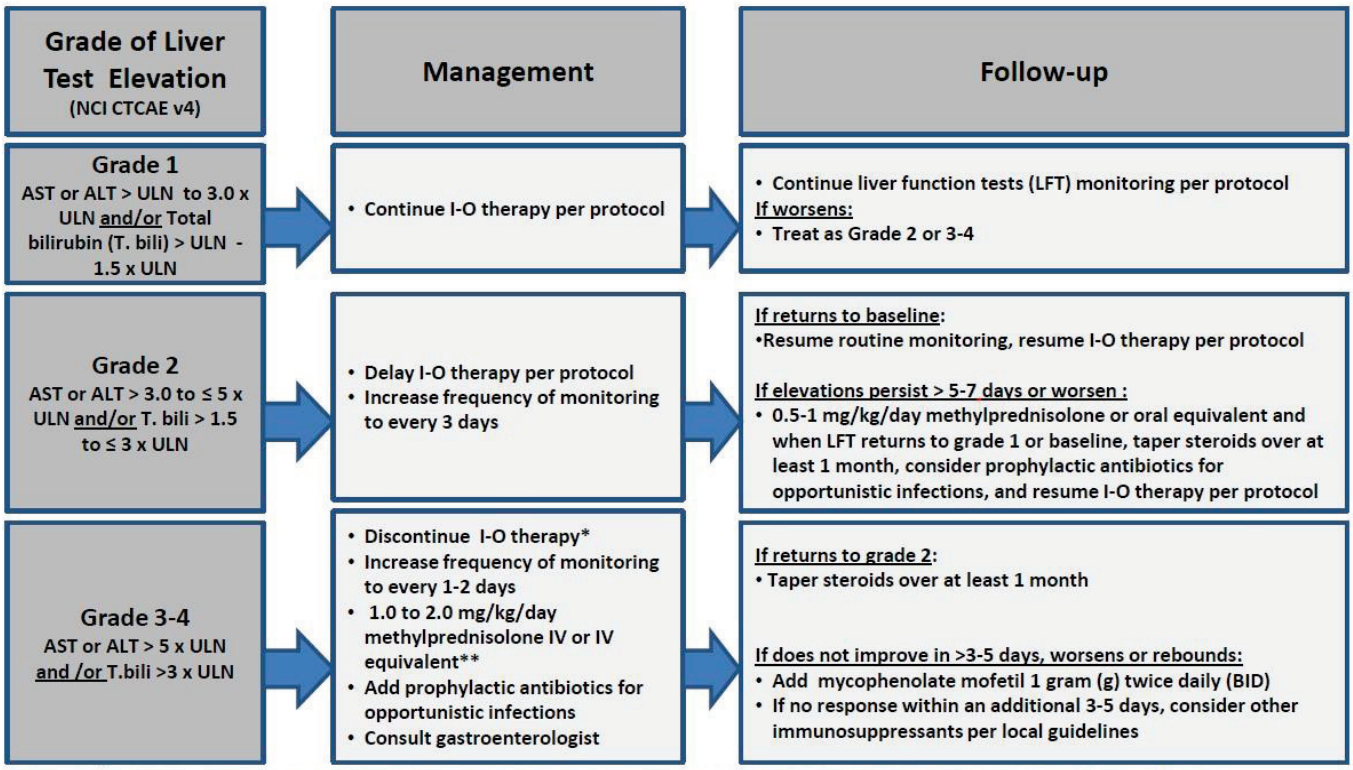
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

c. Hepatic Adverse Event Management Algorithm

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

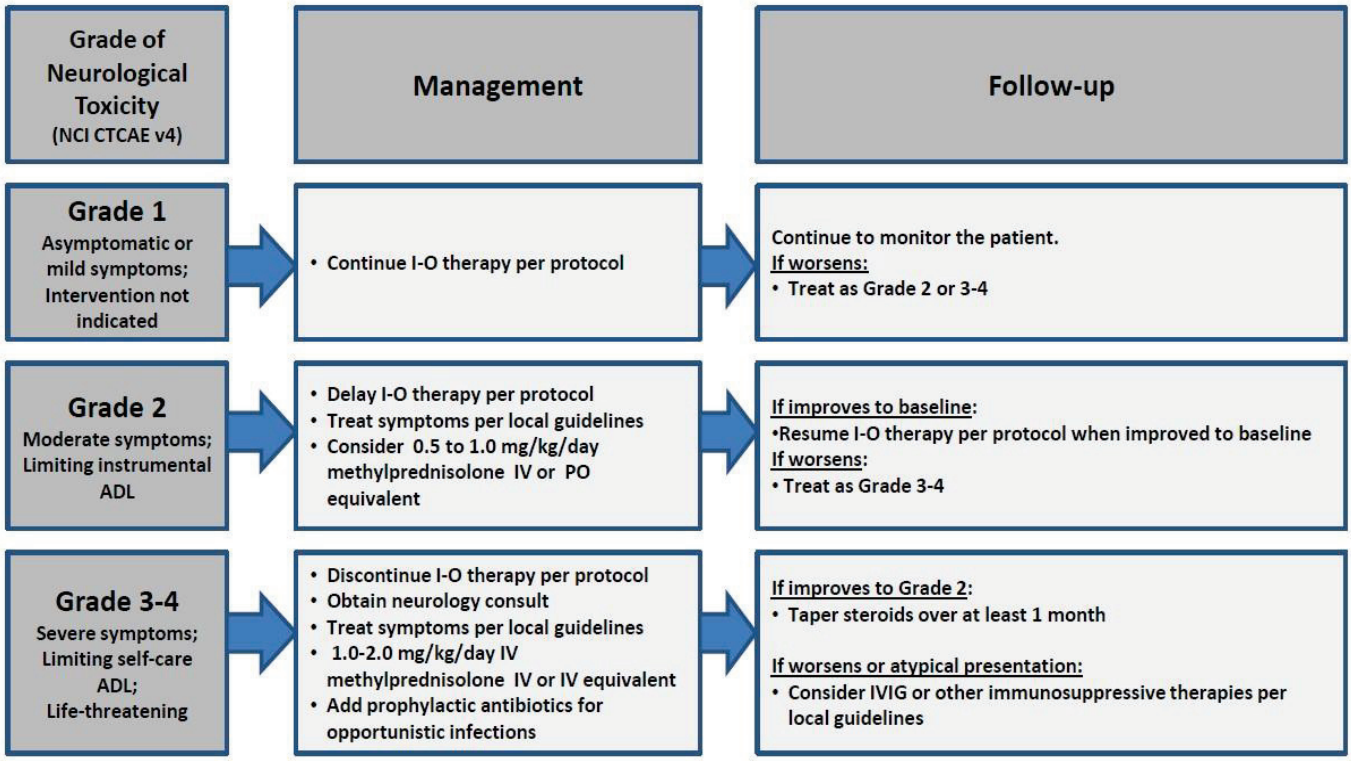
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

d. Neurological Adverse Event Management Algorithm

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

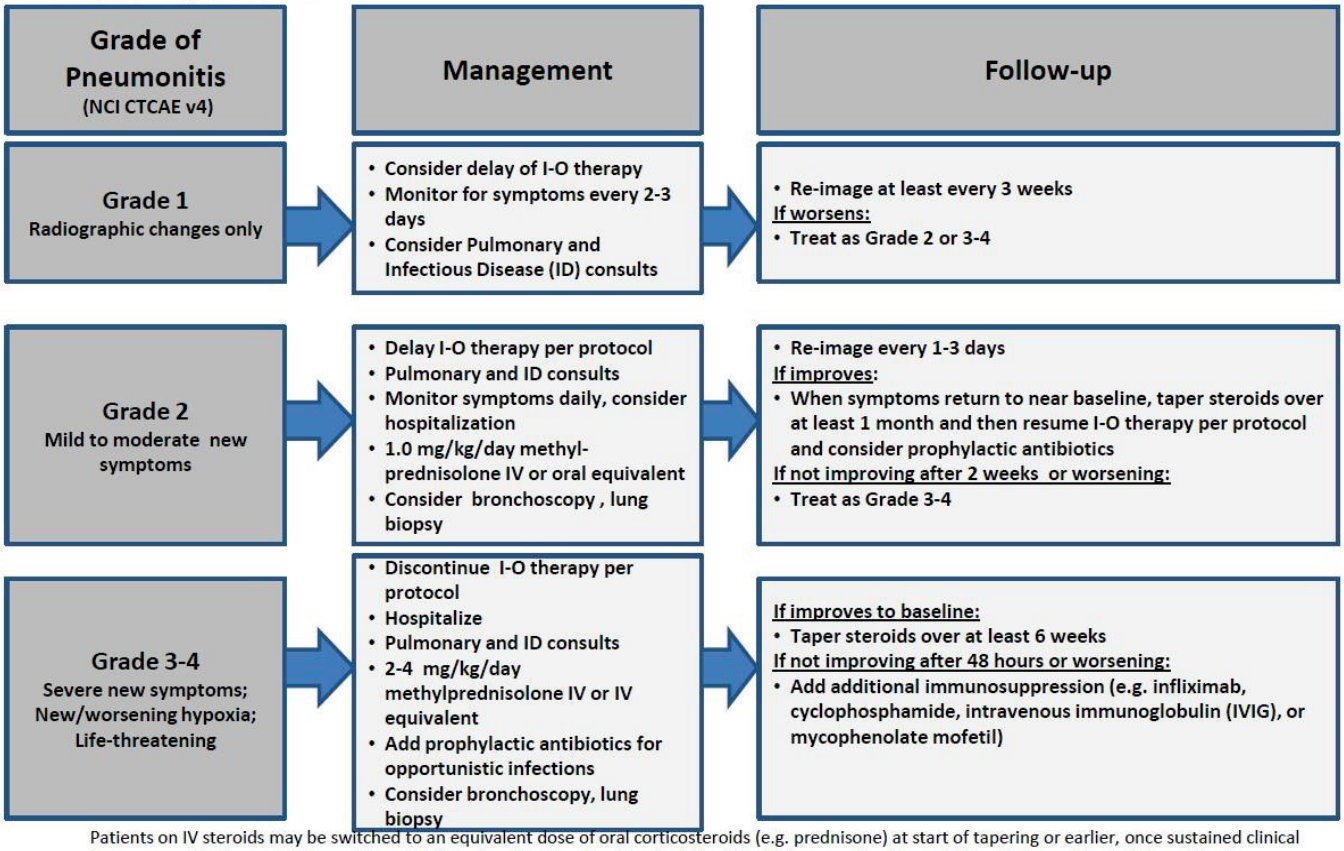


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

e. Pulmonary Adverse Event Management Algorithm

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

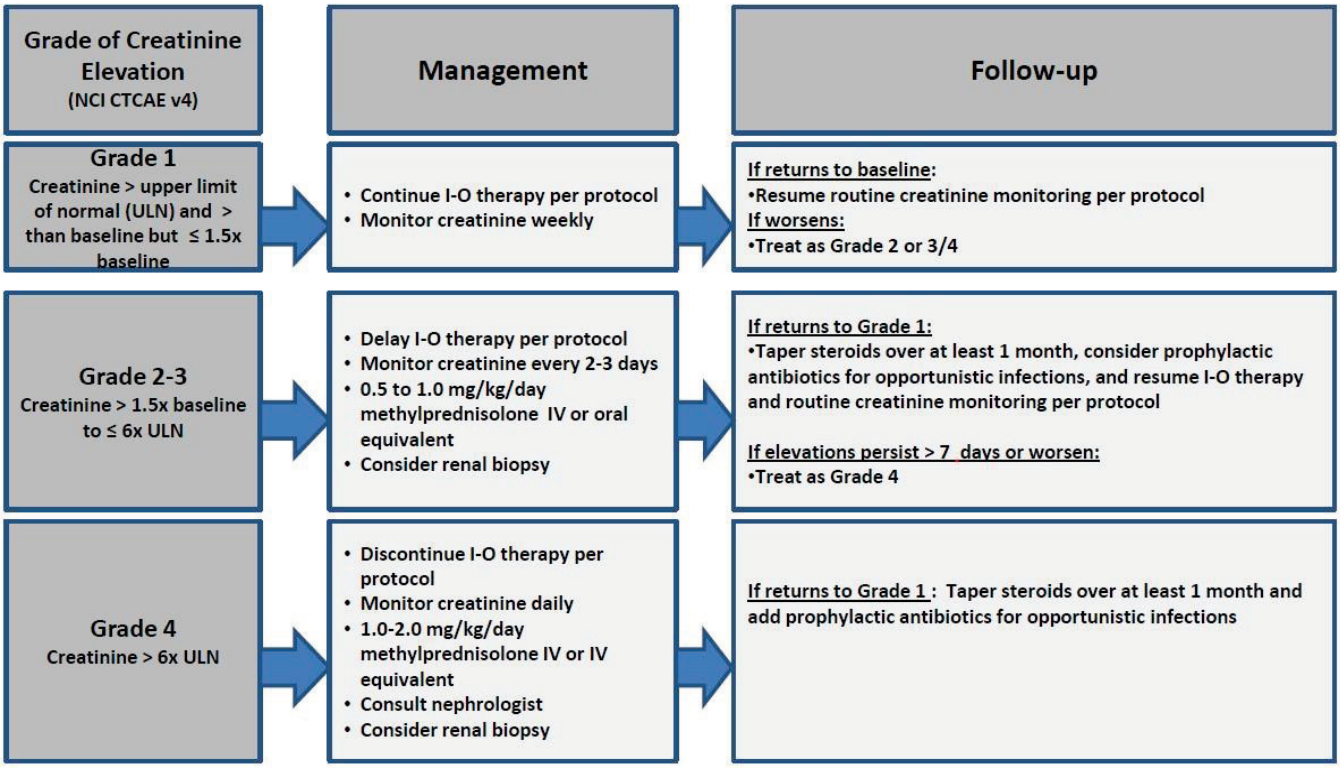


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

f. Renal Adverse Event Management Algorithm

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

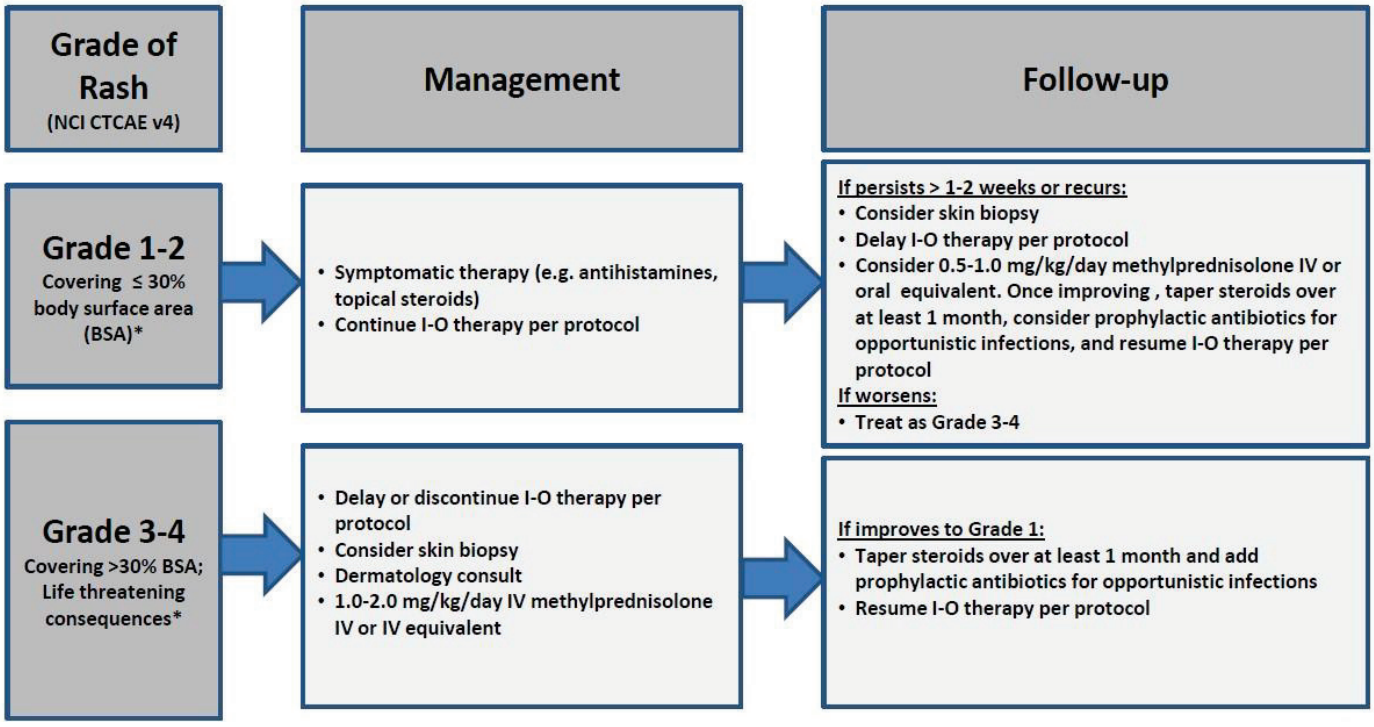


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

g. Skin Adverse Event Management Algorithm

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

18.4 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information.

CYP2D6	
SUBSTRATES	
Amitriptyline (hydroxylation)	Methamphetamine
Amphetamine	Metoclopramide
Betaxolol	Metoprolol
Bisoprolol	Mexitetine
Brofaromine	Mianserin
Buturolol	Mirtazapine (hydroxylation)
Bupropion	Molindone
Captopril	Morphine
Carvedilol	Nortriptyline (hydroxylation)
Cevimeline	Olanzapine (minor, hydroxymethylation)
Chlorpheniramine	Ondansetron
Chlorpromazine	Orphenadrine
Cinnarizine	Oxycodone
Clomipramine (hydroxylation)	Papaverine
Clozapine (minor pathway)	Paroxetine (minor pathway)
Codeine (hydroxylation, o-demelhylation)	Penbutolol
Cyclobenzaprine (hydroxylation)	Pentazocine
Cyclophosphamide	Perhexiline
Debrisoquin	Perphenazine
Delavirdine	Phenformin
Desipramine	Pindolol
Dexfenfluramine	Promethazine
Dextromethorphan (o-demethylation)	Propafenone
Dihydrocodeine	Propranolol
Diphenhydramine	Quetiapine
Dolasetron	Remoxipride
Donepezil	Risperidone
Doxepin	Ritonavir (minor)
Encainide	Ropivacaine
Fenlluramine	Selegiline
Flecainide	Sertindole
Fluoxetine (minor pathway)	Sertratine (minor pathway)
Fluphenazine	Sparteine
Haiofantrine	Tamoxifen
Haloperidol (minor pathway)	Thioridazine
Hydrocodone	Tiagabine
Hydrocortisone	Timolol
Hydroxyamphetamine	Tolterodine
Imipramine (hydroxylation)	Tramadol
Labetalol	Trazodone
Loratadine	Trimipramine
Maprotiline	Tropisetron
m-Chlorophenylpiperazine (m-CPP)	Venlafaxine (o-desmethylation)
Meperidine	Yohimbine
Methadone	

INHIBITORS	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxeline
Cimelidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Deiavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diitiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Vaiprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine
CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	
Carbamazepine	Diazepam (minor; hydroxylation, N-demethylation)
Cevimeline	
Cerivastatin	
Digitoxin	Nefazodone
Diltiazem	Nelfinavir
Disopyramide	Nevirapine
Docetaxel	Nicardipine
Dolasetron	Nifedipine

Donepezil	Niludipine
Doxorubicin	Nimodipine
Doxycycline	Nisoldipine
Dronabinol	Nitrendipine
Enalapril	Omeprazole (sulfonation)
Erylhromycin	Ondansetron
Estradiol	Oral contraceptives
Ethinyl estradiol	Orphenadrine
Ethosuximide	Paclitaxel
Etoposide	Pantoprazole
Exemestene	Pimozide
Dofetilide (minor)	Pioglitazone
Felodipine	Pravastatin
Fentanyl	Prednisone
Fexotenadine	Progesterone
Finaxteride	Proguanil
Fluoxetine	Propafenone
FLUTAMIDE	
Substrates	
Glyburide	*Quercetin*
Granisetron	Quetiapine
Halofantrine	Quinidine
Hydrocortixone	Quinine
Hydroxyarginine	Repaglinide
Ifosfamide	Retinoic acid
Imipramine	Rifampin
Indinavir	Risperidone
Isradipine	Ritonavir
Itraconazole	Salmeterol
Ketoconazole	Saquinavir
Lansoprazole (minor)	Sertindole
Letrozole	Sertraline
Levobupivicaine	Sibutramine
Lidocaine	Sildenafil citrate
Loratadine	Simvastatin
Losartan	Sirolimus
Lovastatin	Sufentanil
Methadone	Tacrolimus
Mibefradil	Tamoxifen
Miconazole	Temazepam
Midazolam	Teniposide
Mifepristone	Terfenadine
Mirtazapine (N-demethylation)	Testosterone
Montelukast	Tetrahydrocannabinol
Navelbine	Theophylline
Toremifene	Tiagabine
Trazodone	Tolterodine
Tretinoin	Vincristine
Triazolam	Warfarin (R-warfarin)
Troglitazone	Yohimbine
Troleandomycin	Zaleplon (minor pathway)
Venlafaxine (N-demethylation)	Zatoestron
Verapamil	Zileuton
Vinblastine	Ziprasidone

	Zolpidem Zonisamide
INDUCERS	
Carbamazepine Dexamethasone Ethosuximide Glucocorticoids Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Phenytoin Primidone Progesterone Rifabutin Rifampin Rofecoxib (mild) St John's wort Sulfadimidine Sulfinpyrazone Troglitazone
INHIBITORS	
Amiodarone Anastrozole Azithromycin Cannabinoids Cimetidine Clarithromycin Clotrimazole Cyclosporine Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice Indinavir Isoniazid Itraconazole	Ketoconazole Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371)

18.5 Translational Medicine – Duplex Sequencing for Determining Measurable Residual Disease

a. Objective

1. To test duplex sequencing (DS) against flow cytometry in patients treated under **S0106**.

b. Hypothesis

That ultrasensitive mutation detection by duplex sequencing (DS) will be better at predicting relapse than the conventional method of flow cytometry. Our goal is to finish this proposal with a locked down model of MRD prediction of relapse. This may in the end include only one parameter (e.g., DS) or a combination of parameters (e.g., DS, flow, and clinical variables). This MRD metric will then be employed in the prospective myeloMATCH trials for validation (note, flow will still initially be the MRD endpoint until "beaten" by another metric prospectively).

c. Background and Rationale

1. Preliminary Data and Study Justification

Relapse is the primary obstacle to cure in acute and chronic leukemia. The detection of measurable residual disease (MRD) is a direct measure of disease burden (and thus, treatment efficacy), and is the strongest predictor of relapse. MRD guides treatments and is an established trial endpoint in chronic myeloid leukemia (CML). Recent collaborative efforts by the FNIH, NCI, FDA, academia, and industry have further demonstrated the importance in acute lymphoblastic leukemia (ALL). Our labs have played a major role is establishing MRD as a standard of care procedure, as a measurement of outcomes in clinical trials in CML and ALL. MRD measurement in AML is associated with relapse, but it is technically more difficult to perform and standardize and has not yet been integrated into trial design and outcome. There is an acknowledged need recognized by the U.S. Cooperative groups and CTEP that AML needs accurate and reproducible molecular methods to predict response and relapse. This project proposal specifically addresses that unmet need, and will develop, validate, and integrate molecular diagnostics into AML trials and therapy.

2. Rationale to Test Duplex Sequencing (DS) Against Flow Cytometry in Patients

The need for more accurate MRD assessment is shown in **Figure 1**, which is from a recently published metaanalysis of MRD and outcomes in adult AML (1). The results show that a substantial number of patients with MRD positivity do ***not*** relapse, while a substantial number of those that are MRD negative ***do*** .

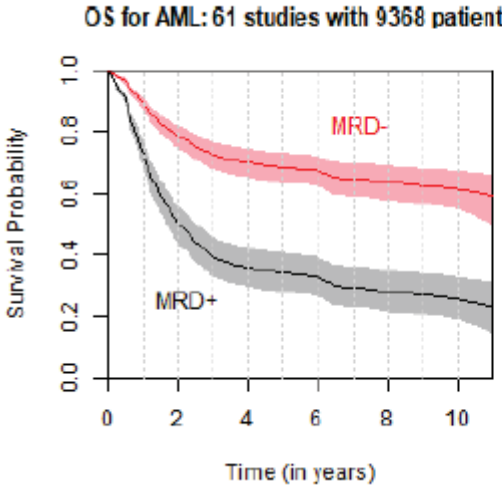


***Figure 1**. Meta-analysis of nearly 10,000 AML cases with MRD assessment. In the vast majority of cases, flow cytometry was the assay used for MRD detection. As such, flow will be used as the benchmark against which we will measure genomic assessments of MRD. (Short et al. JAMA Oncology 2020)*

Quantitative genetic testing of MRD may eventually 1) be used as an early indication of novel drug efficacy, 2) serve as a reliable early endpoint in phase 2 clinical trials 3) guide targeted drug therapy, and 4) yield understanding of tumor response issues such as clonal competition, selection, and evolution. However, an improved measurement of MRD would be an important, if not essential, development to best harness the

predictive potential of MRD.

The NCI is launching a precision medicine initiative in AML ("myeloMATCH"). The initiative will use rapid NGS to identify mutations and will preferentially enter patients onto trials where targeted agents exist to the detected mutation. These phase II trials will be use flow cytometry as a measure of MRD and will use the achievement of MRD as an endpoint. Further, there will be a set of trials based on "erasing" MRD. Thus, a more accurate measurement of MRD is needed to better predict long term outcomes (essentially, pulling the two curves in Figure 1 farther apart).

MyeloMATCH has identified duplex sequencing DS as a highly sensitive NGS method that may supplant, or complement, MRD assessment by flow cytometry. This proposal intends to test DS against flow cytometry in patients from S016, where outcome results and flow cytometry measurements already exist. This will allow for a more efficient integration into prospective myeloMATCH trials, where DS can be compared in real time to flow cytometry. Note that initially flow cytometry will be the assay study of choice for MRD assessments until prospective comparisons are complete.

3. Expected Distribution of Duplex Sequencing (DS) Against Flow Cytometry in Patients

We have just completed DS on 69 diagnostic and remission samples from **S0106**. Of 69, flow cytometry detected MRD in 10 pts, while 59 were MRD negative. DS detected more MRD, with MRD positive in 42 cases, and MRD negativity found in 27 cases ($p<0.001$).

4. Cut-points Used

The optimal cutoffs for outcome prediction are not known for either flow cytometry or DS. From a practical standpoint, the limits of detection of flow cytometry is ~0.01%, and this can vary from patient to patient, both from disease and sample effects (many studies will define any MRD <0.1% as

negative). The detection limit for DS is ~0.001%, but again this limit is influence by sample input, quality, and perhaps even specific mutation (e.g., FLT3ITD v. NPM1). One of the goals of this proposal is to have enough samples with both flow and DS data to more precisely define cut-offs for the prospective myeloMATCH trial tests.

Note in the above distribution counts *any* MRD counted as positive.

d. Experimental Design and Methods

1. Description of Duplex Sequencing (DS)

Duplex Sequencing (DS) is an ultra-high accuracy NGS method with an error rate below one-in-ten-million (Schmmidt et al. Nature Methods 2015). It is highly effective for high-resolution MRD detection through digital tabulation of tens of millions of individual DNA molecules to assess the proportion carrying AML-associated mutations. The principal of DS is that sequencing libraries are made from both sides of the DNA molecule. Mutation calls are only made when there are changes to complementary base pairs (e.g. C and G) at the same base pair address. Thus, the limitation of conventional NGS created by random errors made in the process of library preparation is corrected by including second strand information. We have used this method to great success in detecting BCR-ABL kinase domain mutations in CML and Ph+ ALL (refs). Results shown from a spike in experiment of 5 AML mutation cell lines is shown below. DS has the benefit of fully objective MRD quantification using any standard Illumina sequencer and without the need for expert interpretation of results. We will use a standardized ~60,000 BP panel comprising a collection of genes and hotspots that are mutated in >95% of adult AMLs. We will use this panel to carry out low depth standard NGS in the time-of-diagnosis samples and very deep (20-40,000x) DS at the MRD time points and look for low frequency mutations in the latter that were found clonally in the former. This approach has the advantage of being fairly simple, quite sensitive.

2. Analytic Performance of Duplex Sequencing (DS)

The TwinStrand Duplex Sequencing AML MRD assay consists of a panel designed to target 29 genes or gene regions that are recurrently mutated in AML patients. 90%-95% of adult AML patients carry a mutation in at least one panel gene, which makes the assay a powerful, near-universal tool to detect MRD in AML patients. The flexible nature of the assay's targeted enrichment strategy makes it very easy to expand to a larger collection of genes for increased sensitivity and applicability, to add new therapeutically-relevant targets as they are discovered, and to eventually develop patient-specific assays for sub one-in-one million sensitivity. The first part of this document describes the scientific and technical approaches designed to address the seven individual Project Activities identified in the SOW as necessary to support the NCI's MyeloMATCH Precision Medicine Initiative. The second part of the document explains the technical approach to accomplish the Example Project: Expansion of the AMLMRD panel by incorporating additional genes that are covered in the Oncomine Myeloid Research Assay.

3. Analytical Validation of the AML MRD Assay

The development and analytical validation of the AML MRD assay was the main goal of Phase I of our NCI-funded AML SBIR grant (R44CA233381, PIs J. Salk, J. Radich, PO Greg Evans), which we successfully accomplished a year ago. The assay was exhaustively validated using a mutation standard built with DNA from cell lines with known AML mutations spiked into peripheral

blood DNA from a healthy young donor. The Mutant Allele Frequency (MAF) ranged from 10-2 to 10-5 (Fig. 1). The mutation standard was sequenced in triplicate to test precision in addition to sensitivity and specificity of the AML MRD assay. All mutations, including mutations with the lowest MAF, were consistently detected, demonstrating the sensitivity of the assay to detect mutations at frequencies of at least 1x10-5. The Duplex Sequencing MAF closely correlated with the expected MAF in the 3 replicates (r2 values of 0.98, 0.96 and 0.95 for replicates, 1, 2, and 3, respectively), demonstrating high concordance between predicted and obtained MAF and precision (reproducibility) within the intended range of detection (Fig. 1). The specificity of the assay for a limit of detection (LOD) of 10-5 was 100%.

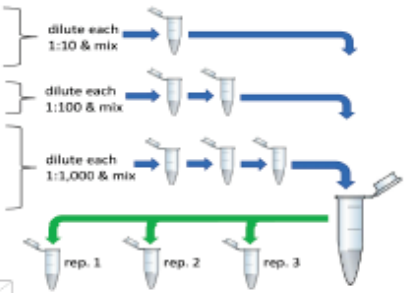
To further validate technical performance of the assay we spiked DNA from an AML patient, containing five previously characterized AML mutations, into peripheral blood DNA from a healthy young donor.

This experiment mimics the detection of a low frequency AML clone, simulating the real clinical scenario of MRD in AML patients with multiple mutations.

Dilutions ranged from 1:100 to 1:10,000 to test our goal of detecting an AML clone with an LOD of 0.01% (1:10,000). Predicted and Duplex MAF were highly correlated (r2=0.92). Most of the mutations in the dilution series were detected for all genes, with all single mutations ≥ 0.01% detected (Fig. 2). The combined information from the 5 mutations enabled the robust detection of the AML clone across every dilution tested (100% sensitivity). None of the mutations were detectable in normal DNA (100% specificity), indicating low background and lack of contamination.

A.

Cell Line	Gene	Mutation	Dilution	Predicted MAF
K-562	TP53	Q136fs	1:100	$1x10^{-2}$
BT-549	TP53	R249S	1:500	$2x10^{-3}$
CA46	TP53	R248Q	1:1,000	$1x10^{-3}$
SW1271	NRAS	Q61R	1:5,000	$2x10^{-4}$
LS1034	TP53	G245S	1:10,000	$1x10^{-4}$
OCI-AML3	NRAS	Q61L	1:25,000	$4x10^{-5}$
SK-BR-3	TP53	R175H	1:50,000	$2x10^{-5}$
LS180	KRAS	G12D (het.)	1:50,000	$1x10^{-5}$
SW620	KRAS	G12V	1:100,000	$1x10^{-5}$



B.

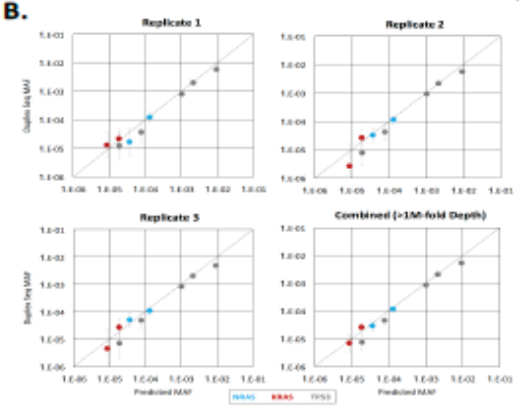


Figure 1. AML MRD assay validation. A. Experimental design. Nine cell lines containing different mutations in *TP53*, *NRAS*, and *KRAS* were spiked into human control DNA to achieve the indicated predicted Mutant Allele Frequencies (MAF). Three replicates of the mutation standard were sequenced at a mean depth of ~350,000x. **B. Assay validation.** In the 3 replicates, the observed Duplex Sequencing MAF correlated closely with the Predicted MAF (r2 values of 0.98, 0.96 and 0.95 for replicates, 1, 3, and 3, respectively). Error bars represent Wilson 95% binomial confidence intervals. All mutations, including those at the lowest frequencies, were seen in all replicates.

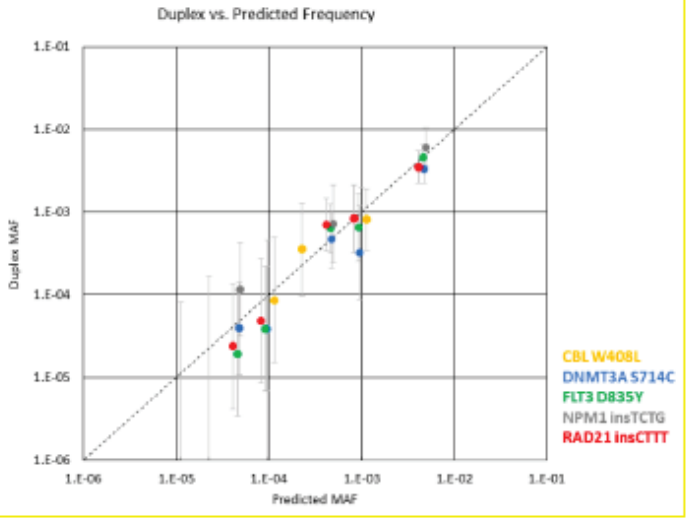


Figure 2. AML patient DNA harboring 5 known mutations was diluted from 1:100 to 1:10,000 in control DNA and Duplex Sequenced. MAFs were highly correlated with expected values based on dilution factor, with r^2=0.92. Error bars are 95% Wilson binomial confidence intervals.

e. Specimens, Acquisition of Specimens and Data Scoring Measures

Frozen cells will be shipped the Radich Lab. The primary source of samples will be from bone marrow, but where there are concurrent bone marrow and peripheral blood samples, we will perform DS on both, as we wish to determine if peripheral blood in the future can be used to measure MRD rather than bone marrow (as is now the standard of care in CML).

Mutations will be assessed as a continuous variable VAF. This will allow a direct comparison to the continuous variable of flow cytometry (e.g., a X-Y plot), as well as comparisons based on arbitrary categorical cutoffs.

f. Statistical Design

1. Clinical Endpoints

The primary clinical endpoints are time to relapse (TTR), relapse-free survival (RFS), and overall survival (OS). TTR is measured from date of CR to date of relapse, with patients last known to be alive without relapse censored at date of last contact; death without relapse is considered a competing event. RFS is measured from date of CR to first of date of death or relapse, with patients last known to be alive without relapse censored at date of last contact. OS is measured from date of CR to date of death from any cause, with patient last known to be alive censored at date of last contact.

MRD by flow is measured both quantitatively (percent of cells with MRD) and as a binary variable (no MRD observed versus any MRD observed). MRD by DS is measured as a sequence of binary variables (marker present/absent for all markers evaluated; marker at baseline still present at remission; new marker at remission; any marker observed at remission).

2. Sample Size Estimate

We request BM samples among 200 patients who achieved complete remission from **S0106**. 101 will be selected based on having flow data available (170 patients from S0106 have flow data; 69 have already been analyzed; this project requests BM samples from the remaining 101). An additional 99 patients without flow data but with baseline and remission BM samples will be requested; those 99 patients will be selected randomly from all patients available. In addition, we will request blood samples from 100 patients who have flow data available. We will randomly select the 100 from among the 170 with flow results; we will stratify the random selection to maintain the percent of patients who are Flow MRD positive and negative in the sub-sample and full sample.

3. Statistical Justification for Sample Size Estimate

BM samples: The **S0106** trial has flow outcome data on 170. We have DS completed on 69 of these patients. We request an addition 101 samples to have paired DS and flow data on all 170 patients to maximize the precision in characterizing these paired samples and comparing flow and DS. We request BM from an additional 99 patients to improve the precision of hazard ratios for DS.

Blood samples: We request blood samples from 100 patients with flow data available. All 100 will have DS from marrow available through this proposal and

prior work. 100 samples will allow us to compare and characterize differences in using blood versus marrow for DS evaluation and blood DS versus flow.

4. Statistical Analysis Methodology

McNemar's test will be used to evaluate concordance of MRD measurements on paired samples (Flow versus BM DS; BM DS versus blood DS; Flow versus blood DS).

Cox regression models will be used to evaluate associations with RFS and OS. Cause-specific Cox regression models and Fine and Gray subdistribution hazard models will be used to evaluate TTR.
Hazard ratios and 95% confidence intervals and C-statistics will be reported.

Event-rate assumptions for power calculation are based on the observed **S0106** data and are detailed in the following section.

5. Power Calculations for Statistical Tests

For McNemar's test to describe the power available we follow the methodology of Connor (Connor et al.
Biometrics 1987).

To compare flow versus BM DS MRD: with n=170 paired samples and using a two-sided test with alpha=0.05, we will have 90% power if the proportion Flow positive and DS negative is 3% and the proportion Flow negative and DS positive is 18%.

To compare flow versus blood DS MRD: with n=100 paired samples and using a two-sided test with alpha=0.05, we will have 87% power if the proportion Flow positive and DS negative is 3% and the proportion Flow negative and DS positive is 24%.

To compare BM DS MRD versus blood DS MRD: we are interested in characterizing the concordance. It is possible that there will not be any patients who are discordant with DS MRD negative in BM but positive in blood, in which case McNemar's odds ratio and confidence interval may not be well-defined. In this case we will calculate the proportion of patients who are MRD positive by DS in both blood and marrow and calculate an exact binomial confidence interval. The width of the interval will depend on the proportion. With n=100, if the proportion is 0.50 the exact confidence interval will be (0.40, 0.60); if the proportion is 0.80 the exact confidence interval will be (0.71, 0.87); if the proportion is 0.90 the exact confidence interval will be (0.82, 0.95).

Power for the Cox regression models is characterized by the number of events observed: among the 170 patients with flow data, there have been 74 deaths and 66 relapses; 23 patients died without prior relapse and 15 patients who have relapsed have not died. Therefore, there are 74 deaths for OS analyses, 89 events (relapses and deaths) for RFS analyses, and 66 relapses for TTR analyses.

In the cohort of patients with both flow and DS (n=170), when using an two-sided alpha of 5%, this cohort will have approximately 90% to detect a hazard ratio of magnitude 2.0 for RFS, 2.15 for OS, and 2.2 for TTR. C-statistics will be calculated to descriptively characterize the predictive performance of in Han et al. (Statistics in Medicine, 2017). We believe these HRs (or HRs more extreme) to be achievable regression models but will not be formally tested in comparison per the issusuch tests detailed with DS in BM. (Patkar et al. Leukemia 2021)

With the additional 99 patients with BM DS data we expect similar event rates as with the n=170 with flow data and so with n=269 patients with BM DS data, we expect 117 deaths of OS analysis, 140 RFS events for RFS analyses, and 104 relapses for TTR analyses. This sample size gives us additional power: when using a two-sided alpha of 5%, this cohort will have approximately 90% to detect a hazard ratio of magnitude 1.7 for RFS, 1.85 for OS, and 2.0 for TTR. In addition, with n=270, the confidence intervals will have greater precision (intervals will be more narrow; width will depend on magnitude of HR) and additional descriptive subset analyses can be feasible. In addition, with n=269 more complicated multivariable models can be fit (since the number of covariates is limited by the number events; a rough rule-of-thumb is 1 covariate term for every 10-15 events). It will be important to characterize the role of DS MRD in multivariable models controlling for the important prognostic factors of age, performance status, and baseline cytogenetic risk category (4 levels: favorable, intermediate, unfavorable, unknown).

With 100 patients with blood DS data, we expect similar events rates as in the n=170 with flow data; so with n=100 we expect 43 deaths for OS analyses, 52 RFS events for RFS analyses, and 38 relapses for TTR analyses. When using an two-sided alpha of 5%, this cohort will have approximately 90% to detect a hazard ratio of magnitude 2.5 for RFS, 2.65 for OS, and 2.85 for TTR.

Informed Consent Model for S1612
Specimen Submission: FLT3 Screening

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making additions, deletions, or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	62.1 (targeted above 55)
Flesch-Kincaid Grade Level	8.9 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line,_____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is

through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Informed Consent Model for S1612
Specimen Submission: FLT3 Screening

Study Title for Study Participants: Comparing New Treatment Options to One of the Standard Treatment Options for Older Patients with Newly Diagnosed Acute Myeloid Leukemia

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: S1612, A 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

What is the usual approach to my leukemia?

You are being asked to take part in this study because you have acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS). Also, you and/or your doctor did not think you should get intensive chemotherapy. People who are not in a study are usually treated with single-agent chemotherapy such as azacitidine or decitabine, or with combinations of more intense therapies. Your doctor should discuss with you what option he or she would recommend if you were not in a clinical trial. For participants who receive the usual approach for this cancer, anywhere from 0 to 10 out of 100 are free of cancer at five years.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this screening step is to allow researchers to learn if a certain blood and bone marrow test (called a biomarker) can help predict how a person's AML/MDS will respond to study drugs. All participants that are in the study will take part in the biomarker study. For the biomarker test, researchers will take a little less than an extra teaspoon of bone marrow and about 2 teaspoons of blood. These will be taken at the time you have bone marrow and blood drawn to diagnose your AML/MDS. If you don't have enough bone marrow, then just the blood will be used. If you don't have blood available from your previous blood draws, you will be asked to have another blood draw for this testing. Researchers will look at the biomarker, called FLT3, before you begin the treatment part of the study to make sure that participants with the biomarker take part in

all of the study treatment groups. Later the researchers will use the information to see if the level of the FLT3 biomarker predicts if certain treatments work better than others. The use of this biomarker is investigational. This biomarker is not being used to assign you to any specific treatment group. We expect that about 500 participants will have this biomarker test each year of this study. We expect that a total of between 550 to 1,700 people will take part in the biomarker research, and between 500 to 1,556 people will take part in the treatment portion of the study. The treatment portion of the study is designed to let the researchers expand the study if the treatment seems to be working, or stop it if the treatment doesn't seem to be working. Because of this, it is difficult to know exactly how many people might take part in the study overall.

What are the study groups?

The study has two steps: the initial screening step where we will test for the biomarker, and the study treatment step which will be discussed in a separate consent form.

All participants will have the biomarker test. You will have to meet additional requirements before you can begin treatment on the study treatment step. If you don't meet the criteria to go on to the study treatment, you will not be able to be treated on the study treatment step. Your treatment at that point will be decided between you and your study doctor. If you do meet the criteria to go on to the study treatment, you will receive a separate consent form that will explain the study treatment.

The study chart below is meant to help you understand the study design. Start reading at the top of the chart and read down, following the arrows.

Specimen Submission: FLT3 Screening

↓

You agree to have specimens submitted for FLT3 testing
Your specimens are submitted for FLT3 testing
FLT3 testing is performed on your specimen

↓

Treatment Study Randomization

You will receive another consent form that explains the treatment portion of the study. If you agree to take part in the treatment study, you will be randomized to one of the study treatment groups.

How long will I be in this study?

The FLT3 screening step will take approximately 2-3 days from the time your specimen is taken at your doctor's office and shipped to the laboratory for examination.

What extra tests and procedures will I have if I take part in this study?

The exams, tests and procedures you will have on the treatment step are part of the usual approach for your cancer. The only required test/procedure as part of the screening step is the biomarker test for FLT3.

Before you begin the study:

You will need to have the following extra test in order to be in the study:

* Biomarker test for FLT3

An additional sample of bone marrow (less than one teaspoon) and of blood (about two teaspoons) will be taken for the study at the time your bone marrow and blood are taken to diagnose your disease (within about 6 weeks before you start treatment on the study). The blood and bone marrow have to be sent to the lab within a day after they are collected, so if you had blood and bone marrow drawn previously for diagnosis, you will be asked to have more blood and bone marrow drawn for this testing. If you do not have enough bone marrow available, just the blood will be taken. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study.

Common side effects of a bone marrow biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. Common side effects of a blood draw are bruising, pain, and/or bleeding at the site of the draw.

If there is any blood or bone marrow left after the mandatory testing, the researchers would like to keep it and store it for biobanking. This is not required for you to take part in the study. This will be discussed in the section on optional studies.

Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information in a secure database. The results of the biomarker test will not be given to you or your doctor.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the *bone marrow or blood* that will be used for this study.

What possible risks can I expect from taking part in this study?

If you choose to take part in the screening part of this study, there is a risk that:

- **As with all medical screening tests, there is a chance of a false positive or a false negative result. A "false positive" refers to the identification of a biomarker that is not present. A "false negative" is the failure to find a biomarker that indeed exists. The tests have been designed to ensure that the possibility of incorrect results is low.**

Either a false positive or a false negative test will not affect your treatment assignment.

- **If you have to have another blood draw to get more blood, you may have pain, bruising, bleeding, or swelling at the site of the blood draw. If you have to have another biopsy to get more bone marrow you may have pain, bruising, bleeding, swelling, and/or infection at the site of the biopsy.**
- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual.**
- **You may be asked sensitive or private questions which you normally do not discuss.**
- **There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.** "*(For non-US participants, please verify existence of such laws before including the following text.)* **There are laws against misuse of genetic information, but they may not give full protection. The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This law does not cover life insurance, disability insurance and long-term care insurance.**
- **There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.**

Let your study doctor know of any questions you have about possible risks. You can ask the study doctor questions about risks at any time.

What possible benefits can I expect from taking part in this study?

Your study treatment will not be based on the results of this biomarker test, so your treatment will not be any better or worse depending on the results. This biomarker test is meant to help ensure that people with the biomarker take part in all study treatment groups. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or Food and Drug Administration (FDA).

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* **Institutional Review Board at** _____*(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

There is no cost to you or your insurance associated with this biomarker screening. If you need an extra biopsy to collect more tissue for this screening, the biopsy cost will be provided by the study. However, if you take part in the treatment study, you and/or your health plan/insurance company will need to pay for the costs of caring for your cancer while in this treatment study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for. Other costs will be addressed in more detail in the consent form for the treatment you are offered.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and any drug and device companies supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor_____*(insert name of study doctor[s])* at_____*(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. FUTURE CONTACT:

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

YES NO

2. OPTIONAL SAMPLE COLLECTIONS FOR LABORATORY STUDIES AND/OR BIOBANKING FOR POSSIBLE FUTURE STUDIES

Circle your choice of "yes" or "no" at the end of this section that explains this Optional Study.

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your bone marrow and/or blood. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, a sample of bone marrow and/or blood, taken at the same time as other marrows are being drawn for regular cancer care, will be collected. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by *SWOG* and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) Less than one teaspoon of additional bone marrow and about 2 teaspoons of additional blood will be collected during your regular bone marrow and blood draws before you start treatment, after about 2 months of treatment, and after about 4 months of treatment. Blood is collected from a vein in your arm. Bone marrow is collected during a procedure where a needle is inserted into the marrow of your hip,

called a bone marrow biopsy. If you do not have bone marrow available, the researchers will only collect a blood sample.
Your bone marrow and/or blood and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.

2) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any future research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to a bone marrow biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. *(For non-US participants, please verify existence of such laws before including the following text.)* There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.

2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and *SWOG* staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Screening Study
(Specimen Submission: FLT3 Screening)

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many participants. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

Informed Consent Model for S1612
Treatment Study

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making additions, deletions, or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	63.7 (targeted above 55)
Flesch-Kincaid Grade Level	8.7 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line,_____ indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is

through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Informed Consent Model for S1612
Treatment Study

Study Title for Study Participants: Comparing New Treatment Options to One of the Standard Treatment Options for Older Patients with Newly Diagnosed Acute Myeloid Leukemia

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: S1612, A 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

What is the usual approach to my leukemia?

You are being asked to take part in this study because you have acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS). Also, you and/or your doctor did not think you should get intensive chemotherapy. People who are not in a study are usually treated with single-agent chemotherapy such as azacitidine or decitabine, or with combinations of more intense therapies, that are approved by the FDA. There is not currently an FDA-approved medication for patients that have AML but who cannot tolerate intensive chemotherapy. These patients are usually treated with azacitidine or decitabine, or with palliative medications (medications to help with symptoms but that do not treat cancer). Your doctor should discuss with you what option he or she would recommend if you were not in a clinical trial. For patients who receive the usual approach for this cancer, anywhere from 0 to 10 out of 100 are free of cancer at five years.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using different new treatment options to one of the current standard treatment options given for patients with AML or MDS who cannot tolerate or do not want to get intensive chemotherapy. The investigators will keep testing new treatments to see if they have any different effects on patients and their cancer when compared to the standard. Each patient will only get one type of treatment on the study. This is described more below. If one of the new treatments seems to help patients more than the current standard, the study will start to use that

treatment as the new standard. If any of the treatments is not as helpful for any reason, or the bad effects are too severe, then that treatment will no longer be used in this study. The investigators want to use this study to find better treatment options for AML or MDS patients who do not get intensive chemotherapy.

At any time, the study will have one standard treatment group. The number of experimental treatment groups being tested at any time might be from one to four. The current standard treatment group and the experimental treatment groups that are currently open are discussed below. Some of the drugs used on the study are FDA approved to treat AML and/or MDS, and some are not. This is also discussed below.

There will be between about 500 and 1,556 people taking part in this study.

What are the study groups?

As discussed above, this study will have several treatment groups, but not all of them are going to be open at the same time. You can only take part in one of the currently open groups. The groups that are currently open are outlined below. Your doctor will decide whether you need to be admitted to the hospital for any part or all of your treatment.

- Group A will get the usual drug used for this type of cancer, azacitidine alone. Azacitidine is a drug used for this type of cancer when a person cannot get intensive chemotherapy safely. You will get the drug in cycles that are 28 days long. You will get the drug either as a shot under the skin or by an IV in your vein. You will get drug for 7 out of the first 12 days, and then have a break from the drug for the remainder of the 28-day cycle. Azacitidine has not been approved by the FDA to treat AML or all forms of MDS.

- Group B will get the usual drug used for this type of cancer, azacitidine just like Group A. Group B will also get a study drug called nivolumab. Nivolumab will be given by an IV into your vein on Days 1 and 15 of each 28-day cycle. Nivolumab is approved by the FDA to treat some types of cancers, but not AML or MDS.

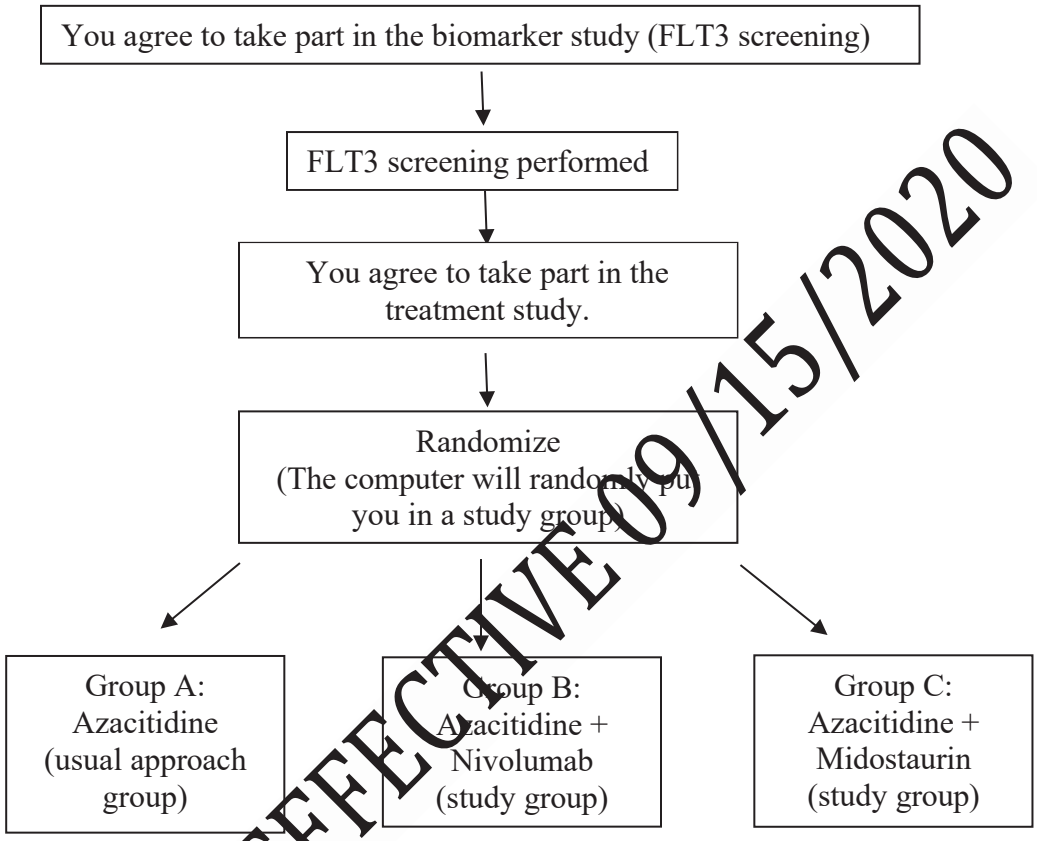
- Group C will get the usual drug used for this type of cancer, azacitidine, just like Group A. Group C will also get a study drug called midostaurin. Midostaurin will be taken by mouth as capsules twice a day on Days 8-21 of each 28-day cycle. Midostaurin has been approved for use by the FDA for patients with FLT3 + AML (AML with a specific mutation in a gene called FLT3) when used in combination with the drugs cytarabine and daunonibicin, but not in combination with azacitidine.

The cycles for all study groups will repeat until your disease gets worse or your or your doctor decide that you should stop.

A computer will by chance assign you to one of these treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others. Some study groups do not allow patients with certain physical

conditions to participate. If you have one of the conditions, you can still be in the study, but the computer will not assign you to a study group that does not allow that condition.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the top and read down, following the lines and arrows.



How long will I be in this study?

You will receive the study treatment for as long as you and your doctor think the treatment is helping you. After you stop taking study treatment, your doctor will continue to watch you for side effects and follow your condition for up to 5 years after you are registered to the study. At minimum, you will have clinic visits every 3 months for the first year, every 6 months for the second and third years, and then annually until 5 years after you are randomized to study treatment.

What extra tests and procedures will I have if I take part in this study?

All of the exams, tests, and procedures you will have are part of the usual approach for your cancer.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You may also have the following discomforts:

- **Spend more time in the hospital or doctor's office**
- **Be asked sensitive or private questions about things you normally do not discuss**
- **May not be able to take part in future studies**

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. Your study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, and some may never go away.**
- **Some side effects may make it hard for you to have children.**
- **Some side effects may be mild. Other side effects may be very serious and may even result in death.**

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- **If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.**
- **Your study doctor will work with you to treat your side effects.**
- **Your study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

STUDY GROUPS A, B, and C:

Possible side effects of azacitidine, the usual approach for this type of cancer:

Possible Side Effects of Azacitidine (*Updated 1/22/18)*

COMMON, SOME MAY BE SERIOUS **In 100 people receiving azacitidine, more than 20 and up to 100 may have:**
• **Anemia which may require blood transfusion** • **Constipation, diarrhea, nausea, vomiting** • **Tiredness, fever** • **Swelling and redness at the site of the medication injection** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Loss of appetite**
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving azacitidine, from 4 to 20 may have:**
• **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Fluid around heart** • **Abnormal heartbeat** • **Swelling and redness of the eye** • **Pain** • **Bleeding from multiple sites including the nose** • **Internal bleeding which may cause black tarry stool, blood in vomit, or coughing up blood** • **Heartburn** • **Difficulty swallowing or sleeping** • **Sores in the mouth** • **Chills** • **Swelling of arms, legs** • **Weight loss** • **Muscle weakness** • **Dizziness, headache** • **Worry, confusion, depression** • **Shortness of breath, cough, postnasal drip** • **Hair loss, itching, rash** • **Increased sweating** • **Sores on the skin** • **Low blood pressure which may cause feeling faint** • **Pale skin**

RARE, AND SERIOUS **In 100 people receiving azacitidine, 3 or fewer may have:**
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Kidney damage which may cause swelling, may require dialysis**

Reproductive risks: Men: You should not father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of pregnancy prevention to use while in this study.

STUDY GROUP B: -

In addition to side effects outlined above for azacitidine, people who are in Group B may also experience the possible side effects of nivolumab listed below. Some side effects of either drug might also be more frequent because of the drug combination.

Possible Side Effects of BMS-936558 (Nivolumab)

Special Precautions **Side effects of BMS-936558 (nivolumab) may happen any time during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 is used in combination with ipilimumab. Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS **In 100 people receiving BMS-936558 (nivolumab), more than 20 and up to 100 may have:**
• **Tiredness**

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving BMS-936558 (nivolumab), from 4 to 20 may have:

- **Anemia which may require blood transfusion**
- **Swelling and redness of the eye**
- **Pain**
- **Diarrhea, nausea**
- **Dry mouth**
- **Fever**
- **Swelling and redness at the site of the medication injection**
- **Bruising, bleeding**
- **Pain or swelling of the joints**
- **Loss of appetite**
- **Reaction during or following drug infusion which may cause fever, chills, rash**

BMS-936558 may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**
- **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.**
- **Skin: itching; rash, blisters including inside the mouth; loss of skin pigment**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.**

RARE, AND SERIOUS
In 100 people receiving BMS-936558 (nivolumab), 3 or fewer may have:

- **Dry eyes**
- **Sores in the mouth which may cause difficulty swallowing**

BMS-936558 may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness**
- **A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma**
- **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.**
- **Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.**
- **Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine**
- **Swelling of the brain (meningitis/encephalitis), which may cause: headache, stiff neck, confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)**
- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**
- **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.**
- **Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased.**

<u>Additional Reproductive Risks for Group B</u>: Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 31 weeks after the last dose of nivolumab.

STUDY GROUP C:

In addition to side effects outlined above for azacitidine, people who are in Group C may also experience the possible side effects of midostaurin listed below. Some side effects of either drug might also be more frequent because of the drug combination.

Possible Side Effects of Midostaurin

COMMON, SOME MAY BE SERIOUS In 100 people receiving midostaurin, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting

OCCASIONAL, SOME MAY BE SERIOUS *(updated 11/16/21)* In 100 people receiving midostaurin, from 4 to 20 may have:
• Anemia, which may require blood transfusion • Infection, especially when white blood cell count is low • Pain • Constipation • Swelling of arms, legs • Tiredness, fever • Bruising, bleeding • Headache • Shortness of breath • Itching

Additional Reproductive Risks for Group C: Sexually-active men must use a condom while receiving midostaurin and for five (5) months after the last dose. Vasectomized men must also use a condom to avoid delivering drug in the seminal fluid.

Let your study doctor know if any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study drugs are better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____
(insert name of center) **Institutional Review Board at_____***(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

Nivolumab and midostaurin will be supplied at no charge while you take part in the study. The costs of getting nivolumab and midostaurin ready and giving them to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the drugs may not continue to be supplied while you are on the study. Although this is not likely, if it occurs, your study doctor will talk to you about your options.

Azacitidine is commercially available and will not be supplied. You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor, SWOG, and any drug company supporting the study
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor_____*(insert name of study doctor[s])* at_____*(insert telephone number).*

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study.

Participant's signature_____

Date of signature_____