To: CTEP Protocol and Information Office

From: Alice Mims, M.D.

Date: 08/16/2021

Re: Amendment 1 of Protocol #10317: "A Phase 1 Study of Nivolumab in Combination with Decitabine and Venetoclax in Relapsed/Refractory Acute Myeloid Leukemia."

SUMMARY OF CHANGES – Protocol

I. OSU Changes, 08/16/2021

#	Section	Comment(s)
1.	Header	• Updated protocol version date
2.	Title Page	• Updated title to "A Phase 1 Study of Nivolumab in Combination with Decitabine and Venetoclax in Relapsed/Refractory Acute Myeloid Leukemia" • Added Revision # / Version # / Version Date
3.	Table of Contents	• Updated Table of Contents
4.	Throughout	• Updated superscripts throughout the protocol due to updated references • Formatting updates
5.	1	• Updated primary objectives • Added new secondary objectives
6.	2.1	• Replaced background section with relapsed/refractory AML section
7.	2.4	• Replaced rationale section with new information
8.	2.5.1	• Updated minimal residual disease (MRD) assessment
9.	2.5.4	• Added section for Pharmacokinetic (PK) and Pharmacodynamic (PD) studies
10.	3.1	• Updated eligibility criteria
11.	3.2	• Updated exclusion criteria to exclude patients who have received any prior BCL-2 inhibitor therapy and patients who have received prior hypomethylating therapy for treatment of AML
12.	3.3	• Updated inclusion table to include more patients in each category
13.	5.1	• Replaced Summary Table for Specimen Collection with updated table
14.	5.4.1.3	• Added shipping collection instructions for collection of

#	Section	Comment(s)
		blood for ventoclax, OATP1B1 biomarker and nivolumab pharmacokinetic studies
15.	5.5.3	• Added instructions for shipping of specimens to Ohio State PharmacoAnalytical Shared Resource (PhASR)
16.	5.6	• Replaced biomarker plan table with new information
17.	5.7	• Removed integral laboratory study
18.	5.8	• Added the following exploratory/ancillary correlative studies: flow cytometry, cytogenetics with kayotyping and AML FISH panel, tetramer analysis and cytokine production up re-simulation with antigen peptide, venetoclas OATP1B1 biomarker and nivolumab PK studies
19.	6.1	• Replaced agent administration table with updated table
20.	6.3	• Changed hematological DLT requirements. Failure to recover platelet count ≥25,000 (*previously 20,000*), or hemoglobin ≥7 will be considered hematological DLT.
21.	6.5.1	• Updated duration of therapy in cases of CR to consider CR/CRi.
22.	7.2	• Added new information for hematologic AE due to decitabine or venetoclax
23.	7.4	• Added dosing delays and modifications once at least MLFS is achieved
24.	7.6	• Changed the average time to respond to decitabine with venetoclax from 1.9 months to 1.3 months • Added instructions for patients who achieve a CR or Cri within 1.3 months' time yet also experience a DLT
25.	9.3	• Added new information to analysis of secondary endpoints regarding new exploratory/ancillary correlative studies
26.	10.1.1	• The SPEER grades have been updated. • Added New Risk: o Less Likely: CD4 lymphocytes decreased o Rare: Enterocolitis; Eye disorders - Other (Vogt-Koyanagi-Harada); Hepatobiliary disorders - Other (immune-mediated hepatitis); Renal and urinary disorders - Other (immune-mediated nephritis) • Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements: o Added: CD4 lymphocytes decreased • Provided Further Clarification:

#	Section	Comment(s)
		• Immune system disorders - Other (sarcoid granuloma) is now reported as Immune system disorders - Other (sarcoidosis).
27.	11	• Removed "Integral TP53 mutation" row from study calendar • Updated Venetoclax instructions to say "Venetoclax will be given on Days 1-28 of induction cycles and Days 1-21 of maintenance cycles." • Updated correlative collection calendar
28.	12.1	• Added <5% blasts in bone marrow aspirate as requirement for detected morphologic complete remission
29.	14	• Updated references list
30.	Appendix C	• Changed title of Appendix C to "Recommendations for initial management of electrolyte abnormalities and prevention of tumor lysis ivolumab pharmacokinetic studies • Added "See Appendix [TLS]"
31.	Appendix F	• Added Appendix F: Pharmacokinetic Study Sample Handling and Shipment
32.	Appendix G	• Added Appendix G: Medication Diary for Venetoclax

II. Recommendations for future post activation amendments:

#	Section	Comments
1.	Title Page	Change the IND number **PI Response:** Done.
2.	Schema	Change nivolumab administration to Days 1 and 15. **PI Response:** Nivolumab is given days 1-5 for cycles 2-3 of induction and for all maintenance cycles, but is only given day 15 of cycle 1 of induction. This is reflected in the schema.
3.	8.3.1	Reinsert the statement "excursions permitted to 15-30°C (59-86°F)." This is found in the decitabine package insert. It was not my intention that this statement be removed. **PI Response:** Re-inserted (now section 8.3.1)
4.	9.1	The first sentence after the table should read "Feasibility will be met if at least 9 of 13 patients are able to complete 3 cycles of therapy." **PI Response:** Study design section has changed; this is no longer

#	Section	Comments
		applicable.
5.	9.2	The accrual numbers do not add up correctly in the Planned Enrollment Report Table. Please correct the totals with your next amendment submission. **PI Response:** This is corrected.

NCI Protocol #: 10317

Local Protocol #: OSU 19305

ClinicalTrials.gov Identifier: NCT04277442

TITLE: A Phase 1 Study of Nivolumab in Combination with Decitabine and Venetoclax in Relapsed/Refractory Acute Myeloid Leukemia

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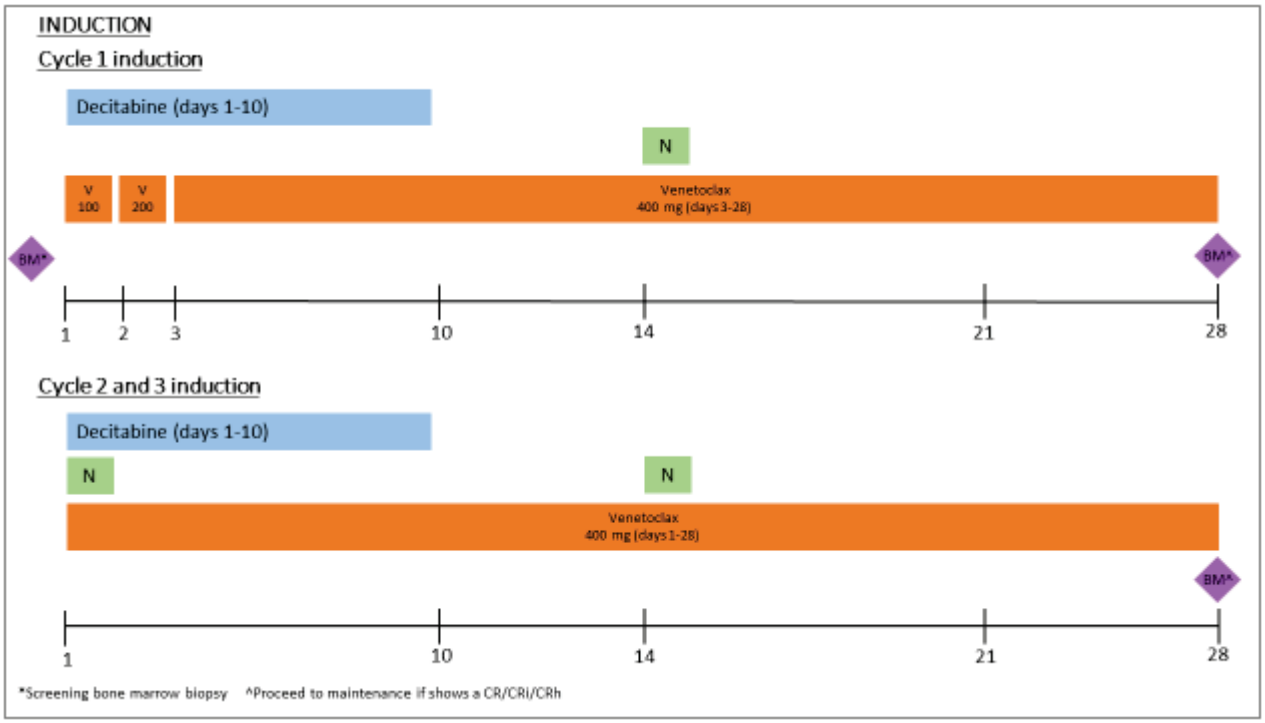
NCI-Supplied Agent(s): nivolumab (NSC 748726)
Other Agent(s): decitabine (NSC 127716, supplier - commercial), venetoclax (NSC 766270, supplier - commercial)

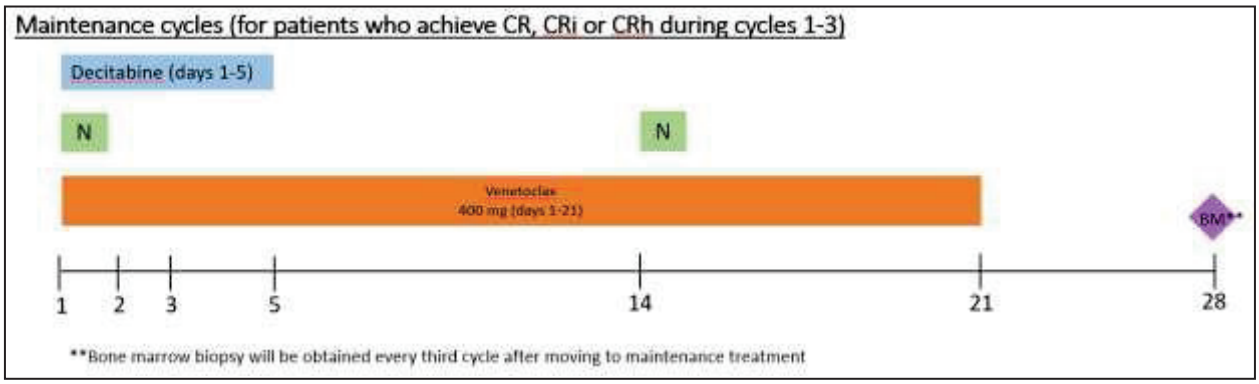
IND #:
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original/ Version 1/ 7-5-2019
Revision 1 / Version 1 / 9-15-2019
Revision 2 / Version 1 / 10-23-2019
Revision 3 / Version 1 / 12-30-2019
Revision 4 / Version 1 / 01-30-2020
Revision 5 / Version 1 / 08-16-2021

SCHEMA



Induction treatment (28 day cycle up to 3 cycles) will include the following:
Nivolumab (N) at 240mg on Day 15 for cycle 1 and Days 1 and 15 for cycles 2-3.
Decitabine 20 mg/m^2 intravenously on Days 1-10 for up to 3 cycles.
Venetoclax (V) 100mg PO on Day 1, 200mg on Day 2, 400mg on Days 3-28 of cycle (and cycle 2-3 of induction if needed).
If CR, CRi, or CRh is achieved during cycles 1-3, patients will proceed with maintenance at the time response is noted.
If no response is achieved by cycle 3, patients will come off study.
Bone marrow biopsy will occur on Day 28 (+/- 2 days) for up to 3 cycles to determine treatment response.



Maintenance treatment (28 day cycle) for patients achieving CR or CRi will include the following:
Nivolumab (N) will be given on Days 1 and 15.
Decitabine (D) 20 mg/m^2 intravenously on Days 1-5.
Venetoclax (V) 400mg po daily on Days 1-21.
Treatment will continue until one of the following occurs: loss of response/disease progression, bone marrow/stem cell transplantation, unacceptable toxicities, or patient withdrawal

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To obtain the safety and maximum tolerated dose (MTD) of decitabine and venetoclax in combination with nivolumab for relapsed/refractory (R/R) AML patients.

1.2 Secondary Objectives

1.2.1 To determine the composite CR rate (CR+CRi) rate in R/R AML patients who are treated with decitabine and venetoclax in combination with nivolumab.

1.2.2 To determine the overall response rate (CR+CRi+CRh+MLFS) rate in R/R AML patients who are treated with decitabine and venetoclax in combination with nivolumab.

1.2.3 To observe and record anti-tumor activity. Although the clinical benefit of this combination of drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.4 To determine progression free survival (PFS) for R/R AML patients receiving combination therapy.

1.2.5 To determine the overall survival (OS) for R/R AML patients receiving this combination therapy.

1.2.6 To determine minimal residual disease at best response and follow throughout treatment.

1.2.7 To determine the frequency of GVHD including veno-occlusive disease in patients who subsequently receive allogenic transplantation after this combination therapy.

1.2.8 To perform pharmacokinetic (PK) and pharmacodynamics (PD) of the combination of nivolumab with decitabine plus venetoclax.

2. BACKGROUND

2.1 Relapsed/Refractory AML

Acute myeloid leukemia (AML) is an aggressive clonal bone marrow malignancy that has very poor long-term survival with traditional therapies. Even with adaptation of cytogenetic and molecular risk-stratified therapies, 10-40% of patients do not achieve a complete remission (CR) after intensive induction therapy and are deemed to have primary refractory disease. For the patients able to achieve CR, greater than 50% subsequently experience disease relapse. For patients who relapse, only a small fraction undergo successful salvage treatment with ability to attain a second CR. Therefore, this leaves a large unmet clinical need for treatment of both relapsed and refractory (R/R) AML.

Traditionally, R/R AML is treated with intensive chemotherapy re-induction (aka. salvage) regimens, typically comprised of a high-dose cytarabine backbone with a variety of anthracycline and alkylating counterparts. However, a large number of patients are unable to tolerate such intensive chemotherapy, thus, regimens that are better tolerated are needed.

2.2 CTEP IND Agent

2.2.1 Nivolumab

Nivolumab 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.

The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Adverse events (AEs) associated with Nivolumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab must be withheld for drug-related toxicities and severe or life-threatening AES and prednisone may be given.

The proposed dosing of nivolumab is 240 mg every 2 weeks starting on Day 14 of cycle 1. This is the package insert dosing scheme used when nivolumab is combined with other agents (namely, ipilimumab). We will be combining nivolumab with two other agents, therefore this is consistent with current practice. Weight based dosing will allow us to mitigate adverse events, especially when combined with other agents.

2.3 Other Agent(s)

2.3.1 Decitabine

Decitabine is a cytidine nucleoside analog that inhibits cytosine methylation, thereby causing hypomethylation of DNA and re-expression of silenced genes.

Drug interaction studies with decitabine have not been conducted. In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. In vitro metabolism studies have suggested that decitabine is not a substrate for human liver cytochrome P450 enzymes. As plasma protein binding of decitabine is negligible (<1%), interactions due to displacement of more highly protein bound drugs from plasma proteins are not expected.

The proposed dosing of decitabine is 20 mg/m^2 daily on days 1-10 of induction cycles up to 3 cycles and on days 1-5 of maintenance cycles. This 20 mg/m^2 dosing is the

package insert dosing for the 5 day regimen. We plan on administering for 10 days during cycles 1-3, as opposed to the package insert 5 days, as the shorter 5-day dosing scheme appears to be inferior to the longer 10-day dosing scheme in *TP53*m AML patients per recent publications described below.

2.3.2 Venetoclax

Venetoclax is a B-cell lymphoma-2 (BCL-2) inhibitor which is an anti-apoptotic protein.

Venetoclax is predominantly metabolized by CYP3A4/5. Venetoclax had no large effect on QTc interval (i.e., > 20 ms) and there was no relationship between venetoclax exposure and change in QTc interval. Gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect venetoclax bioavailability. Avoid grapefruit products, Seville oranges, and starfruit during treatment.

There is also a risk of developing tumor lysis syndrome (TLS) with venetoclax. For prophylaxis, patients should be instructed to drink 6 to 8 glasses water each day, starting 2 days before the first dose, on the day of the first dose of venetoclax, and each time the dose is increased. Consider IV hydration and/or uric acid reducing agents in patients at risk for TLS.

The proposed dose for venetoclax is 400 mg daily with ramp-up to this dose during days 1-3 of cycle 1 and continue on 400mg on days 4-21 of cycle 1 (28 day cycle) with subsequent cycle doses of 400mg on days 1-21. Dose ramp up will be 100 mg on day 1 and 200 mg on day 2 followed by the goal dose of 400 mg on day 3 and onwards. There will be dose adjustments for venetoclax based on the FDA label if concurrent use with moderate or strong CYP3A inhibitors (See Section 6.3.1 and 6.3.1.1)

2.4 Rationale

2.4.1 AML Treatment with Hypomethylating Agent and Venetoclax: In recent years, the new standard of care for newly diagnosed AML patients that cannot tolerate intensive induction chemotherapy has transitioned to treatment with a hypomethylating agent (HMA) and venetoclax. Phase 3 data with this regimen in the upfront AML setting showed CR+CRi rate of 66.4%.[4] However, this combination has not been proven to be as effective in the R/R AML setting. Gaut et al performed a retrospective study of venetoclax combinations in the relapsed AML setting. In the eight patients who had received azacitidine (AZA) with venetoclax, 2 patients experienced a response (1 PR and 1 CRi) and in the 5 patients who had received decitabine with venetoclax, 2 patients experienced a CRi (no CRs were seen with either HMA), which showed a CRi rate of 23.1% (3/13 patients).[3] Vigil et al described outcomes of patients with R/R AML who received venetoclax in combination with AZA (1 patient) and decitabine (8 patients) and combined the overall response rate was 44% (4 patients) and 3 patients achieved CRi (33%), but again no CRs were seen.[5] A larger retrospective study performed by DiNardo et al investigated 39 R/R AML patients who received venetoclax combinations, 9 patients responded (21%) and 8 of these patients received an HMA. Of these responders, 2 patients who received AZA achieved CR/CRi (one patient each) and 2 patients who received decitabine achieved CR/CRi (one patient each),

thus, 2 CRs were seen in this study.[6] Therefore, there is room to improve on these results with this combination in the R/R AML setting.

The studies above all investigated giving decitabine for a 5-day course. However, there is evidence that a 10-day course of decitabine in combination with venetoclax may be more beneficial in certain patient populations, notably R/R AML.[1] DiNardo, et al performed a prospective phase 2 study in various groups of AML patients and treated patients with an initial 10-day course of decitabine with venetoclax followed by 5-day decitabine with venetoclax once CR/CRi was achieved. In the R/R AML cohort (n=55), the ORR was 62% (34 patients) and the CR/CRi rate was 24%/18% (13/10 patients). This study also exhibited an acceptable toxicity profile with expected treatment-emergent adverse events of grade 3/4 neutropenia (50% of all patients in the study) and febrile neutropenia (29%), but a 30-day mortality of only 3.6%.

2.4.2 **PD-1/PDL-1 expression in AML:** Co-expression of Tim-3 and PD-1 identified a CD8+ T cell exhaustion phenotype in murine AML models with deficiency in ability to produce IFN-gamma, TNF-alpha, and IL-2 in response to PD-1 and Tim-3 ligand expressing cells.[7] The evaluation of immunotherapy in AML is supported by the observation of increased expression of PD-1 in the T cells in the leukemia microenvironment compared to healthy individuals. Daver, et al analyzed the PD-1 expression on bone marrow (BM) aspirates of 74 AML patients (36 untreated, 38 relapsed) and 8 healthy controls using multi-parameter flow cytometry and showed that all T cell subpopulations (CD4 T effector cells, CD4 T regulatory cells, and CD8 T cells) had significantly higher PD-1 expression in untreated and relapsed AML patients when compared to the healthy controls.[8] These findings further support the development of anti-PD-L1/PD-1 therapy for the treatment of AML.

2.4.3 **Targeting PD-1/PDL-1 in AML:** Both in vitro and in vivo studies in development show promising results with PD-1/PDL-1 inhibition in AML. In murine AML models, anti-PD-L1 monoclonal antibody therapies were not curative, but increased the proliferation and function of cytotoxic T cells at tumor sites, reduced AML tumor burden and resulted in long-term survival in mice.[7] In a recent phase II study by Daver, *et al* the use of nivolumab in combination with AZA was evaluated in 70 patients with relapsed AML.[9] Of these 70 patients, 22% (n = 15) achieved CR/CRi, with median OS of 17.1 months compared to 4.9 months in non-responders. The safety profile showed grade 3 and grade 2 immune-mediated toxicities each at 11% (there were no grade 4 events) including pneumonitis, colitis, nephritis, skin rash, and hypophysitis. All cases of immune related adverse events responded rapidly to steroids. There are ongoing trials assessing check point blockade in AML in the relapsed/refractory setting in combination with AZA in the post-transplant setting for minimal residual disease (MRD) and for patients at high risk of relapse. There is also a Phase II trial evaluating nivolumab in combination with standard induction therapy in the first-line therapy for AML and high-risk MDS (NCT02464657).[10] Nine of these patients underwent subsequent allogeneic transplant with 4 patients with GVHD seen and no veno-occlusive disease reported thus far. Each of these aforementioned clinical trials are performed in all-comers of AML.

2.4.4 **Rationale for combination of decitabine, venetoclax and nivolumab for AML:** The combination of PD-1/PDL-1 inhibitor with hypomethylating agent is supported by evidence of upregulation of PD-L1, PD-L2, PD-1 and CTLA4 mRNA expression in patients treated with epigenetic therapy as demonstrated by Yang, et al.[11] This study also

showed that treatment of leukemia cells with decitabine resulted in a dose-dependent upregulation of these genes. Furthermore, To investigate this clinically, Daver et al performed a phase 2 study combining azacitidine (an HMA) and nivolumab (an anti-PD-1) in relapsed/refractory AML.[12] This combination in 70 patients showed an overall response rate (ORR) of 33% with a 22% CR/CR with incomplete count recovery. However, the ORR and CR/CRi rates with HMA combined with venetoclax in the relapsed/refractory AML setting is about 10 percentage points that the PD-1/HMA combination. Therefore, we propose that the triple combination of HMA with venetoclax and PD-1 inhibition will lead to increased response rates in the relapsed/refractory AML population.

Hence we propose the combination of hypomethylating agent and venetoclax with a PD-1 inhibitor in the AML population. We are interested in exploring a 10-day course of decitabine and venetoclax along with PD-1 inhibitor, nivolumab. The key innovation in this research proposal is the use of combination of three novel agents- nivolumab, venetoclax and decitabine for relapsed/refractory AML. Combining epigenetic therapy with immunotherapy has been shown to have promising synergistic effect with in vivo studies and early clinical studies, by upregulating the cytotoxic T cell response and reviving the innate immune surveillance. Thus, a positive result from this trial has the potential to change the treatment paradigm for AML patients. By understanding the interaction between nivolumab, venetoclax and decitabine and its effects in the tumor microenvironment, we might obtain useful insights on manipulating the timing of these treatments to obtain durable remission even in the post-transplant setting in this patient population.

2.5 Correlative Studies Background

2.5.1 Minimal residual disease (MRD) assessment

We propose that decitabine, venetoclax and nivolumab in combination will help achieve durable response in relapsed/refractory AML. We will be using flow cytometry (aka. immunophenotyping), cytogenetics (karyotyping along with an AML FISH panel), and next generation sequencing (NGS) to detect minimal residual disease. Minimal (ie. measurable) residual disease is defined as persistence of leukemic cells at levels below morphologic detection. In AML specifically, it can be used to assess treatment response. Furthermore, in AML the presence of MRD has strong and independent prognostic significance as patients with MRD have an increased relapse risk and decreased survival.[13] However, this data on MRD is in relation to patients receiving standard intensive chemotherapy regimens and mostly in the upfront treatment setting. Little is known about MRD assessment utilization in patients receiving HMA/venetoclax combinations, especially in the relapsed/refractory AML setting; the most appropriate timepoint(s) to assess MRD and depth of response in relation to survival are poorly understood. Therefore, with this study we aim to gather important information on MRD assessments in patient's receiving HMA/venetoclax combinations notably in the relapsed/refractory setting. Technologies to measure MRD include immunophenotyping, cytogenetics, and mutational analysis. Utilizing NGS to monitor mutations with associated targeted therapies (*FLT3-ITD, IDH1/2*) and mutations with prognostic significance (*CEBPA, NPM1*) has been shown to be feasible in patients with

AML.[14] Therefore, we plan to utilize NGS testing of patients' bone marrow to determine if mutant clones persists following combination therapy with decitabine, venetoclax, and nivolumab.

2.5.2 T cell response assessment

We propose that decitabine, venetoclax and nivolumab in combination will enhance T cell mediated cytotoxicity in AML. We will study the T cell response against both tumor associated antigen (TAA) and tumor specific antigen (TSA) which are neo-antigens formed by peptides that are created by tumor-specific DNA alterations that result in the formation of novel protein sequences. The most common and well characterized TAAs in AML, including WT-1, Survivin, hTERT and MUC-1. We will also evaluate other markers, such as checkpoint molecules and T cell exhaustion markers. T cell recognition of neo-antigens has been found to play a major role in checkpoint blockade therapy for solid tumors such as melanoma and are proposed to do the same in AML. In early-phase trials studying active specific immunotherapy for AML, many leukemia antigens have shown clinical effectiveness.[15] Furthermore, tumor-reactive T cells can be directed against neo-antigens or leukemia-associated antigens. It has also been shown that acute leukemias evade the immune system through checkpoint molecules PDL-1 and CTLA-4.[16] Finally, T cell exhaustion has been demonstrated to not only occur in AML, but to be a dominant cause of T cell dysfunction.[17,18]

2.5.3 DNA methylation studies

We propose that the DNA methylation and biologically effective dosing of decitabine and venetoclax will not be affected by the addition of nivolumab. We will study the level of global DNA methylation as well as methylation levels of specific genes involved in immune checkpoint, such as PD-L1, PD-L2, PD-1 and CTLA4. DNA methylation (and thus inactivation) of tumor suppressor genes has been linked to malignant transformation and it has been demonstrated that decitabine decreases global DNA methylation.[19] In AML patients who received hypomethylating agents, a higher level of methylation was associated with a poorer prognosis compared a lower level of methylation.[20] Furthermore, it has been shown that AML patients with increased PD-L1 methylation had a significantly prolonged OS and decreased risk of relapse.[21]

2.5.4 Pharmacokinetic (PK) and Pharmacodynamic (PD) studies

While the combination of decitabine and venetoclax has been studied and is currently being utilized clinically, adding nivolumab to this combination is novel. Venetoclax has low bioavailability, high inter-patient PK variability, and is susceptibility to drug-drug interactions (DDIs) through inhibition of intestinal CYP3A4, P-glycoprotein (P-gp), and BCRP and liver CYP3A4 and OATP1B1. Antifungal agents, which are routinely administered concurrently with venetoclax, are moderate-to-strong inhibitors of CYP3A4, and the drug transporters P-gp, BCRP, and OATP1B1. The unpredictable PK properties of venetoclax and high DDI potetial warrant detailed plasma PK evaluation of venetoclax during AML therapy.

Plasma biomarker assays for OATP1B1 activity will also be incorporated to determine

OATP1B1 activity in relation to antifungal and venetoclax treatment (DOI: 10.1124/dmd.119.089474). As liver uptake by the transporters OATP1B1 can be a rate-limiting step to CYP3A4-mediated drug metabolism, and azoles and echinocandins are potent inhibitors of OATP1B1, we will also measure plasma biomarkers for OATP1B1 activity before and after administration antifungal/venetoclax. In order to assess the degree of OATP1B1 inhibition, analysis of glycochenodeoxycholate sulfate (GCDGA-S) and chenodeoxycholate-24-glucuronide (CDCA-24G) levels will be performed in plasma samples as validated surrogate endogenous substrates of OATP1B1/OATP1B3. Previous clinical studies have indicated that the AUC of GCDCA-S can be increased >20-fold following treatment with OATP1B1/3 inhibitors, whereas CDCA-24G is only detectable after the administration of OATP1B1/3 inhibitors. In addition to these bile acids, the co-proporphyrins CP-I and CP-III will be examined as OATP1B1/3 biomarkers. These compounds are known OATP1B1/3 substrates in vitro, and their plasma levels are significantly increased in Oatp1a/1b gene cluster knockout mice, compared with wild-type animals (up to 18.4-fold) as well as in humans receiving OATP1B1/3 inhibitors. The selectivity of CP-I and CP-III for OATP1B1 and OATP1B3 has been confirmed by the demonstration that these compounds are not transported by OCT1, OCT2, OAT3, or NTCP.

Antibody drug clearance has been demonstrated as an early biomarker for outcomes from immune checkpoint inhibitor therapy in some disease populations [32037060, 32089494]. In particular, baseline clearance (CL0, the clearance of the first dose of antibody drug) and/or changes in clearance over time significantly associate with PFS and/or overall survival (OS) for CTLA4-targeted [31709718], PD1-targeted [28573468, 28182273, 29891725, 30018117, 31710163, 761097Orig1s000], and PDL1-targeted agents [30980481, 29243223] (low baseline clearance and decreasing clearance over time correlates with better outcomes). Sex is also a significant covariate for nivolumab clearance in patients with advanced solid tumors [PMC6767401, PMC5270302]. Elevated baseline clearance is also observed in patients with cancer-associated cachexia, and decreasing clearance over time trends with weight gain in patients who are responding to therapy. It is not currently known if CL0 or change in CL over time for nivolumab will serve as a predictive biomarker in this patient population, so we aim to evaluate this within the trial.

Integration of venetoclax, decitabine, and nivolumab PK/PD will allow assessment of exposure-response relationships.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed acute myeloid leukemia (AML).

3.1.2 Relapsed or refractory AML without any other reasonable treatment options

3.1.3 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of nivolumab in combination with venetoclax and decitabine in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials if combination therapy deemed to warrant further assessment after this pilot study.

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Patients must have adequate organ and marrow function as defined below:

- total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN), (except for patients with Gilbert's disease)
- AST(SGOT)/ALT(SGPT) ≤5 × institutional ULN
- glomerular filtration rate (GFR) >40 mL/min/1.73 m^2

3.1.6 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.7 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.8 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.9 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.10 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better. A baseline troponin should be within normal limits and baseline oxygen saturation should be greater than or equal to 92%. A baseline ECG should be normal, or with stable changes if patient has chronic ECG changes.

3.1.11 Active infection is permitted if the infection is under control.

3.1.12 WBC must be ≤25,000 at time of Day 1 of study treatment. Cytoreduction with Hydrea and leukopheresis is allowed.

3.1.13 Risks from venetoclax and nivolumab to the developing human fetus cannot be ruled out.For this reason and because decitabine is knowns to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Contraception use should be continued 6 months after the completion of all study treatments for

women of child bearing potential. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 7 months after completion of decitabine, venetoclax, or nivolumab administration.

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making are allowed to participate as long as the patient has a Legally Authorized Representative (LAR) or caregiver.

3.2 Exclusion Criteria

3.2.1 Patients who have received any prior BCL-2 inhibitor therapy

3.2.2 Patients who have received prior hypomethylating therapy for treatment of AML are excluded

3.2.3 Patients with *known autoimmune disease.* Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.2.4 Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

3.2.5 Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses $\leq$10 mg daily prednisone equivalents are permitted in the

absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if ≤10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (*e.g.*, contrast dye allergy) or for treatment of non-autoimmune conditions (*e.g.*, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

3.2.6 Patients with hyperleukocytosis requiring immediate cytoreductive chemotherapy (WBC ≥100,000 with symptoms of leukostasis)

3.2.7 Isolated extramedullary leukemia of CNS involvement with leukemia

3.2.8 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia.

3.2.9 Patients who are receiving any other investigational agents.

3.2.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to decitabine, venetoclax, or nivolumab

3.2.11 Patients with uncontrolled intercurrent illness.

3.2.12 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.13 Pregnant women are excluded from this study because fetal risk has been demonstrated with decitabine with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with decitabine, breastfeeding should be discontinued if the mother is treated with decitabine. These potential risks may also apply to other agents used in this study.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

Planned distribution of subjects

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	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	4	0	0	**8**
White	12	16	3	3	**34**
More Than One Race	0	0	0	0	**0**
Total	**16**	**20**	**3**	**3**	**42**

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4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD),

- AP: clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the

Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation,
- IRB-signed CTSU IRB Certification Form, and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol PI (i.e., the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen

  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select LAO-OH007, and protocol number 10317,

- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Protocol Specific Requirements For 10317 Site Registration

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
  - This training will need to be completed before the first patient enrollment at a given site.
  - Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and DVulih@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website ➔ Regulatory ➔ Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.5 Checking Site Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.2 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in Section 5.3.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU 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.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 10 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Baseline		
Pre-venetoclax/azole	• 4 mL Peripheral Blood (EDTA-containing vacutainer) – OATP1B1 plasma biomarker	OSU PharmacoAnalytical Shared Resource for ChOP-KC
	• 10 mL of bone marrow aspirate in sodium heparin tubes (mandatory) • 15 mL blood in ACD tubes (mandatory)	Ohio State Leukemia Tissue Bank
	• Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation	
Cycle 1 Day 14 (C1D14)		
Pre-venetoclax, 1h, 2, 4, 7h, 24h Pre-nivolumab, 4h after end of infusion	• 4 mL Peripheral Blood (EDTA-containing vacutainer) – Venetoclax plasma levels, OATP1B1 plasma biomarker assay • 3 mL Peripheral Blood (red top vacutainer) – Nivolumab serum levels	OSU PharmacoAnalytical Shared Resource for ChOP-KC
Day 28+/- 1 day of cycles 1, 2, and 3		
	• 10 mL of bone marrow aspirate in sodium heparin tubes (mandatory) • 15 mL blood in ACD tubes (mandatory)	Ohio State Leukemia Tissue Bank
	• Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation	
Day 28 +/- 1 day every 3 cycles starting with cycle 6 (ex. Cycles 6, 9, 12…)		
	• 10 mL of bone marrow aspirate in sodium heparin tubes (mandatory) • 15 mL blood in ACD tubes (mandatory)	Ohio State Leukemia Tissue Bank
	• Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation	
Day 28 +/- 1 day of end of every cycle starting with cycle 4 (excluding cycles 6, 9, 12… as above)		
	• 10 mL blood in ACD tubes (mandatory)	Ohio State Leukemia Tissue Bank
	• Correlatives: DNA methylation	
Induction Cycle 2 Day 1		

Pre-nivolumab, 4h after end of infusion	3 mL Peripheral Blood (red top vacutainer) – Nivolumab serum levels	OSU PharmacoAnalytical Shared Resource for ChOP-KC
Maintenance Cycle 1 (Day 1)		
Pre-nivolumab, 4h after end of infusion	3 mL Peripheral Blood (red top vacutainer) – Nivolumab serum levels	OSU PharmacoAnalytical Shared Resource for ChOP-KC
Maintenance Cycle 3 (Day 14)		
Pre-nivolumab, 30 min after end of infusion	3 mL Peripheral Blood (red top vacutainer) – Nivolumab serum levels	OSU PharmacoAnalytical Shared Resource for ChOP-KC
End of Treatment/Relapse		
	• 10 mL of bone marrow aspirate in sodium heparin tubes (mandatory) • 15 mL blood in ACD tubes (mandatory)	Ohio State Leukemia Tissue Bank
	• Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation	
~ 2 weeks after last nivolumab infusion	• 3 mL Peripheral Blood (red top vacutainer) – Nivolumab serum levels	OSU PharmacoAnalytical Shared Resource for ChOP-KC

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Procurement Kits

Institutional supplies should be used for shipping specimens.

5.2.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:

- Bone marrow aspirates collected must be sent to the corresponding lab on the same day of collection. Bone marrow aspirate can be collected Monday through Friday
- Fresh blood specimens may be collected and sent Monday through Friday.

5.3 Specimen Tracking System Instructions

5.3.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

5.3.2 Specimen Labeling

5.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date (to be added by hand)

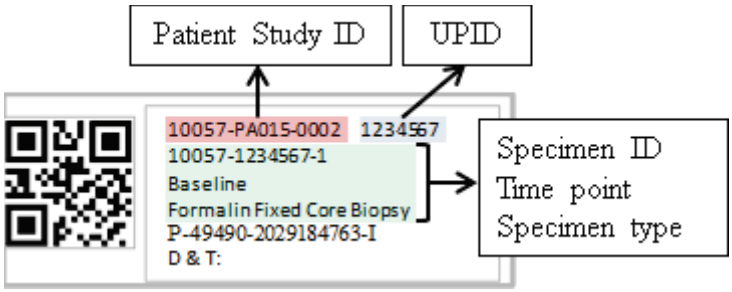
5.3.2.2 Tissue Specimen Labels \

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)

5.3.2.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

5.3.3 Overview of Process at Treating Site

5.3.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration with eligibility specimen analysis:

1. Site enters first step data into OPEN.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends first step registration data, including the IDs and a TAC of "NOT REG" directly to Rave.
4. The specimen tracking system in Rave is utilized for the specimen that contributes to eligibility determination.
5. Site enters second and any subsequent step data into OPEN including results of specimen analysis.
6. IWRS receives all data from OPEN, then sends it onto Rave with either the treatment

TAC or a TAC of "SCRN FAIL".

7. In addition to the specimen tracking forms completed to determine eligibility, data entry for screen failure patients should include Histology and Disease, all forms in the Baseline folder, any lab forms connected to eligibility determination, and Off Treatment/Off Study.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.3.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number or relevant dates, and include the UPID and patient study ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

5.4 Specimen Collection

5.4.1.1 Collection of Bone Marrow Aspirate in Sodium Heparin Tubes for Processing

1. Label EDTA tube(s) according to the instructions in Section 5.4.2.
2. Collect 8-10 mL of bone marrow aspirate in each EDTA (purple top) tube(s).
3. Tubes should be inverted gently at least 3 times.
4. Tubes may be kept at ambient temperature after collection and during shipment

5.4.1.2 Collection of Blood in ADC Tubes for Whole Blood Processing

1. Label ADC tubes according to the instructions in Section 5.4.2.
2. Collect up to 10 mL blood in each EDTA tube(s) and gently invert tube to mix.
3. Tubes should be inverted gently at least 3 times.
4. Tubes may be kept at ambient temperature after collection and during shipment

5.4.1.3 Collection of Blood for Venetoclax, OATP1B1 biomarker and nivolumab pharmacokinetic studies

1. See Appendix F

5.5 Shipping of Specimens from Clinical Site to Other Laboratories

5.5.1 Shipping of Specimens to Ohio State CLIA Certified Lab

5.5.1.1 Bone marrow aspirate will be collected and sent as normally for molecular sequencing to Ohio State University sequencing laboratory

5.5.2 Shipping of Specimens to Ohio State Leukemia Tissue Bank

5.5.2.1 Specimen Shipping Instructions
Notify the Leukemia Tissue Bank when patient arrives and orders have been pended. The LTB staff will pick up the samples when complete.

5.5.2.2 Shipping Address
If needed to send to the Leukemia Tissue Bank directly, please see the following address:
300 West Tenth Avenue, Lobby
Columbus, OH 43210

5.5.2.3 Contact Information for Assistance
Chris Manring, Clinical Laboratory Manager

614 688-9862 or 614-688-4754 or email: Christopher.manring@osumc.edu

5.5.3 Shipping of Specimens to Ohio State PharmacoAnalytical Shared Resource (PhASR)

5.5.3.1 See Appendix F

5.6 Biomarker Plan

Biomarker Name AND **Lab PI and Site**	**Assay (CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose**	**Tissue/Body Fluid Tested and Timing of Sample Collection**	**M/O**	**Use of NCI Resources (No / Pending Approval / Approved)**	**Funding Source(s)**
Immunophenotyping Gerard Lozanski, MD/The Ohio State University, Director of Flow Cytometry Laboratory Gerard.Lozanski@osumc.edu	Multiparameter flow cytometry CLIA: Y No Review Required	Exploratory Depth of Response assessment.	Bone marrow biopsy aspirate - Baseline - End of cycle 1, 2, and 3 Every 3 months starting with cycle 6 - Relapse/EOT	M	ETCTN Biorepository: No CIMAC: No NCLN Genomics Laboratory: No	NO1 correlative funding budget
Cytogenetics Cecelia Miller, PhD/The Ohio State University, Director of Cytogenetics	Karyotype and FISH analyses CLIA: Y No Review Required	Exploratory Depth of Response assessment.	Bone marrow biopsy aspirate - Baseline - End of cycle 1, 2, and 3 Every 3 months starting with cycle 6 - Relapse/EOT	M	ETCTN Biorepository: No CIMAC: No NCLN Genomics Laboratory: No	NO1 correlative funding budget
Global and gene-specific DNA methylation Chris Oakes, PhD (PI) /The Ohio State University, Experimental Hematology Lab Christopher.Oakes@osumc.edu	Quantitative DNA methylation with MassARRAY CLIA: N No Review Required	Exploratory To assess global DNA methylation and methylation levels of specific genes involved in immune checkpoint.	Peripheral blood - Baseline - End of each cycle (both induction and maintenance) -Relapse	M	ETCTN Biorepository: No CIMAC: No NCLN Genomics Laboratory: No NCLN PD Laboratory: No	NO1 correlative funding budget

Biomarker Name AND **Lab PI and Site**	**Assay (CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose**	**Tissue/Body Fluid Tested and Timing of Sample Collection**	**M/O**	**Use of NCI Resources (No / Pending Approval / Approved)**	**Funding Source(s)**
Next generation sequencing AML mutational analysis with Variant Allele Frequency James Blachly, MD (PI)/ The Ohio State University, Experimental Hematology Lab James.Blachly@osumc.edu	Amplicon Sequencing for 96 gene panel CLIA: N No Review Required	Exploratory Depth of Response assessment.	Bone marrow biopsy aspirate - Baseline - End of cycle 1, 2, and 3 - Every 3 months starting with cycle 6 - Relapse/EOT	M	ETCTN Biorepository: No CIMAC: No NCLN Genomics Laboratory: No NCLN PD Laboratory: No	NO1 correlative funding budget
Tetramer analysis and Cytokine Production up re-stimulation with antigenic peptide Meixiao Long, MD, PhD (PI)/ The Ohio State University, Experimental Hematology Lab Meixiao.Long@osumc.edu	Flow cytometry and functional assay CLIA: N No Review Required	Exploratory To identify tumor specific T-cell response to AML cells. These include T cells specific for tumor associated antigen (WT1 and MUC1) as well as T cells recognized tumor specific “neoantigen”.	Peripheral blood: - Baseline - After cycles 1, and 3 of induction and cycles 3 and 9 of maintenance Bone marrow biopsy aspirate: - Baseline - End of cycles 1, 2, and 3 - Every 3 months starting with cycle 6 - Relapse/EOT	M	ETCTN Biorepository: No CIMAC: No NCLN Genomics Laboratory: No NCLN PD Laboratory: No	NO1 correlative funding budget
Venetoclax and OATP1B1 biomarker studies Sharyn Baker, PharmD PhD/ The Ohio State University, Division of Pharmaceutics and Pharmacology Baker.2480@osu.edu	LC/MS-MS and ELISA CLIA: N No Review Required	Exploratory To assess the effect of antifungal agent on venetoclax plasma PK and OATP1B1 plasma biomarker	Peripheral blood - Baseline Cycle 1 (Day 14/15)		ETCTN Biorepository: No CIMAC: No NCLN Genomics Laboratory: No	U24 ChOP-KC
Nivolumab PK studies Mitch Phelps, PhD/ The Ohio State University, Division of Pharmaceutics	LC/MS-MS and ELISA CLIA: N	Exploratory To assess the PK of nivolumab in combination with	Peripheral blood - Cycle 1 (Day 14) -		ETCTN Biorepository: No	U24 ChOP-KC

and Pharmacology Phelps.XX@osu.edu	No Review Required	venetoclax/decitabine	- Induction Cycle 2 (Day 1) - - Maintenance Cycle 1 (Day 1) - - Maintenance Cycle 3 (Day 14) - - End of Treatment/Relapse		CIMAC: No NCLN Genomics Laboratory: No	

5.7 Integral Laboratory Studies

None

5.8 Exploratory/Ancillary Correlative Studies

5.8.1 Flow Cytometry

5.8.1.1 Specimen(s) Receipt and Processing at Ohio State University's Leukemia Tissue Bank

5.8.1.2 Site(s) Performing Correlative Study

This exploratory biomarker will be performed locally at the participating institution, then the immunephenotyping raw data will be reviewed centrally at The Ohio State University's Flow Cytometry Clinical Lab.

5.8.2 Cytogenetics with karyotyping and AML FISH panel

5.8.2.1 Specimen(s) Receipt and Processing at Ohio State University's Leukemia Tissue Bank

5.8.2.2 Site(s) Performing Correlative Study

This exploratory biomarker will be performed at locally and the chromosome pictures will be sent for central review at The Ohio State University's Cytogenetics Clinical Lab.

5.8.3 Next generation sequencing AML mutational analysis with Variant Allele Frequency

5.8.3.1 Specimen(s) Receipt and Processing at Ohio State University's Leukemia Tissue Bank

5.8.3.2 Site(s) Performing Correlative Study

This exploratory biomarker will be performed at The Ohio State University's Experimental Hematology Lab.

5.8.4 Tetramer analysis and Cytokine Production up re-stimulation with antigen peptide

5.8.4.1 Specimen(s) Receipt and Processing at The Ohio State University's Leukemia Tissue Bank

5.8.4.2 Site(s) Performing Correlative Study

This exploratory biomarker will be performed at The Ohio State University's Experimental Hematology Lab.

5.8.5 Global and gene-specific DNA methylation

5.8.5.1 Specimen(s) Receipt and Processing at The Ohio State University's Leukemia Tissue Bank

5.8.5.2 Site(s) Performing Correlative Study

This exploratory biomarker will be performed at The Ohio State University's Experimental Hematology Lab.

5.8.6 Venetoclax, OATP1B1 biomarker and nivolumab PK studies

5.8.6.1 Specimen(s) Receipt and Processing at The Ohio State University's PharmacoAnalytical Shared Resource

5.8.6.2 Site(s) Performing Correlative Study
This exploratory biomarker will be performed at The Ohio State University for the ChOP-KC.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered as either an outpatient or inpatient basis as appropriate. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose Scheduling			
Dose level	Venetoclax*	Decitabine	Nivolumab
Dose level -2	Cycle 1 Day 1 100mg Cycle 1 Day 2 200mg Cycle 1 Day 3-14 400mg Cycle 2 and beyond Day 1-14 400mg	<u>Induction</u> 20 mg/m^2 intravenously on Days 1-10 <u>Maintenance</u> 20 mg/m^2 intravenously on Days 1-5	Flat dose of 240mg every 2 weeks starting on Day 15 of Cycle 1 and continue Day 1 and 15 with cycle 2 and subsequent cycles
Dose level -1	Cycle 1 Day 1 100mg Cycle 1 Day 2 200mg Cycle 1 Day 3-21 400mg Cycle 2 and beyond Day 1-21 400mg		
Dose level 1	Cycle 1 Day 1 100mg Cycle 1 Day 2 200mg Cycle 1 Day 3-28 400mg Cycle 2 and Cycle 3 (if needed) Day 1-28 400 mg Maintenance cycles Day 1-21 400 mg		

Regimen Description

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Nivolumab	Take precaution for infusion/anaphylactic reaction	240mg in max of 160ml NS	IV over 30 minutes	Days 1 and 15 (day 15 only for cycle 1)	28 days (4 weeks)
Decitabine	Premedicate with ondansetron 30 minutes prior to chemotherapy	20 mg/m^2 in 150ml NS	IV over 60 minutes	Days 1-10 for induction cycles and Days 1-5 for maintenance cycles	
Venetoclax*	Take with a meal and water. Premedicate with allopurinol and adequate hydration.	Four 100 mg tablets	PO in the a.m.	Daily, days 1-28 (with ramp up for cycle 1 only – Day 1 100mg, Day 2, 200mg, and Day 3 400mg) [note: days 1-21 for maintenance cycles]	

*Please see Section 6.4.1.1 for dose adjustments with concurrent CYP3A inhibitor use

6.2 Order of administration

When infusions of nivolumab and decitabine are administered on the same day, nivolumab should be administered first, followed by decitabine. There should be 30 minutes of time between infusions.

6.2.1 Other Agent(s)

6.2.1.1 Nivolumab

No specific premedications are required, but diphenhydramine, hydrocortisone, and epinephrine should be available in case of an infusion reaction or anaphylactic reaction. There are no known issues with intravenous solutions.

6.2.1.2 Decitabine

Premedicate with 8 mg oral ondansetron 30 minutes prior to chemotherapy. There are no known issues with intravenous solutions.

6.2.1.3 Venetoclax

Provide anti-hyperuricemic agents (allopurinol 300 mg daily, begin at least 72 hours prior to starting treatment with venetoclax) and adequate hydration to all patients prior to first dose and continue through ramp-up phase. Patients should be instructed to drink 6 to 8 glasses water each day, starting 2 days before the first dose, on the day of the first dose of venetoclax, and each time the dose is increased.

Tablets should be taken orally once daily, at approximately the same time, with a meal and water. Do not chew, crush, or break tablets.

If a dose is missed by less than 8 hours, take the missed dose right away and take the next dose as usual. If a dose is missed by more than 8 hours, the patient should wait and take the next dose at the usual time.

Patients should not take an additional dose if they vomit after taking venetoclax. They should take the next dose at the usual time the following day.

Tell the patient to Avoid grapefruit products, Seville oranges, and starfruit during treatment.

6.3 Definition of Dose-Limiting Toxicity

The dose limiting toxicity period (DLT) will be defined as the time period from the start of nivolumab therapy on C1D15 to the end of cycle 3. DLT will be defined as non-hematologic toxicity of ≥ grade 3 with the exception of grade 3 nausea and vomiting that resolves to < grade 3 within 72 hours, and infection (infection-related toxicities such as fever/sepsis, see below). The grade 3/4 toxicity, designated to be DLT, should be considered drug-related. Patients with transient grade ≥ 3 electrolyte abnormalities that are not clinically significant and are correctable within 24 hours will not be considered a DLT. Patients with ≥ grade 3 transient liver function test abnormalities (AST, ALT, or alkaline phosphatase) that resolve to < grade 2 within 5 days will not be considered DLT only if it is self-limited without steroid treatment. Grade 3 or 4 infection will not constitute DLT unless it is felt that the infection resulted from unexpectedly complicated myelosuppression (degree or duration).

Hematological DLT will be considered as failure to recover neutrophil count (ANC≥500), or platelet count ≥25,000, or hemoglobin ≥7 by Day 42 in patients with <5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of evidence of disease by flow cytometry in the bone marrow. For patients with ≥ 5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry/cytogenetics, failure to recover neutrophil, platelet count, or hemoglobin may not be considered DLT as this could be the result of persistent disease.

Specifically with nivolumab, any patient who requires high dose steroids (any dose greater than the equivalent to 20 mg prednisone daily) will be considered to have experienced a DLT and will be taken off nivolumab but allowed to remain on decitabine and venetoclax.

Management and dose modifications associated with the above adverse events are outlined in Section 7.

6.3.1 Evaluable for toxicity

Patients evaluable for safety/toxicity: Any patient receiving study treatment during the DLT eval period- start of nivolumab C1D15 to end of cycle 3. Therefore, any patients who do not receive nivolumab will not be evaluable for safety and will be replaced.

6.3.2 Evaluable for response

Patients evaluable for response: Any patient who receives all of the 3 study drugs. These patients will not be replaced.

6.3.3 Progressive disease stopping rule

Stopping rule: if >50% of patients have disease progression prior to finishing cycle 3, the study PI and sponsor will consider stopping the study due to ineffective treatment.

6.4 General Concomitant Medication and Supportive Care Guidelines

Do not administer live attenuated vaccines prior to, during, or after treatment until B-cell recovery occurs.

6.4.1 Concomitant Medications with Venetoclax

Venetoclax is predominantly metabolized by CYP3A4/5. Concomitant use of venetoclax with strong inhibitors of CYP3A at initiation and during ramp-up phase is contraindicated. For patients who have completed the ramp-up phase and are on a steady daily dose, reduce the dose by at least 75% when used concomitantly with strong CYP3A inhibitors. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor
Avoid concomitant use of moderate CYP3A inhibitors or P-gp inhibitors. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the dose by at least 50%. Resume the dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.
Avoid concomitant use with strong CYP3A inducers or moderate CYP3A inducers.
Venetoclax may cause a significant increase in Cmax and AUC of warfarin. International normalized ratio (INR) should be monitored closely in patients receiving warfarin.

6.4.1.1 Venetoclax Dose Adjustments with Common Antifungals and Other CYP3A Inhibitors

The dose of venetoclax should be adjusted to the following doses if taken with these antifungal medications:

Posaconazole:
Ramp-up Day 1- 20 mg venetoclax
Ramp-up Day 2- 50 mg venetoclax
Day 3 and onward- 70 mg venetoclax
Moderate CYP3A Inhibitors (ex. Fluconazole/Isavuconazole):
Ramp-up Day 1- 50 mg venetoclax
Ramp-up Day 2- 100 mg venetoclax
Day 3 and onward- 200 mg venetoclax
Strong CYP3A Inhibitors (ex. Voriconazole):
Ramp-up Day 1- 20 mg venetoclax

Ramp-up Day 2- 50 mg venetoclax
Day 3 and onward- 100 mg venetoclax

Because there is a potential for interaction of nivolumab, decitabine, and venetoclax with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix D (Patient Drug Interactions Handout and Wallet Card) should be provided to patients if available.

6.4.2 Prophylaxis and Management of Tumor Lysis Syndrome

Upon treatment of hematologic malignancies there is a potential for TLS, especially in those with elevated pretreatment LDH levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the risk for TLS, all patients on this study will be considered high risk for TLS and will receive tumor lysis prophylaxis, including hydration (e.g., oral, intravenous) and treatment with an agent to reduce the uric acid level (e.g., allopurinol, rasburicase). Patients will not be eligible for study if WBC >25,000 as per current recommendations of venetoclax with hypomethylating agents per the FDA label.

It is recommended that all subjects receive the following TLS prophylaxis measures:
• Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) prior to initial study therapy administration (ideally at least 72 hours prior when possible) and continued until each subject has completed a week at their highest dose level of venetoclax.
• Chemistry and hematology laboratory tests to be performed the morning of the first dose of venetoclax. The investigator's decision to proceed with venetoclax treatment initiation will be based on these laboratory values.
• Rasburicase (given at a flat dose of 6 mg IV x 1, or per institutional standards) must be administered per institutional guidelines for subjects with elevated uric acid level at baseline (> ULN) as prophylaxis prior to the initial dose of venetoclax. For subjects with a contraindication to rasburicase (i.e., glucose-6-phosphate dehydrogenase [G6PD] deficiency), the TLS risk-mitigation plan must be reviewed with the Overall PI.
• Chemistry laboratory tests must be performed STAT at least at the following time points: pre-dose (within 4 hours before venetoclax administration), and ever 12 hours during the venetoclax ramp-up period. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
• If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see Appendix C (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]), for additional laboratory assessments and management guidelines. If aggressive correction of electrolytes abnormalities was performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any further treatment for approximately 24 hours.
• Hematology laboratory tests will be performed pre-dose (within approximately 4 hours before venetoclax administration), and approximately 24 hours post-dose after the first dose of venetoclax.
• During the dose ramp-up period, the subsequent dose should not be administered until the 24

hours post-dose laboratory values are reviewed by the investigator.

* All laboratory assessments may be taken within +/- 2 hour window, and 24 hour laboratory assessments within a +/-3 hour window, if necessary.

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression/loss of response
- Bone marrow/stem cell transplantation
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.5.1 Duration of Therapy in cases of CR

If the patient achieves a CR/CRi, even if MRD negative, the patient should continue on therapy as long as none of the above instances in 6.5 occurs. However, venetoclax may be interrupted, and the subsequent cycle of decitabine may be delayed to allow for absolute neutrophil count recovery from day 29 of current cycle until absolute neutrophil count reached at least 500/μL or

up to 14 days, then a bone marrow biopsy should be done to assess for continued CR/CRi. If patient remains in CR/CRi then dose reductions can occur as follows. For recurrent Grade 4 neutropenia and thrombocytopenia that lasts >6 weeks from Day 1 of cycle: first dose reduction will be to decrease venetoclax to 14 days (days 1-14 of the cycle), the second dose reduction will be to decreased to 7 days (days 1-7 of the cycle), the third dose reduction will be to reduce decitabine to 4 days (days 1-4 of the cycle), and the fourth/final dose reduction will be to reduce decitabine to 3 days (days 1-3 of the cycle). If Grade 4 thrombocytopenia and neutropenia recurs after all of these four dose reductions and lasting >56 days, patient will be taken off study.

6.6 Duration of Follow-Up

Patients will be followed for up to 3 years after initiation of therapy or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dose Delays/Modifications for DLT

Study treatment (all three drugs) will be held for any patients experiencing a DLT.

Non-hematologic DLT: Patients may restart therapy when the adverse event recovers to CTCAE ≤grade 1 or to the patient's baseline values. If study treatment is restarted and another non-hematologic DLT is encountered, the patient must be removed from the study.

Hematologic DLT: After the 42 day period and confirmed hematologic DLT: If peripheral blasts are absent AND the bone marrow blasts are less than 5%, then the patient may restart study treatment with decrease of decitabine to 5 days from 10 days of therapy.

If treatment is delayed >6 weeks for an adverse event the patient must be permanently discontinued from study therapy.

Patients requiring > two dose delays for the same event should go off protocol therapy.

Please see specific modifications for Nivolumab (Section 7.3)

Drugs may be resumed per protocol. If a specific agent (e.g. decitabine or nivolumab or venetoclax) is permanently discontinued for toxicity, the other two agents may be continued on study. Decitabine and venetoclax doses should not be reduced following toxicity and dose interruption, they should continue at the same dose as stated in the protocol.

7.1.1 Dose Delays/Modifications for other adverse events

All three study drugs will be held for adverse events requiring interruption until the toxicity can be evaluated, then resumed unless a drug needs to be permanently discontinued.

7.2 Dose modifications of Decitabine and Venetoclax for non-DLTs

Subjects who experience a ≥ grade 3 non-hematologic toxicity with 10 days of decitabine in the first cycle will have their dose reduced to 5 days in the second cycle.

Non-hematologic due to Decitabine or Venetoclax: Any subject who experiences a non-hematological AE related to the agent of Grade 3 or 4 that is an escalation from his or her status at baseline should have the agent temporarily held until the toxicity Grade returns to less than Grade 3. The agent should be permanently discontinued if the non-hematological toxicity persists as Grade 3 or 4 for more than 21 days, despite the temporary interruption of the agent and patients should be taken off treatment with this agent.

Hematologic AE due to decitabine or venetoclax: Decitabine and/or venetoclax doses should not be reduced following toxicity and dose interruption. Dose reductions of decitabine and venetoclax are allowed in the following manner. For recurrent Grade 4 non that lasts >6 weeks from Day 1 of cycle: first dose reduction will be to decrease venetoclax to 14 days (days 1-14 of the cycle), the second dose reduction will be to decreased to 7 days (days 1-7 of the cycle), the third dose reduction will be to reduce decitabine to 4 days (days 1-4 of the cycle), and the fourth/final dose reduction will be to reduce decitabine to 3 days (days 1-3 of the cycle). If Grade 4 thrombocytopenia and neutropenia recurs after all of these four dose reductions and lasting >56 days, patient will be taken off study.

7.3 Missed doses of Decitabine and Venetoclax

Decitabine: If decitabine is missed/held, it may be restarted within 48 hours from time of missed dose, and the missed days can be made up. If longer than this period, patients will wait for further therapy until next cycle of treatment.

Venetoclax: If a dose is missed by less than 8 hours, take the missed dose right away and take the next dose as usual. If a dose is missed by more than 8 hours, the patient should wait and take the next dose at the usual time. Patients should not take an additional dose if they vomit after taking venetoclax. They should take the next dose at the usual time the following day. If a dose is vomited within one hour of ingestion, it will be considered a missed dose and recorded as such on the patient diary. The dose will not be repeated that same day but the patient will follow regular schedule starting the next study dosing day. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose.

7.4 Dosing delays and modifications once at least MLFS is achieved

Each subsequent cycle of treatment with decitabine+venetoclax should be administered as per the FDA decitabine/venetoclax label. Per the label, if grade 4 thrombocytopenia and/or neutropenia occurs, hold both decitabine and venetoclax until the neutropenia and thrombocytopenia resolve to a grade 2 or less. Please refer to Section 6.5.1 for further details. If a decitabine/venetoclax cycle is delayed, nivolumab should also be held and then restarted on Day 1 of the next cycle when decitabine/venetoclax is restarted.

7.5 Nivolumab

Please refer to the Nivolumab Investigator Brochure or Appendix E to the protocol for toxicity management algorithms which include specific treatment guidelines. These algorithms should

be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study PI or drug monitor is recommended.

Adverse events associated with Nivolumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab must be withheld for drug-related toxicities and severe or life-threatening AES.

- **Drug will be held for any indication suggestion of cardiac dysfunction of any grade pending evaluation**
- **Drug will be permanently discontinued for treatment related grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur**
- **Treatment as clinically indicated for cardiomyopathy**

Cardiac *	Management/Next Dose for Nivolumab Cardiac Toxicities
Less than grade 2	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 without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below.
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 MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. . If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus.. May 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). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off protocol 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.	

All Other Events	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose.
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below).
Grade 3	Hold until ≤ Grade 1 OR baseline and patient no longer on steroid treatment if initiated (exceptions as noted below). Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events.
Grade 4	Off protocol therapy.
Recommended management: As clinically indicated	

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment

- Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose*.
Grade 2	Hold* until 1≤ Grade resolved. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy.
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold at investigator discretion until ULN or baseline. Resume at same dose level.
Grade 2	Grade 2 (3X UNL to 5X UNL): Hold until grade 1 (UNL-3X UNL) or baseline. Resume at same dose level at investigator discretion.
Grade 3	Grade 3 (5X UNL to 20X UNL) Hold until grade 1 or baseline. Resume at same dose level at investigator discretion with return to grade 1 or baseline within 7 days without steroids. If persistent or steroids are required, off protocol therapy.
Grade 4	Off protocol therapy.

Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis. Please note: Grades for liver function follow UNL rather than multiples of baseline.
Recommended management: see Hepatic AE management algorithm

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold until baseline. No change in dose.
Grade 2	Hold until baseline. No change in dose.
Grade 3	Resume at same dose level at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. If persistent or steroids are required off protocol therapy.
Grade 4	Off protocol therapy.
See GI AE Algorithm for management of symptomatic colitis. Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require systemic steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**
≤ Grade 1	Continue at same dose level if asymptomatic at investigator discretion.
Grade 2	Continue at same dose level if asymptomatic at investigator discretion. If symptomatic, resume at same dose level when resolved
Grade 3	Continue at same dose level if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop diabetes mellitus should be taken off treatment.
Grade 4	Hold until grade 2. Resume at same dose level if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis or diabetes mellitus should be taken off treatment.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated.	

For treatment management of symptomatic pancreatitis, please follow the Hepatic AE Management Algorithm.

Pneumonitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO_2. Resume no change in dose after pulmonary and/or infectious disease (ID) consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required.
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off protocol treatment.
Grade 4	Off protocol therapy.
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified, including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary AE Management Algorithm	

Other GI NauseaVomiting	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis, duodenitis, and other immune AEs or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment, patients should go off protocol therapy.
Grade 4	Off protocol therapy
Patients with Grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab**
Grade 2	No change in dose.
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Grade 4	Off protocol therapy.
Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.	

Neurologic events	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy).
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, and myasthenia gravis should be off study.	
Recommended management: See Neurologic AE Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab**
≤ Grade 1	*Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 4	Off protocol therapy.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients	

must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.
Recommended management: See Endocrine Management Algorithm

Renal	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Infusion reaction	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Fever	**Management/Next Dose for Nivolumab**
≤ Grade 1	Evaluate and continue at same dose level.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	
See section 6.7 – Treatment of Nivolumab-Related Infusion Reactions.	

Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate

endocrine testing including cortisol, Cortrosyn® adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), and thyroxine (T4) must be obtained to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Any patient started on corticosteroids initially, who is determined to not require steroid treatment for an autoimmune AE, may resume therapy after a 2-week observation period without further symptoms at the discretion of the PI or investigator.

Any patient requiring high dose steroids (any dose greater than the equivalent to 20 mg prednisone) will be considered to have experienced a DLT and will be taken off nivolumab. These patients will be allowed to continue receiving decitabine and venetoclax on study.

Patients requiring high dose steroid treatment for autoimmune or inflammatory events should go off study treatment except for a short course of tapering steroids for infusion reaction, skin rash or endocrine events.

Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids.

Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.
Patients may be dose-delayed for evaluation and restarted depending on results. Any patient started on corticosteroids initially who is determined to not require steroid treatment for an autoimmune adverse event may resume therapy after a 2-week observation period without further symptoms at the discretion of the PI or investigator.

If doses of nivolumab are missed/delayed other than reasons for toxicity, they may be given +2 days of scheduled dose.

7.6 Special circumstances

Given that the average time to respond to decitabine with venetoclax is 1.3 months, it is possible that many patients could achieve a CR or CRi within this time yet also experience a DLT. Patients who achieve a CR or CRi within the this average 1.3 months' time to response, yet also experience a DLT, will be evaluated and treated at the discretion of the PI and sponsor. These patients will not automatically be taken off study, as we do not want to discontinue a study treatment that is providing benefit without determining if the specific DLT is significant enough to

warrant this.

If a patient experiences a DLT attributed to nivolumab requiring the use of high dose steroids (≥20 mg prednisone daily, or the equivalent), they will be allowed to continue on study receiving decitabine with venetoclax.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the commercial agents administered in this study can be found in Section 10.1.

8.1 Investigational Agent

8.1.1 Nivolumab

Description: Nivolumab Injection 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 dihydrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Storage: Vials of Nivolumab injection must be stored at 2°- 8°C (36°- 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.
If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-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.

Stability: Refer to the package label for expiration.
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 8 hours of the total 24 hours can be at

room temperature (up to 25°C, 77°F) and room light. The maximum 8-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.

Route of Administration: Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

Agent Ordering: Nivolumab is supplied by Bristol-Myers Squibb for this study 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 fluoropolymer film-laminated rubber stoppers and aluminum seals

8.2 Agent Ordering and Agent Accountability

Availability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). 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 participating investigator at that institution.

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, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient sequence number and for each agent on this protocol.

Investigator Brochure Availability: The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

• CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
• NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov

• PMB policies and guidelines:
http://ctep.cancer.gov/branches/pmb/agent_management.htm

• PMB Online Agent Order Processing (OAOP) application:
https://ctepcore.nci.nih.gov/OAOP

• CTEP Identity and Access Management (IAM) account:
https://ctepcore.nci.nih.gov/iam/

• CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

• IB Coordinator: IBCoordinator@mail.nih.gov

• PMB email: 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)

8.3 Commercial Agent

8.3.1 Decitabine

Description: Decitabine (Dacogen) is supplied as a sterile, lyophilized white to almost white powder, in a single-dose vial, packaged in cartons of 1 vial. Each vial contains 50 mg of decitabine.

Preparation: Reconstitution with 10 mL of Sterile Water for Injection results in a concentration of 5 mg/mL. Immediately after reconstitution, the solution should be further diluted with infusion fluids, such as 0.9% sodium chloride Injection or 5% dextrose injection to a final drug concentration of 0.1 - 1 mg/mL.

Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using **COLD** infusion fluids (2°C - 8°C) and stored at 2°C - 8°C for a maximum of 4 hours. Diluted stored solution must be used within 4 hours from the time of preparation.

Use the diluted, refrigerated solution within 4 hours from the time of preparation or discard.

Storage: Store vials at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

Stability: Refer to the package label for vial expiration. Refer to Preparation (above) for infusion stability.

Route of Administration: Intravenous

Agent Ordering: The agent is commercially available.

8.3.2 Venetoclax

Description: Venetoclax tablets are supplied as oblong, bi-convex pale yellow or beige tablets that contain 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic, iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. Each tablet is debossed with "V" on one side and a "100" corresponding to the tablet strength on the other side. The 100 mg tablets are available in 120 and 180 count bottles.

How Supplied: 10 mg, 50 mg, 100 mg tablets

Storage: Store at or below 86°F (30°C).

Stability: Refer to the package label for expiration.

Route(s) **of Administration:** oral with a meal and water at approximately the same time each day. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

Agent Ordering: agent is commercially available

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This will be a phase 1 study determining the maximum tolerated dose (MTD) with an expansion cohort examining the signal for efficacy will be conducted for this study.

Adult AML patients (>= 18 years) with relapsed or refractory disease are eligible. All patients on study must have primary refractory disease following at least one induction regimen or have relapsed disease following induction or consolidation or aHSCT.

Nivolumab in a fixed dose will be administered in combination with decitabine and venetoclax. For the induction phase of this study, patients will be treated with 10 days of decitabine the first 10 days of the cycle. Patients can be treated with up to 3 cycles of 10-day decitabine course before moving on to the maintenance phase of the study. For the maintenance phase, patients will be treated with 5 days of decitabine the first 5 days of the cycle and this treatment will continue until one of the following occurs: loss of response/disease progression, bone marrow/stem cell transplantation, unacceptable toxicities, or patient withdrawal.

For all patients on study, if CR, CRi, or CRh is achieved during cycles 1-3, patients will continue on study at the time response is noted with the maintenance phase treatment. If no response is achieved by cycle 3,

patients will come off study. Bone marrow biopsy will occur on Day 28 (+/- 2 days) for up to 3 cycles to determine treatment response, then Day 28 (+/- 2 days) every third cycle.

Three dose levels (DL 1, -1, -2) illustrated in Section 6.1 are to be examined, and 3+3 design will be used to determine the safe and tolerable dose level. DLT will be defined in Section 6.4, and DLT observation period will be defined as the time period from the start of nivolumab therapy on C1D15 to the end of cycle 3 (can include induction and maintenance cycles based on how many induction cycles are needed). Dose escalation process will follow the rules specified below. Patients who do not finish DLT observation period due to reasons other than DLT will need to be replaced.

Number of Subjects with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended maximally tolerated dose. At least 6 subjects should be entered at the recommended phase 2 dose.

We expect to enroll a minimum of 6 patients (6 patients treated at DL 1 with 1 or less patient experience DLT) and a maximum of 18 patients (6 at each of the DL 1, -1 and -2) for dose finding part. Once the MTD is determined, patients will be accrued to the expansion cohort to be treated at MTD. Including 6 patients treated at MTD from the dose escalation part, we plan to accrual additional 24 R/R AML patients to the expansion cohort. A total of 30 patients will be treated at MTD to decide whether the response rate (CR rate), P, is less than or equal to 30% (combination drug not of interest) or greater than or equal to 50% (combination drug is promising). If the number of responses out of 30 patients is 13 or more, the hypothesis that $P \leq 30\%$ is rejected with a target error rate of 0.10 and an actual error rate of 0.084. If the number of

responses is 12 or less, the hypothesis that P ≥ 50% is rejected with a target error rate of 0.20 and an actual error rate of 0.181.

To estimate the response rate, defined by CR/Cri, which will be assessed by bone marrow biopsy after cycle 1, cycle 2, cycle 3, then every 3 cycles after this, and at time of relapse. Since this will study will only have a small sample size, it will not be powered to determine an accurate response rate for nivolumab in combination with venetoclax and decitabine. We will plan to estimate response rate, as defined by CR/CRi in all evaluable patients in this study, regardless of dose level of venetoclax, and will not attempt to evaluate response rate for individual dose levels. The response rate along with an exact 95% confidence interval will be reported. However, we can consider our study's response rate in context of recent retrospective studies evaluating venetoclax in combination with HMA as well as the historical response rate with high dose cytarabine-containing regimens where the CR rate is 30-40%. Therefore, a response rate of 50% would be considered promising.

Toxicity will be graded and reported according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All patients who receive any amount of the study drug (Nivolumab) will be evaluable for toxicity.

Dosing schema and dosing alterations can be found in Section 6.1 and Section 7.

9.2 Sample Size/Accrual Rate

The maximum total of 42 patients will be accrued. With the estimated accrual rate of 2-3 patients per month, the maximum accrual time including DLT observation period will be around 18-24 months.

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	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	4	0	0	**8**
White	12	16	3	3	**34**
More Than One Race	0	0	0	0	**0**
Total	**16**	**20**	**3**	**3**	**42**

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9.3 Analysis of Secondary Endpoints

Every report of our secondary objectives (listed above in Section 1.2) will contain all patients included in the study. For the response calculation, the report will contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. However, a response rate analysis based on a subset of patients will explain which patients were excluded and for which reasons. 95% confidence limits will be given.

Data that are collected serially over time will be explored graphically using box plots and/or individual time plots as well as analytically with either repeated measures analysis of variance or Friedman's nonparametric test. This trial will form the basis for a follow up proposal to examine this combination in a phase 1 study in newly diagnosed AML patients with *TP53* mutations.

We will assess MRD by measuring the mutational burden with variant allele frequency, cytogenetics, and flow cytometry before and after response is achieved to see if there is a change in any of these MRD assessment parameters. We will compare these three MRD tests at the same time points to characterize the importance of different MRD tests in different molecular subsets of AML. We will also evaluate MRD status at each time point in relation to disease outcome using chi square test of independence. This will allow us to determine which MRD assessment(s) performed at which timepoint(s) is most meaningful and helpful in determining relapsed/refractory AML outcomes. For T-Cell response and DNA methylation studies, analyses

of the data will be primarily descriptive in nature given the relatively small sample size.

Plasma venetoclax and serum nivolumab concentration-time profiles will be analyzed by non compartmental analysis in Phoenix Winonlin, and subsequently by population mixed effects PK modeling using NONMEM. Pharmacokinetic parameters (e.g., Cmax, AUC, CL, V, and t1/2) will be estimated. For venetoclax PK, concurrent antifungal medications will be grouped as strong (e.g., posaconazole, voriconaxole) or moderate (e.g., fluconazole, isavuconazole) CYP3A4 inhibitors, or OATP1B1 inhibitors (e.g, micagungin) and included as a covariate in the venetoclax population PK model. Associations between: 1) antifungal drug administered and/or venetoclax exposure and changes in OATP1B1 plasma biomarkers from baseline to post-treatment; and 2) drug exposure parameters such as Cmax and AUC with toxicity or response will be performed using standard t-tests or Wilcoxon rank sum tests and illustrated using boxplots or other graphical displays. Values will be log transformed as appropriate to reflect biologic plausibility assessment.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

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.

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.

10.1.1 CAEPR for Nivolumab

Version 2.4, December 2, 2020[1]

Adverse Events with Possible Relationship to Nivolumab (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 3)***
CARDIAC DISORDERS			

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[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]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
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)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
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 (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-mediated nephritis)	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<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 tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		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] Nivolumab 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 lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab 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 Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab 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: Nivolumab 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.

10.1.1.1 CAEPR for decitabine

Version 2.5, March 28, 2019[1]

Adverse Events with Possible Relationship to Decitabine (5-aza-2'-deoxycytidine) (CTCAE 5.0 Term) [n= 1832]			
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Anal mucositis		

	Constipation		
	Diarrhea		
	Mucositis oral		
Nausea			
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		
Fatigue			
Fever			
	Non-cardiac chest pain		
	Pain		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder		
INFECTIONS AND INFESTATIONS			
Infection[2]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Blood bilirubin increased		

Adverse Events with Possible Relationship to Decitabine (5-aza-2'-deoxycytidine) (CTCAE 5.0 Term) [n= 1832]			
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Creatinine increased		
	Lymphocyte count decreased		
Neutrophil count decreased			
Platelet count decreased			
White blood cell 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		
	Headache		
		Intracranial hemorrhage	
	Somnolence		
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 includes all 75 sites of infection 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 (coagulopathy); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (spleen disorder); Bone marrow hypocellular; Eosinophilia; Hemolysis; Leukocytosis
CARDIAC DISORDERS - 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; Anal fissure; Ascites; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; 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; Injection site reaction; Localized edema; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatomegaly)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture; Infusion related reaction; 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; Blood bicarbonate decreased; Blood lactate dehydrogenase 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 increased); Investigations - Other (blood bilirubin decreased); Investigations - Other (blood chloride decreased); Investigations - Other (blood chloride increased); Investigations - Other (blood urea increased); Investigations - Other (elevated ammonia); Investigations - Other (platelet count increased); Investigations - Other (protein total decreased); Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hyperphosphatemia; Hypoglycemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (malnutrition)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Chest wall pain; Generalized muscle weakness; Muscle cramp; 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; 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 aneurysm); 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.

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10.1.1.2 CAEPR for venetoclax

Version 2.0, July 25, 2018[1]

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Venetoclax (ABT-199, NSC 766270)

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 1298 patients.* Below is the CAEPR for Venetoclax (ABT-199).

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, May 8, 2019[1]

Adverse Events with Possible Relationship to Venetoclax (ABT-199) (CTCAE 5.0 Term) [n= 1298]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
	Febrile neutropenia	
GASTROINTESTINAL DISORDERS		
	Constipation	
Diarrhea		
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
INFECTIONS AND INFESTATIONS		
Infection[2]		
INVESTIGATIONS		
	Lymphocyte count decreased	
Neutrophil count decreased		
	Platelet count decreased	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Hypocalcemia	
	Hypokalemia	
	Hypophosphatemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
NERVOUS SYSTEM DISORDERS		
	Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
VASCULAR DISORDERS		
	Hypertension	

[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 INFESTATIONS SOC.

Adverse events reported on venetoclax (ABT-199) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that venetoclax (ABT-199) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (coronary artery disease); Heart failure; Myocardial infarction; Sinus tachycardia; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
GASTROINTESTINAL DISORDERS - Abdominal pain; Belching; Dry mouth; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (Crohn's disease); Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Flu like symptoms; General disorders and administration site conditions - Other (general physical heath deterioration); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); Injection site reaction; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatic function abnormal)
IMMUNE SYSTEM DISORDERS - Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction; Injury, poisoning and procedural complications - Other (laceration)
INVESTIGATIONS - Aspartate aminotransferase increased; Blood bilirubin increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (acute myeloid leukemia); Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Intracranial hemorrhage; Ischemia cerebrovascular; Nervous system disorders - Other (neuropathy peripheral); Peripheral sensory neuropathy; Syncope
PSYCHIATRIC DISORDERS - Confusion; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective;

Dysuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Ovarian rupture
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asphyxia)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Pruritus; Rash acneiform; Rash maculo-papular
VASCULAR DISORDERS - Hypotension; Thromboembolic event

Note: Venetoclax (ABT-199) 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.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event

Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 10.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

10.3.2 Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU

website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.3 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.4 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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 electronic submission within the timeframes detailed in the table below.

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

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 submitted electronically 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 electronically 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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.3.5 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Infection	Any	Any	Regardless
Blood and lymphatic system disorders	Anemia Bone marrow hypocellular	Any	Regardless
Investigations	Lymphocyte count decreased Neutrophil count decreased Platelet count decreased	Any	Regardless

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

*The following paragraph **only** applies to trials using **Medidata Rave**; other trials may delete:*
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. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

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/IDE be reported expeditiously 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. Given that this treatment protocol is for acute myeloid leukemia, it is not anticipated that any secondary leukemia or MDS should be reported.

10.7 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 AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 10 days prior to start of protocol therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Induction cycle 1	Induction cycles 2-3 (If needed)	Maintenance cycles	Relapse/Off Study
Decitabine		D	D	D	
Nivolumab		N	N	N	
Venetoclax		V	V	V	
Informed consent	X				
Demographics	X				
Medical history	X				
Concurrent meds[a]	X	X	X	X	
Physical exam[b]	X	X	X	X	X
Vital signs[c]	X	X			X
Height	X				
Weight	X	X			X
Performance status[d]	X	X			X
Serum Chemistry[e]	X	X	X	X	X
CBC w/diff[f]	X	X	X	X	X
EKG	X				
Adverse event evaluation[g]	X	X	X	X	X
Pregnancy test[h]	X	X	X	X	
Bone marrow[i]	X	X	X	X	X
Correlative studies[j]	X	X	X	X	X

D: Decitabine will be given on Days 1-10 of Induction cycles and Days 1-5 of maintenance cycles
N: Nivolumab will be given on Day 15 of cycle 1 and Days 1 and 15 of all subsequent cycles
V: Venetoclax will be given on Days 1-28 of induction cycles and Days 1-21 of maintenance cycles. Dosing ramp-up on days 1-3 or 1-4 (based on concurrent use of CYP3A inhibitors as outlined in Section 6.3.1)
a: Concurrent medications should be assessed at screening and the beginning of each treatment cycle
b: Physical exam should be performed at Screening, Days 1 and 15 of every cycle and End of Treatment/Relapse
c: Vital signs should be performed at Screening, Days 1 and 15 of every cycle and End of Treatment/Relapse. Vitals signs include blood pressure, heart rate, temperature, oxygen saturation, and respiratory rate.
d: Performance status should be evaluated at Screening, Day 1 of each cycle of therapy, and End of Treatment/Relapse
e: Serum chemistry will include: Na, K, CO2, Cl, BUN, Cr, AST, ALT, AP, TB, TP, albumin, LDH, and uric acid should be performed at screening, pre-dose (within 4 hours prior to venetoclax administration), every 12 hours during venetoclax ramp-up period (see Appendix C for tumor lysis management guidelines), twice weekly otherwise during induction cycles and at the beginning of each maintenance cycle and relapse/EOT
f: CBC with differential. To be performed at screening, twice weekly during induction cycles, and at the beginning of each maintenance cycle and relapse/EOT.
g: Adverse event evaluation: will occur on Days 1 and 15 of every cycle and End of Treatment/Relapse
h: Pregnancy test will occur for women of childbearing potential at Screening and the beginning of each cycle of treatment
i: Bone marrow biopsies will occur at the end of each cycle of induction, then every 3 cycles (starting with cycle 6) and at relapse/EOT.
j: Please see study sample collection table at Section 5.1 and 11.1 for bone marrow and peripheral blood collection time details.

11.1 Correlative collection calendar

Time Point	Correlative	Bone Marrow collection	Peripheral Blood Collection
Baseline			
Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation		X	X
Day 28+/- 1 day of cycles 1, 2, and 3			
Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation		X	X
Day 28 +/- 1 day every 3 cycles starting with cycle 6 (ex. Cycles 6, 9, 12…)			
Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation		X	X
Day 28 +/- 1 day of end of every cycle starting with cycle 4 (excluding cycles 6, 9, 12… as above)			
Correlatives: DNA methylation			X
End of Treatment/Relapse			
Correlatives: Flow cytometry, Cytogenetics, Next-generation sequencing, Tetramer Analysis, and DNA methylation		X	X

12. MEASUREMENT OF EFFECT

Although the clinical benefit of thus drug combination has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated with bone marrow biopsies as per the study calendar.

12.1 Antitumor Effect – Hematologic Tumors

Assessment of clinical response will be made according to the International Working Group criteria {Cheson 2003}. The major criteria for judging response will include physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

Morphologic Leukemia-free State (MLFS)

MLFS requires all of the following:

12.1.1 < 5% blasts in bone marrow aspirate
12.1.2 No extramedullary disease
12.1.3 No blasts with Auer rods

detected Morphologic Complete Remission (CR) **CR requires all of the following:< 5% blasts in bone marrow aspirate**

12.1.4 < 5% blasts in bone marrow aspirate
12.1.5 Neutrophils ≥ 1,000/µL
12.1.6 Platelets ≥ 100,000/µL
12.1.7 No extramedullary disease
12.1.8 No blasts with Auer rods detected
12.1.9 Independent of transfusions

Cytogenetic Complete Remission (CRc)

CRc requires all of the following:

12.1.10 < 5% blasts in bone marrow aspirate
12.1.11 Neutrophils ≥ 1,000/µL
12.1.12 Platelets ≥ 100,000/µL
12.1.13 No extramedullary disease
12.1.14 No blasts with Auer rods detected
12.1.15 Independent of transfusions
12.1.16 Reversion to a normal karyotype with an abnormal karyotype at the time of diagnosis

Morphologic CR with incomplete blood count recovery (CRi)

CRi requires all of the following:

12.1.17 < 5% blasts in bone marrow aspirate
12.1.18 Neutrophils < 1,000/μL or Platelets < 100,000/μL
12.1.19 No extramedullary disease
12.1.20 No blasts with Auer rods detected
12.1.21 If blood counts recover within 14 days of a bone marrow evaluation that is consistent with CRi, the patient will be considered CR at the time when both neutrophil and platelet count recover (neutrophils ≥ 1,000/μL, platelets ≥ 100,000/μL).

Complete remission with hematological improvement (CRh)

CRh meets all Criteria for CR except for residual thrombocytopenia and/or neutropenia defined as:

- Bone marrow blasts <5%
- Absence of circulating blasts on differential from peripheral blood (as determined by flow cytometry or blasts with morphologic Auer rods)
- Absence of extramedullary disease
- Absolute neutrophil count >500/μL
- Platelet count >50,000/μL

Partial Remission (PR)

PR requires all of the following:

12.1.22 ≥ 50% decrease in blasts in bone marrow aspirate to a range of 5-25%
12.1.23 Neutrophils ≥ 1,000/μL
12.1.24 Platelets ≥ 100,000/μL
12.1.25 Independent of transfusions
12.1.26 A value of ≤ 5% blasts may also be considered a PR if Auer rods are detected

Treatment Failure (TF)

Treatment failure will be classified as one of the following:

12.1.27 Resistant disease: Failure to achieve a complete remission (CR, CRc, or CRi) or partial remission. Patients who survive ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.
12.1.28 Death in Aplasia: Patients who survive ≥ 7 days following completion of initial treatment, but die while cytopenic, with an aplastic or hypoplastic marrow obtained within 7 days of death, without evidence of persistent leukemia

12.1.29 Death from Indeterminate cause: Patients who die before completion of treatment or < 7 days following completion of initial treatment; patients who die ≥ 7 days following completion of initial treatment with no peripheral blood blasts, but no bone marrow examination is available; patients who fail to complete the first cycle of therapy

Relapse

Relapse is defined as:

12.1.30 Evidence of morphologic relapse with the reappearance of leukemic blasts in the peripheral blood, blasts with Auer rods, ≥ 5% blasts in the bone marrow, or evidence of extramedullary disease not attributable to any other cause. In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5-20% blasts, a bone marrow biopsy should be repeated within 1 week to distinguish relapse from bone marrow regeneration.

12.1.31 The reappearance of cytologically proven extramedullary disease also indicates relapse. Reappearance of a cytogenetic abnormality is considered a cytogenetic relapse. Evidence of bone marrow morphologic involvement or extramedullary disease required.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role

assignments. To access Rave via iMedidata:

13.2.1 Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and

13.2.2 Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

- To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
- To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site 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 in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section 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.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site

audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program

Guidelines
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Collaborative Agreements Language

The agent(s) supplied by CTEP used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA) 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(s) in this study:

1. Agent(s) may not be used for any purpose 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 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"):

    a. NCI will provide all Collaborators with prior 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 that would tend to restrict NCI's participation in the proposed combination protocol.

    b. 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 Agent.

    c. 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.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available 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.

4. 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.

5. Any data provided to Collaborator(s) for Phase 3 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.

6. 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 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:

Email: ncicteppubs@mail.nih.gov

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

13.4 Genomic Data Sharing Plan

Data Sharing Plan for CTEP study NCI#10317

Acute Myeloid Leukemia is a devastating, difficult-to-treat, and rarely cured malignancy. The timely and accurate dissemination of data generated as part of this project is critical to ensure the broadest possible access for researchers to advance the field.

What data will be generated:
We will generate targeted DNA resequencing (<100 genes), tetramer analysis, cytokine production, and global and gene-specific DNA methylation data from patient tumor and blood samples at different time points. We may generate RNA-sequencing and chromatin profiling in the future (e.g. ChIP-seq) in the future. We do not plan to generate whole-genome or whole-exome sequencing data. The risk of reidentification is therefore low.

What data will be shared:
We will share joint phenotypic and genotype data associated with the patient samples by depositing these data as controlled-access dataset(s) in dbGaP (and Genomic Data Commons [GDC] if permitted), which is an NIH-funded repository that has appropriate controls for protection of data. Additional data documentation and de-identified data will be deposited for sharing along with phenotypic data, which includes demographics (unless a HIPAA protected health identifier), clinical data including cytogenetic studies, and pertinent medical history, consistent with applicable laws and regulations. We will comply with the NIH Genomic Data Sharing Policy (as outlined in NOT-OD-14-124 and updates) and the NCI's existing policies on sharing data on genetics to include secondary analysis of data through the repository. Submitted data will conform to relevant data and terminology standards. Data and associated interpretations will be made available in scientific presentations at local, national, and international meetings, and in published form in an ongoing basis.

Who will have access to the data:
We agree that data will be deposited and made available through dbGaP (and possibly GDC) which is an NIH-funded repository, and that protected data in dbGaP/GDC will be shared with investigators working under an institution with a Federal Wide Assurance (FWA) and could be used for secondary study purposes such as finding genes that contribute to AML pathobiology. We agree that the names and Institutions of persons either given or denied access to the data, and the bases for such decisions, will be summarized and shared with CTEP. Meta-analysis data and associated phenotypic data, along with the data content, format, and organization, will be made available to investigators. All relevant analyses and interpretations will be disseminated as posters, presentations, and papers.

Where will the data be available:
We agree to deposit and maintain the joint genotypic and phenotypic data, and secondary analyses at dbGaP which is an NIH-funded repository and has data access policies and procedures consistent with NIH data sharing policies.

When will the data be shared:
We agree to deposit genetic data into dbGaP repository as soon as possible but no later than one year of the completion of the clinical study follow-up period or upon acceptance of the data for publication, or public disclosure of a submitted patent applications, whichever is earlier.

How will researchers locate and access the data:
We agree we will identify where the data will be available and how to access the data in any publications and presentations that we author or co-author about these data, as well as acknowledge the repository and CTEP in any publications and presentations. As we will be using dbGaP/GDC, which are NIH-funded repositories, these repositories have policies and procedures in place that will provide data access to qualified researchers, fully consistent with NIH data sharing policies and applicable laws and regulations.

13.5 Incidental/Secondary Findings Disclosure Procedure

Samples are not being submitted to the Biobanking and Molecular Characterization Initiative, and neither whole genome sequencing nor whole exome sequencing is otherwise planned under this protocol.

13.6 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

References

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al*. (2009). A new equation to estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
2. Levey, A.S., J. Coresh, T. Greene, *et al*. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 145:247-254.
3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

APPENDIX C RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE ABNORMALITIES AND PREVENTION OF TUMOR LYSIS ivolumab pharmacokinetic studies

See Appendix [TLS]

Abnormality	**Management Recommendations**
Hyperkalemia (Including Rapidly Rising Potassium	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits)	• Recheck potassium, phosphorous, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium <ULN, and no other evidence of tumor lysis • At the discretion of the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization at the discretion of the investigator. Potassium, phosphorous, uric acid, calcium, and creatinine must be rechecked within 24 hours.

Potassium > upper limit of normal	• Perform stat ECG and commence telemetry • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60g • Administer furosemide 20mg IV x1 • Administer calcium gluconate 100 to 200mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT • If potassium < ULN 1 hour later, repeat potassium, phosphorous, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis

Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry • Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60g • Administer furosemide 20mg IV x1 • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV • Administer sodium bicarbonate 1 to 2 mEq/kg IV push • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorous, uric acid, calcium and creatinine every hour STAT
Hyperuricemia	
Uric acid ≥ 8 mg/dL (476 µmol/L)	• Consider rasburicase (dose based on institutional standards) • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour STAT.

Uric acid ≥ 10mg/dL (595 µmol/L) OR Uric acid ≥ 8 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥0.027 mmol/L) from predose level	• Administer rasburicase (dose based on institutional standard) • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation • Notify nephrology • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorous, uric acid, calcium, and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND subject symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring • Telemetry • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorous, uric acid, calcium and creatinine 2 and 4 hours, later if no other evidence of tumor lysis • Calculate corrected calcium and check ionized calcium if albumin low
Hyperphosphatemia	

Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus ≥ 10mg/dL) • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 hour STAT • If phosphorous < 5.0 mg/dL 1 hour later, repeat potassium phosphorus, uric acid, calcium, and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids • Recheck potassium, phosphorous, uric acid, calcium, and creatinine in 1 to 2 hours STAT

APPENDIX D PATIENT WALLET CARD

INSTRUCTIONS FOR PATIENT WALLET CARD TEMPLATE- Give the wallet card to the patient at the time of enrollment. The patient will cut out the wallet-sized information card and retain it at all times

PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis: Acute Myeloid Leukemia

Study Doctor: Alice Mims, MD

Study Doctor Phone #: 843-480-2685

NCI Trial #: CTEP 10307

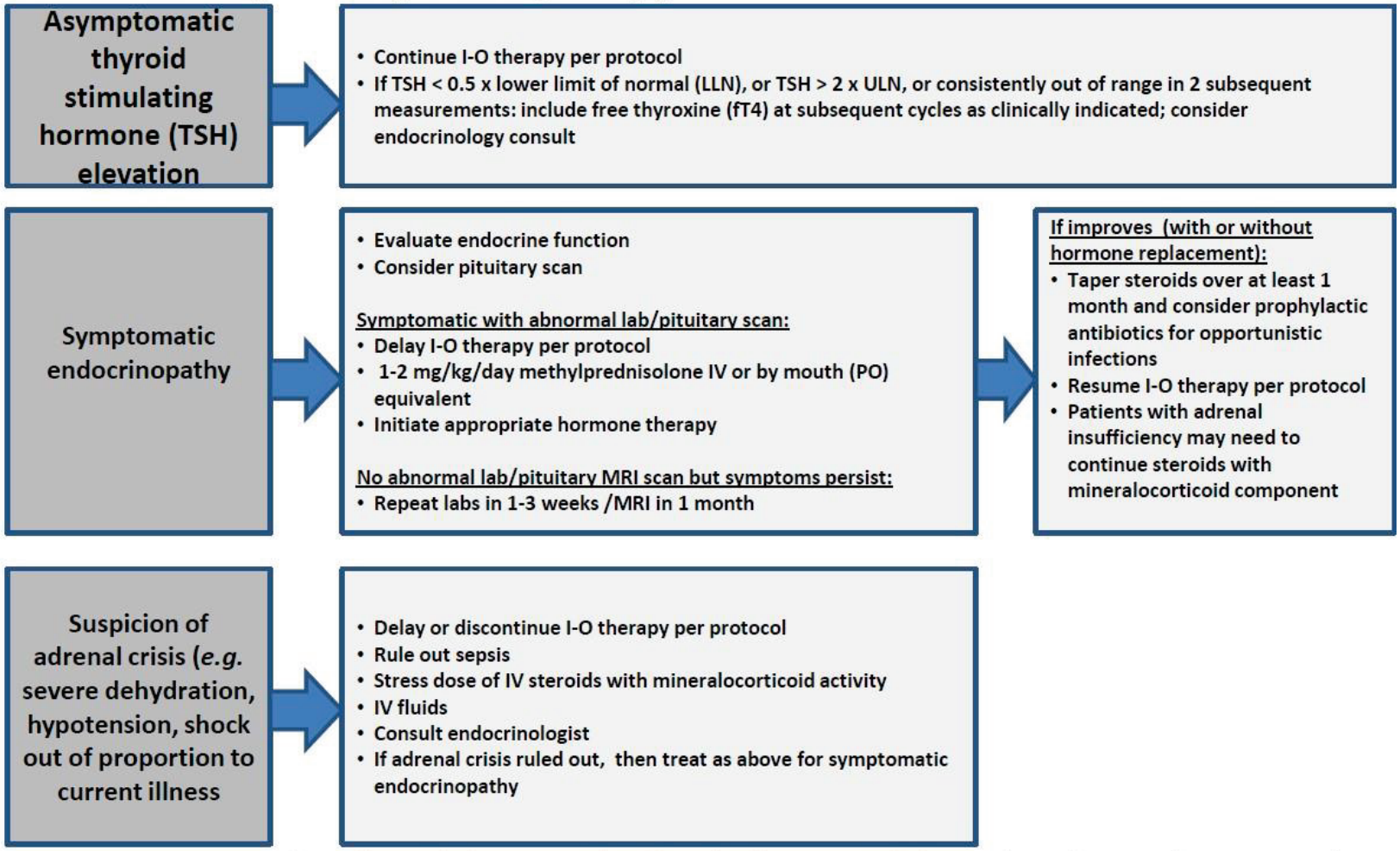
Study Drug(S):
Nivolumab/Venetoclax/Decitabine

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX E NIVOLUMAB AE MANAGEMENT ALGORITHM: MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

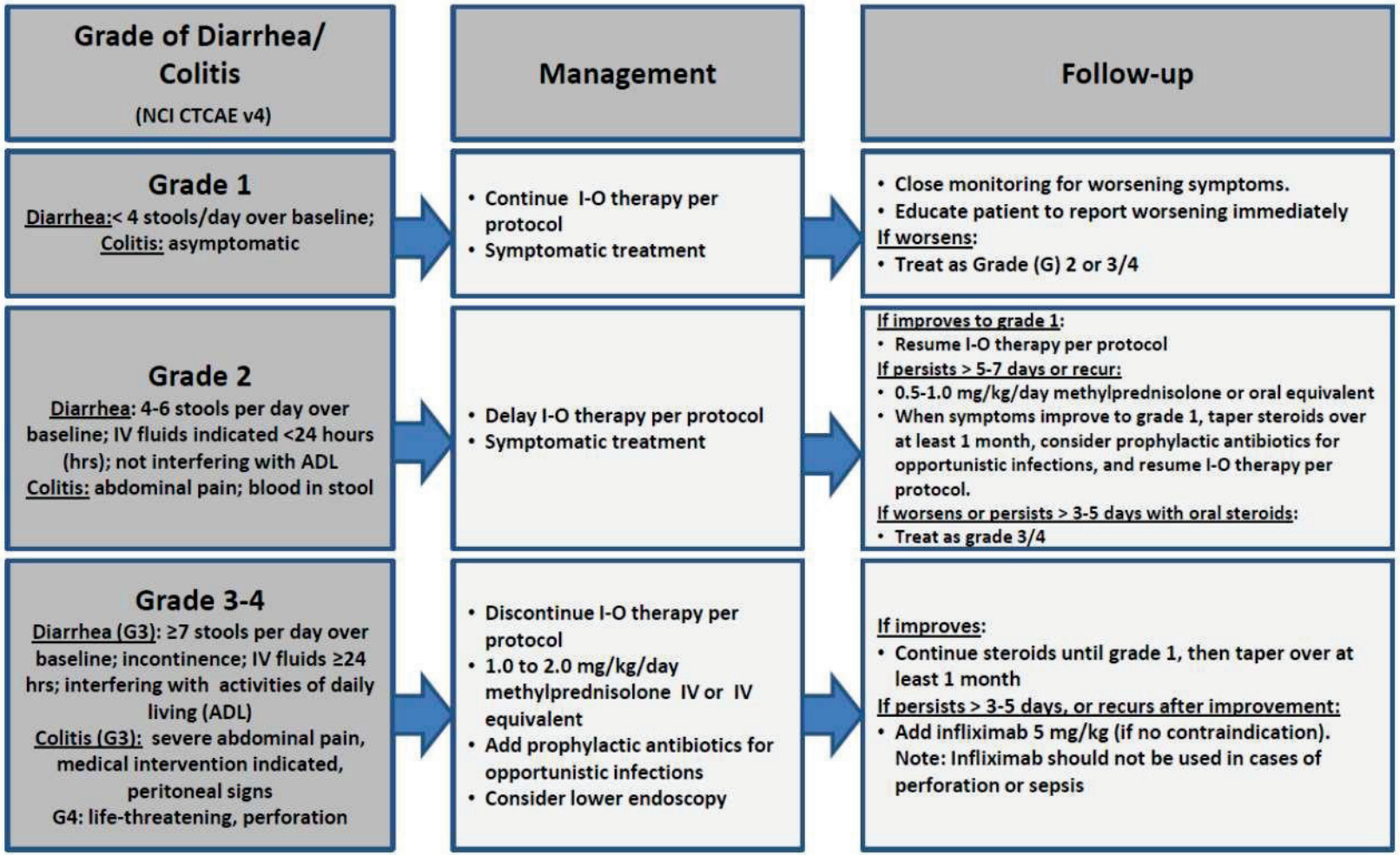
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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.

GI Adverse Event Management Algorithm

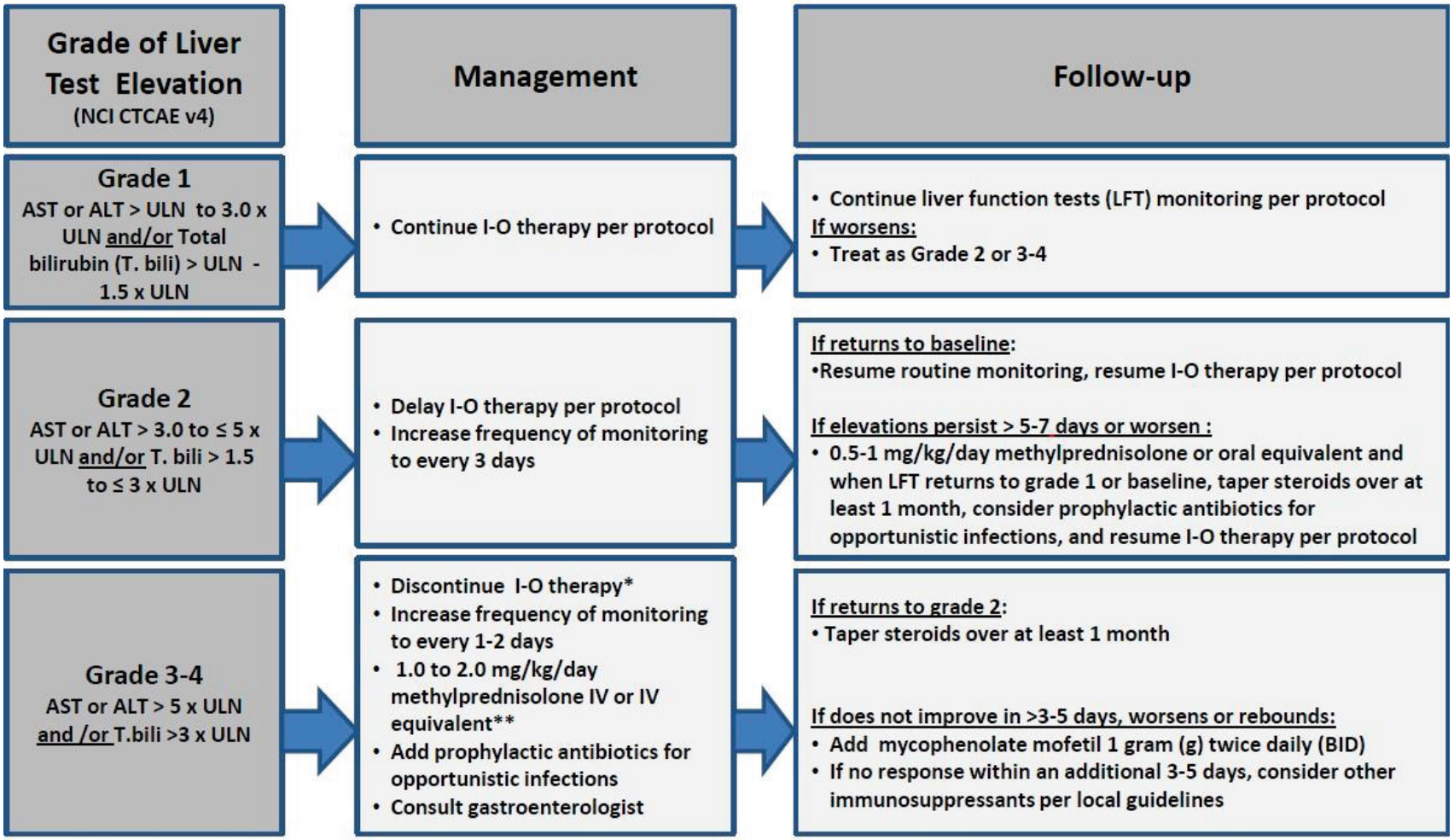
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

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.



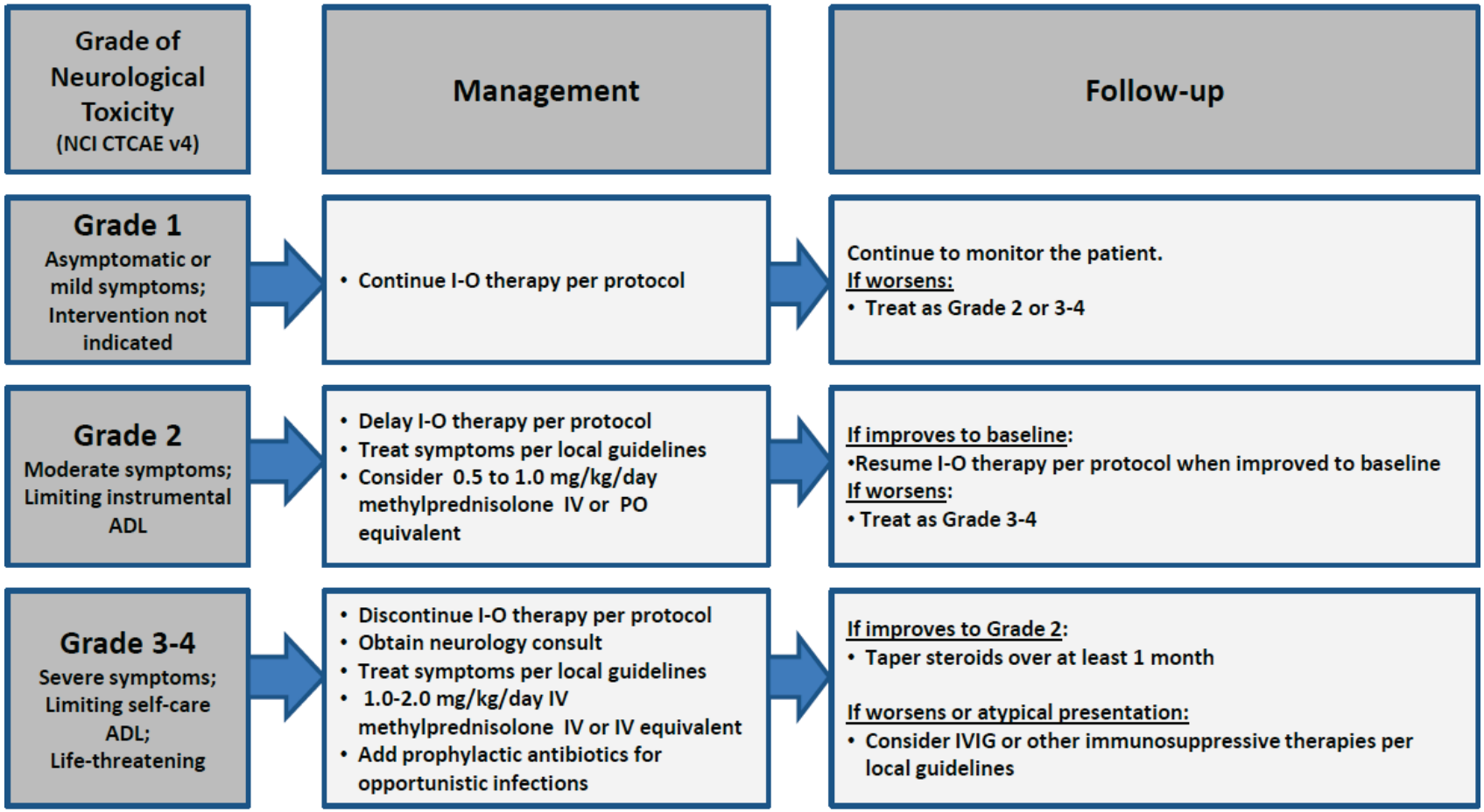
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Neurological Adverse Event Management Algorithm

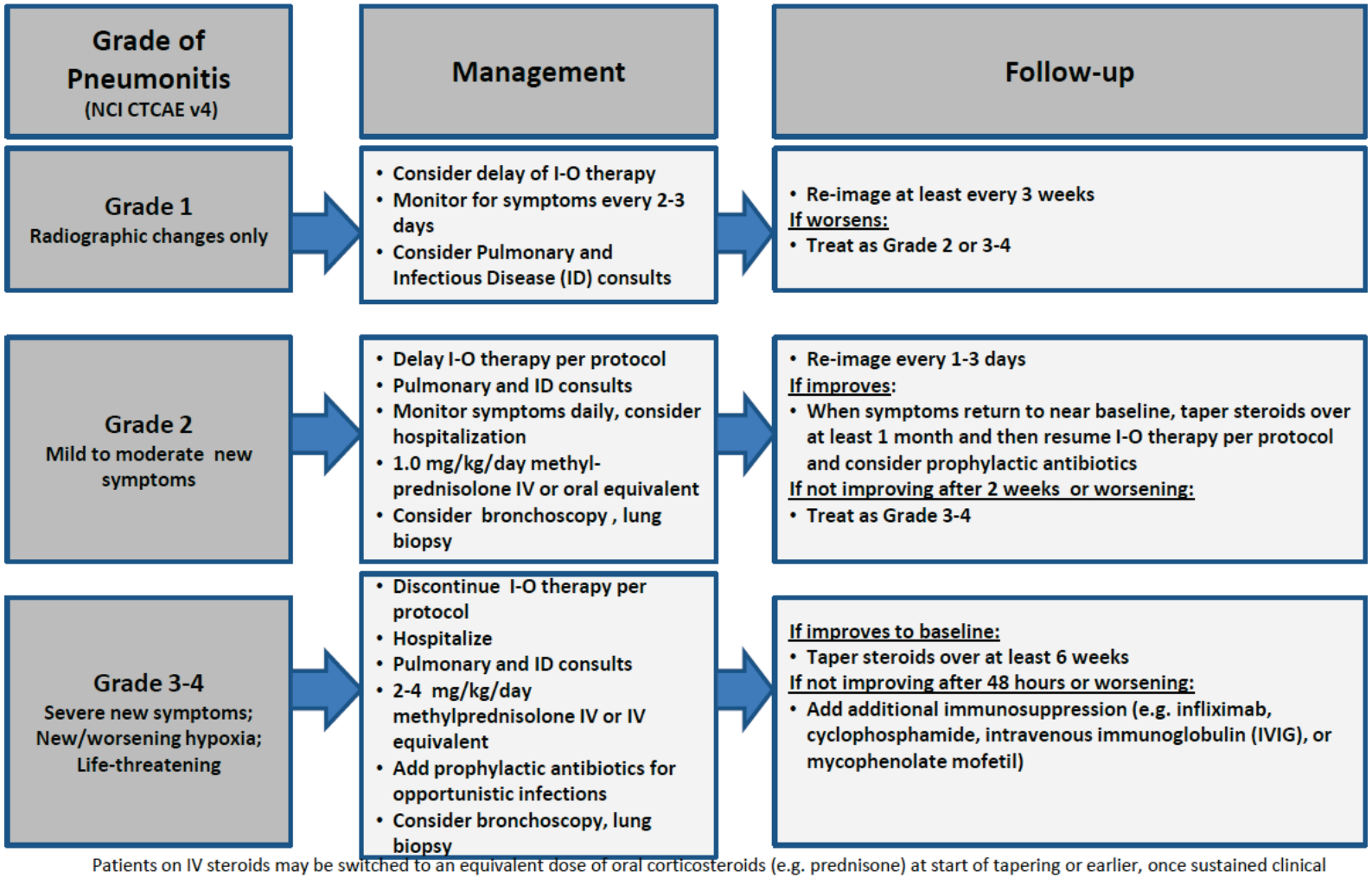
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

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.

Renal Adverse Event Management Algorithm

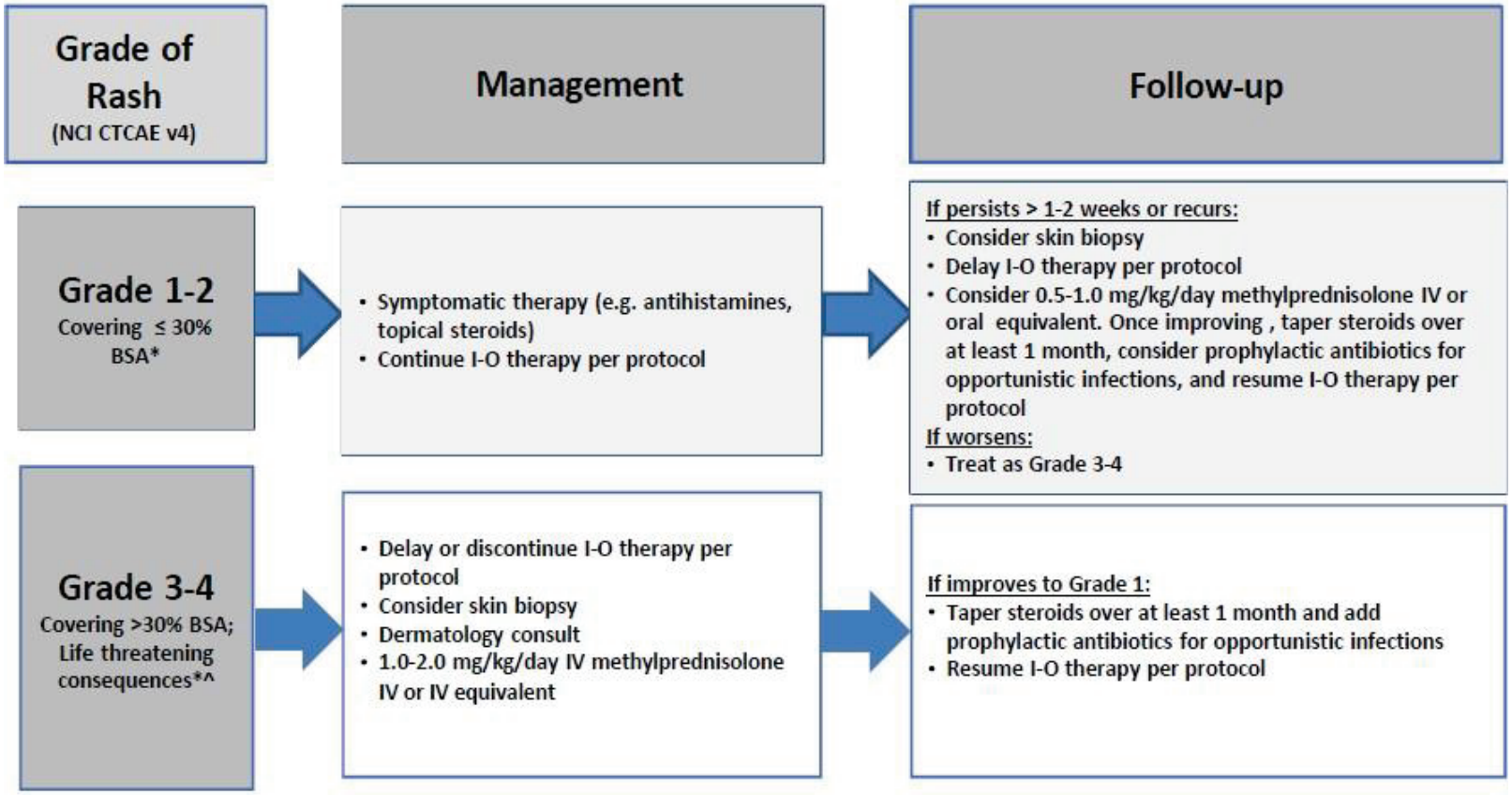
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV 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

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.

Skin Adverse Event Management Algorithm

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

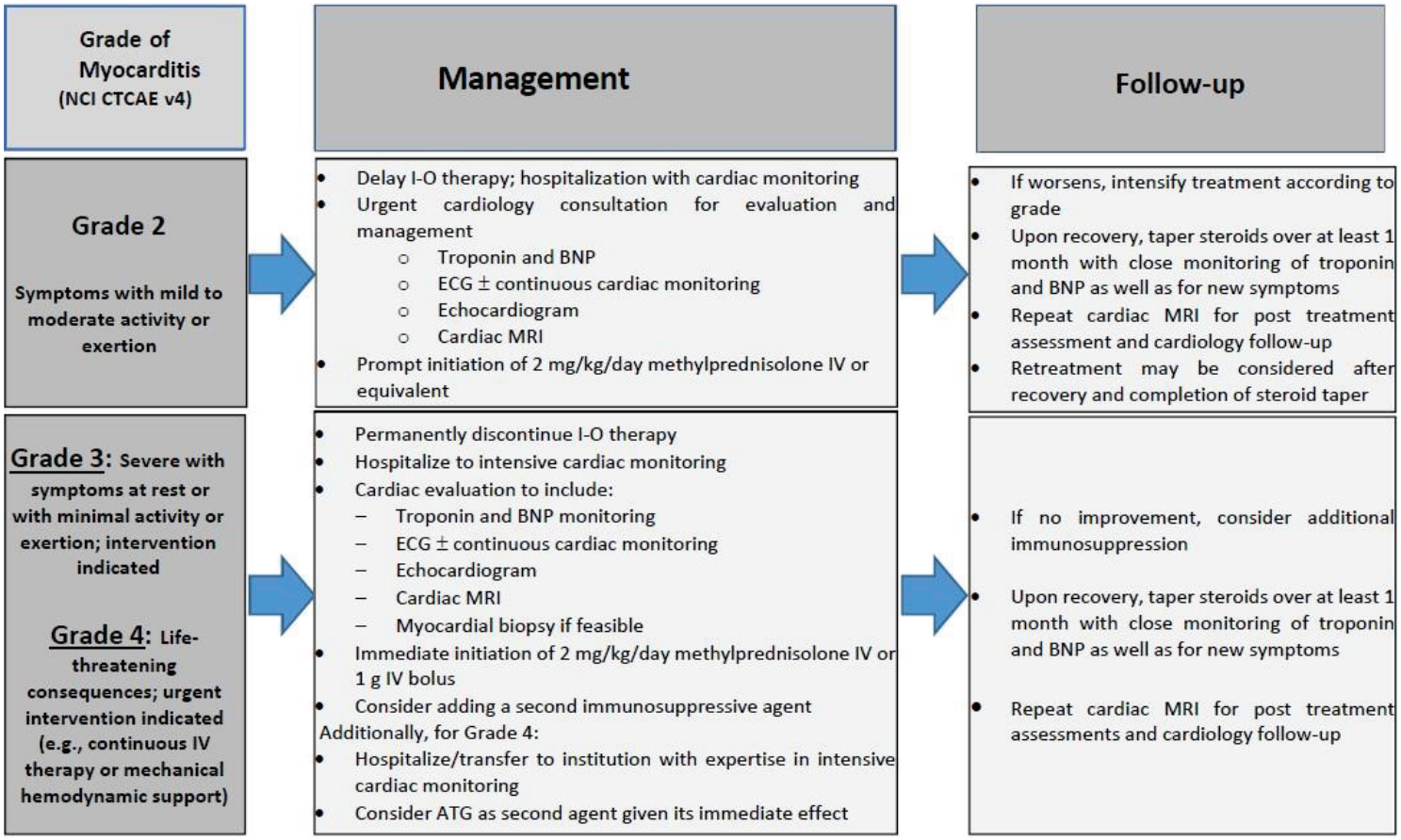


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

APPENDIX F: Pharmacokinetic Study Sample Handling and Shipment

1.1 Venetoclax and OATP1B1 Biomarker Plasma Pharmacokinetic Samples

- The plasma pharmacokinetic profile of venetoclax and OATP1B1 biomarker will be characterized by collecting blood samples (as outlined in the Study Calendar and in the separate PK study worksheet uploaded at the Cancer Trials Support Unit website www.ctsu.org).
- Collection of Specimen(s): patients will have 4 mL samples of blood collected in tubes containing K2 ETDA as an anticoagulant (purple top) at the time points specified below:
    - **Baseline**
    - **Cycle 1 Day 14**
        - **Pre-venetoclax**
        - **1 h post venetoclax**
        - **2 h post venetoclax**
        - **4 h post venetoclax**
        - **7 h post venetoclax**
        - **24h post venetoclax**
- Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.
    - Obtain venous blood by standard phlebotomy technique from a peripheral access point.
- Fill-up the tubes as much as possible until blood flow stops.
- GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis.
- Place samples immediately **on ice** after collection; samples must be processed **within 30 minutes**.

1.1.1 Handling of Specimens(s)

Processing instructions

1. Invert sample 8-10 times immediately before processing.
2. Centrifuge at ~1000-1300 x *g* (i.e., RCF, **not RPM**) for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
3. Carefully remove tube from centrifuge.
4. Using a pipette, transfer equal aliquots of plasma into 2-3 labeled 1.2 mL cryovials (e.g., preferred are external thread, conical self-standing vials like Corning™ 430658 or), not exceeding ~1 mL per cryovial.
5. Label samples as (drug) (matrix) (purpose), including protocol number (#10417), unique patient ID assigned at registration, date of collection, draw time, time point, protocol time point, and initials.
6. Store plasma samples at -70°C or below until shipment.

1.2 Nivolumab Serum Pharmacokinetic Samples

- The plasma pharmacokinetic profile of nivolumab will be characterized by collecting blood samples (as outlined in the Study Calendar and in the separate PK study worksheet uploaded at the Cancer Trials Support Unit website www.ctsu.org).

- Collection of Specimen(s): patients will have 3 mL samples of blood collected in tubes containing heparin as an anticoagulant (red top) at the time points specified below:
  - **Cycle 1 Day 14**
    - **Pre-nivolumab infusion**
    - **4h after end of nivolumab infusion**
  - **Induction Cycle 2 Day 1**
    - **Pre-nivolumab infusion**
    - **4h after end of nivolumab infusion**
  - **Maintenance Cycle 1 (Day 1)**
    - **Pre-nivolumab infusion**
    - **4h after end of nivolumab infusion**
  - **Maintenance Cycle 3 (Day 14)**
    - **Pre-nivolumab infusion**
    - **4h after end of nivolumab infusion**
  - **End of Treatment/Relapse**
    - ~ 2 weeks after last nivolumab infusion
- Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.
  - Obtain venous blood by standard phlebotomy technique from a peripheral access point.
- Fill-up the tubes as much as possible until blood flow stops.
- GENTLY invert each tube several times (8-10 times) immediately after collection and then allow blood to clot for 30-60 minutes at room temperature before centrifugation.

1.2.1 Handling of Specimens(s)

Processing instructions

1. 30-60 minutes after sample collection (blood has clotted), centrifuge at ~1000-1300 x *g* (i.e., RCF, **not RPM**) for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
2. Carefully remove tube from centrifuge.
3. Using a pipette, transfer equal aliquots of serum into 2-3 labeled 1.2 mL cryovials (e.g., preferred are external thread, conical self-standing vials like Corning™ 430658 or), not exceeding ~1 mL per cryovial.
4. Label samples as (drug) (matrix) (purpose), including protocol number (#10417), unique patient ID assigned at registration, date of collection, draw time, time point, protocol time point, and initials.
5. Store serum samples at -70°C or below until shipment.

1.3 Shipping of Specimen(s)

Specimens for venetoclax, OATP1B1 and nivolumab should be stored through the end of Cycle 1 and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has >1 participant on-study). After cycle 1,

nivolumab samples can be shipped in batch every 3 months, or OSUCCC PhASR may contact the study team to request shipment off-schedule.
Please ship 1 aliquots to the OSUCCC PhASR. Once receipt is confirmed, the back-up aliquot may be shipped. The back-up can be shipped at a later date with subsequent batches.

Preparing the shipment
*Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH) with dividers. (e.g., VWR Box item number is 82021-114; divider item number is 82007-154.)
*Please organize the samples by Patient and Time point in the box.
*Do not store in plastic bags (they break on dry-ice and labels will detach).
*A copy of each of the pharmacokinetic sample collection forms (PK study worksheer) for the respective patients or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet.
*Note the study number, PI, and the drugs used/to be measured.
*A name, phone number and email address should be included with samples so that receipt can be acknowledged.
*Please notify the lab by email (phasr@osumc.edu) at least 24 hours prior to shipment.

Shipping
*All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state.
*Overnight shipments should occur on Monday through Wednesday (Tuesday is the preferred day) except when the following day is a holiday.

The OSUCCC PhASR
Attn: Kasey Hill, Ph.D. (Venetoclax/OATP1B1/Nivolumab Samples)
441 Biomedical Research Tower
460 West 12th Avenue
Columbus, OH 43210
Phone: (614) 688-0578
Fax: (614) 292-7766

APPENDIX G: Medication Diary

Important Instructions for your Venetoclax drug dosing:

Please call your clinic team with any questions related to taking your medication, or if you experience any side effects that you are concerned about.

Instructions: When taking Venetoclax as instructed to by your physician, record the date, time, and number of pills taken on the appropriate days.

Clinic phone: _____

Study coordinator name: _____ Phone number:_____