Clinical Study Protocol

VICC HEM2163

Study Title: Phase 2 study of decitabine and cedazuridine in combination with venetoclax for AML relapse after allogeneic hematopoietic cell transplantation

Study Phase: II

IND Number: 157074

Indication: Post-transplant acute myeloid leukemia

Funding source: Funding provided by the National Comprehensive Cancer Network (NCCN) through a grant provided by Taiho Oncology, Inc. (Taiho). Neither NCCN or Taiho are sponsors of this study**.**

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Protocol Synopsis:

Title of study: Phase 2 study of decitabine and cedazuridine in combination with venetoclax for AML relapse after allogeneic hematopoietic cell transplantation

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Objectives:

Primary objective:

1. To assess the effect of DEC-C/venetoclax on the investigator-assessed composite CR rate (CR/CRh/CRi)

Secondary objectives:

1. To assess the rate of partial response (PR) and morphologic leukemia free state (MLFS) following treatment with DEC-C/venetoclax
2. To assess the relapse free survival of patients treated with DEC-C/venetoclax
3. To assess overall survival of patients treated with DEC-C/venetoclax
4. To assess the safety and tolerability of DEC-C/venetoclax in the post-HCT setting
5. To assess the rates of measurable residual disease negativity in patients achieving a CR.

Background and Study Rationale:

Acute myeloid leukemia, excluding acute promyelocytic leukemia, is generally associated with poor clinical outcomes. Patients with poor-risk clinical and molecular features experience a shortened survival with a minority surviving beyond 5 years.[1,2,3,4] Similarly, patients with high-grade myeloid malignancies, including myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML), are at risk for leukemic transformation with rates approaching 40%.[5] For poor-risk patients, allogeneic HCT is the only potentially curative therapy, however, post-HCT relapse is common and as many 85% of poor-risk AML patients will experience recurrence of their underlying disease.[6] In a registry analysis, 15% of post-HCT relapsed AML patients achieved a subsequent complete remission (CR). Less than 5% of patients who relapsed within 6 months, and 12% of patients who relapsed 6-24 months after HCT were alive at 3 years.[7]

Dysregulation of anti-apoptotic proteins, including BCL2, is responsible for tumor maintenance and survival. Venetoclax is a selective BCL2 inhibitor that increases cell death/apoptosis in hematologic malignancies. In chronic lymphoid leukemia, a disease heavily reliant on the loss of apoptosis, overall response rates (ORR) exceed 80% with venetoclax.[8] In AML, anti-apoptotic pathways are more heterogeneous. Venetoclax, in combination with DNMTis or low dose cytarabine, results in CR/CRi rates of 60-75% in the treatment naïve (TN) setting.[9,10] Off-label use in the relapsed/refractory (R/R)

disease is an emerging treatment paradigm with an ORR of 12-51%. In a series of post-HCT AML patients treated with venetoclax-based salvage therapies at Vanderbilt University Medical Center (16/21 with a DNMTi partner), we found the combination is safe and effective with an ORR of 42.1%.[11] Interrupting therapy in patients with a treatment response was associated with improved safety and reduced toxicity after HCT.

Based on our published experience, and other retrospective data in R/R AML, we plan a phase 2 trial to prospectively assess the ORR of venetoclax/DNMTi salvage therapy after allogeneic HCT.[11,12,13] Partnering venetoclax with DEC-C is an intuitive extension of our prior work and combines the efficacy of venetoclax/DNMTi therapy with the convenience of an all-oral treatment regimen which will improve quality of life compared to conventional salvage therapies.

Study Design:
This is an open-label, non-randomized, investigator-sponsored, phase II study of venetoclax in combination with DEC-C in patients with myeloid diseases who relapse with AML after allogeneic HCT.

Patient Populations:
Adult patients, ≥18 years of age with relapse/progression to AML after allogeneic HCT, who have not previously progressed while receiving venetoclax or other BCL-2 inhibitor, are eligible. Subjects with active GVHD, acute or uncontrolled infections, or with white blood cell count ≥25,000/μl that cannot be controlled with hydroxyurea are not eligible.

Patients who develop grade 2-4 graft versus host disease while on study will have treatment interrupted. Subjects will be eligible to resume therapy after GVHD returns to ≤ grade 1 after discussion with the study co-chair(s).

Inclusion Criteria:
1. Age ≥18 years at the time of signing the Informed Consent Form (ICF); must voluntarily sign an ICF and meet all study requirements
2. History of morphologically confirmed AML (per WHO diagnostic criteria) with evidence of disease recurrence (≥5% blasts consistent with prior disease) that occurs after allogeneic HCT. Patients transplanted for another indication (e.g., MDS/CMML) who relapse with AML are eligible to enroll.
3. WBC must be less than 25,000/μl for at least three days prior to C1D1 (hydroxyurea allowed).
4. A bone marrow biopsy must be performed and tissue collected for entrance to the trial
5. Eastern Cooperative Oncology Group Performance Status of 0 - 2
6. Must have adequate hepatic and renal function as demonstrated by the following: ALT (SGPT) and/or AST (SGOT) less than or equal to 3x upper limit of normal (ULN); total bilirubin < 1.5 x upper limit of normal (ULN). Patients with Gilbert's syndrome (hereditary indirect hyperbilirubinemia) must have a total bilirubin of < 3 x

ULN; and calculated creatinine clearance ≥30 ml/min (per the Cockroft-Gault formula).
7. Willingness to abide by all study requirements, including contraception, maintenance of a pill diary, and acceptance of recommended supportive care medications.

Exclusion Criteria:

1. Prior relapse or progression while receiving venetoclax or other commercially available or investigational BCL-2 inhibitor.
2. Anticancer therapy, including investigational agents ≤2 weeks or ≤5 half-lives of the drug, whichever is shorter, prior to C1D1. (Use of hydroxyurea is permitted).
3. Inadequate recovery from toxicity attributed to prior anti-cancer therapy to ≤Grade 1 (NCI CTCAE v5.0), excluding alopecia or fatigue.
4. History of allogeneic hematopoietic cell transplantation (HCT), or other cellular therapy product, within 3 months of signing consent.
5. Clinically active acute or chronic GVHD. Patients must be off calcineurin inhibitors for at least 4 weeks to be eligible.
6. Radiation therapy or major surgery within 3 weeks of signing consent.
7. Active, uncontrolled infection. Patients with infection under active treatment and controlled with antibiotics are eligible. Prophylaxis is acceptable.
8. Inability to tolerate oral medication, presence of poorly controlled gastrointestinal disease, or dysfunction that could affect study drug absorption.
9. Active documented central nervous system leukemia
10. Concurrent treatment with a non-permitted concomitant medication.
11. Other malignancy IF currently being treated or likely to be treated in next 6 months except for basal or squamous cell carcinoma of the skin or cervical carcinoma in situ.
12. Pregnancy or breastfeeding females
13. Known chronic alcohol or drug abuse
14. Clinically significant cardiovascular disease with major event or cardiac intervention within the past 6 months (e.g. percutaneous intervention, coronary artery bypass graft, documented cardiac heart failure) as determined by the investigator
15. Any other condition deemed by the investigator to make the patient a poor candidate for clinical trial and/or treatment with investigational agents.

Dosing Rationale:

At dose level one, subjects will receive escalating doses of venetoclax during a “ramp” phase to a maximum dose of 400mg/day, and then continuously thereafter. This dose was chosen based on the clinical trial dosing in combination with a DNMTi partner. DEC-C will be dosed at decitabine 35mg and cedazuridine 100mg per day on days 1-5 which is consistent with prior study data and approval. Cycles are every 28 days.

Study Duration:

It is estimated that this study will enroll patients from January 2022 through January 2024. Data lock and study closure is expected in January 2025.

Statistical Analysis:
Assuming a historical ORR of 15%, per the phase II efficacy trial, Simon's optimal two-stage design calls for a total of 34 patients. A preliminary efficacy assessment will be performed following enrollment of the first 20 patients. If $\geq$3/20 enrolled patients achieve a CR, this is sufficient to continue enrollment for the remainder of the study. If $\geq$9/34 patients respond, we will reject ($p<0.05$) the null hypothesis that the true response rate of the regimen is less than or equal to 15%. If the true response rate is 35% or greater, this study design has 80% probability of rejecting the null hypothesis. If the true response rate is low at 15%, the probability of early termination is 60% with an expected sample size of 19 patients.

Toxicity will be monitored in the expansion phase using a Bayesian approach. Toxicity monitoring will begin when the 6th patient is evaluable for toxicity. It is expected that the toxicity rate is maintained at approximately 20% (maximum probability of DLT of 0.2, prior distribution (1,1), cohort size 1, and posterior probability > 80%). Enrollment will be paused if toxicity exceeds this rate.

The maximum number of patients enrolled (n=51) reflects an anticipated drop out of 15% (n=5) and enrollment of 6-12 additional patients if dose level 0 is deemed toxic.

Table 1: Schedule of Activities and Assessments – Screening & Cycle 1

Protocol Activities *1 Cycle = 4 weeks (28 days)*	**Screening** (Day-14 to -1)	**CYCLE 1**				
		Day 1-3	**Day 5**	**Day 8**	**Day 15**	**Day 22**
	Clinical Assessments					
Consent, Baseline Characteristics & Eligibility[1]	X					
Physical Exam	X	X[14]		X	X	X
ECOG Performance Status	X	X[14]				
Height	X					
Weight	X	X[14]		X	X	X
Vital Signs (BP, HR & Temp)[2]	X	X	X	X	X	X
Review of Con Meds & Adverse Events[3]	X	X	X	X	X	X
DLT/RP2D Safety Evaluation[4]		X	X	X	X	X
	Laboratory and Other Assessments					
CBC with Differential[5]	X	X	X	X	X	X
Serum Chemistry[5]	X	X	X	X	X	X
Mg, Phos, LDH, Uric Acid	X	X	X	X		
Coagulation Testing (PT/INR, PTT)	X					
Electrocardiogram[6]	X					
Pregnancy Test[7]	X	X[7]				
	Biospecimen Collections					
Bone marrow aspiration and biopsy[8]	X					X[15]
Pharmacodynamic Blood (PD)[9]	X					X
Next Generation Sequencing[10]	X					X
	Treatment					
Anti-TLS hydration/prophylaxis[11]	X	X				
Decitabine/cedazuridine (oral)[12]		X	X			
Venetoclax oral administration (daily)[13]		Ramp	Continuous once daily oral dosing[13]			

Table 2: C1D22 Marrow involved:

Protocol Activities *1 Cycle = 4 weeks (28 days)*	PRE-REMISSION THERAPY				POST-REMISSION THERAPY[16]					POST-TREATMENT	
	CYCLE 2				CYCLE 1		CYCLE 2		CYCLE 3+	EOT (≤10d after last study dose)[17]	Follow-Up (28d + 7d after last study dose)[19]
	Day 1	Day 8	Day 15	Day 22	Day 1, 5	Day 15	Day 1	Day 15	Day 1		
	Clinical Assessments										
Physical Exam	X		X		d1		X		X	X	X
ECOG Performance Status	X				d1		X		X	X	X
Height											
Weight	X				d1		X		X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X
Review of Con Meds & Adverse Events[3]	X	X	X	X	X	X	X	X	X	X	X
DLT/RP2D Safety Evaluation[4]	X										
Survival Follow-Up											X[20]
	Laboratory and Other Assessments										
CBC with Differential[5]	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry[5]	X	X	X	X	X	X	X	X	X	X	X
Mg, Phos, LDH, Uric Acid										X	
Coagulation Testing (PT/INR, PTT)										X	
Electrocardiogram[6]										X	
Pregnancy Test[7]										X	
	Biospecimen Collections										
Bone marrow aspiration and biopsy[8]				X[15]					C3d1	EOT / PD[18]	
Pharmacodynamic Blood (PD)[9]				X						EOT / PD[18]	
Next Generation Sequencing[10]				X					C3d1	EOT / PD[18]	
	Treatment										
Decitabine/cedazuridine (RP2D)[12]					Per Protocol		Per Protocol		Per Protocol		
Venetoclax oral administration (daily)[13]	Per protocol										

Table 3: C1D22 Marrow uninvolved:

Protocol Activities *1 Cycle = 4 weeks (28 days)*	POST-REMISSION THERAPY[16]					POST-TREATMENT	
	CYCLE 1		CYCLE 2		CYCLE 3+	EOT (≤10d after last study dose)[17]	Follow-Up (28d + 7d after last study dose)[19]
	Day 1, 5	Day 15	Days 1, 5	Day 15	Day 1		
	Clinical Assessments						
Physical Exam	d1		d1		X	X	X
ECOG Performance Status	d1		d1		X	X	X
Height							
Weight	d1		d1		X	X	X
Vital Signs[2]	X	X	X	X	X	X	X
Review of Con Meds & Adverse Events[3]	X	X	X	X	X	X	X
DLT/RP2D Safety Evaluation[4]	d1						
Survival Follow-Up							X[20]
	Laboratory and Other Assessments						
CBC with Differential[5]	X	X	X	X	X	X	X
Serum Chemistry[5]	X	X	X	X	X	X	X
Mg, Phos, LDH, Uric Acid						X	
Coagulation Testing (PT/INR, PTT)						X	
Electrocardiogram[6]						X	
Pregnancy Test[7]						X	
	Biospecimen Collections						
Bone marrow aspiration and biopsy[8]					C3d1	EOT / PD[18]	
Pharmacodynamic Blood (PD)[9]						EOT / PD[18]	
Next Generation Sequencing[10]					C3d1	EOT / PD[18]	
	Treatment						
Decitabine/cedazuridine (RP2D)[12]	Per Protocol		Per Protocol		Per Protocol		
Venetoclax oral administration (daily)[13]	Per protocol						

Notes:

1. Informed consent must be obtained before any screening assessments are performed. Screening assessments are to be performed within 14 days prior to Day 1 of Cycle 1 unless otherwise noted. Assessments performed as standard of care within the screening window may be used for screening. Baseline characteristics include but are not limited to demographics, medical and surgical history, extent of disease, prior anti-cancer treatment.
2. Vital Signs to include: Blood pressure (BP), heart rate (HR) and temperature. To be done at least once on days indicated and thereafter, ideally prior to any receipt of study drug. Any additional recordings per local site's standard of care/ treating physician discretion.
3. Review and capture of all concomitant medications will be performed as indicated. Concomitant medications include prescription medications and over-the-counter preparations used by a patient within at least 14 days prior to first dose of protocol-defined treatment and continuing through at least the 28-day Follow-Up study visit. After signing informed consent, adverse events will be collected and followed at least until 28 days after a patient's final protocol-directed treatment with DEC-C/venetoclax (whichever occurs last) or until initiation of another anti-cancer therapy – whichever occurs first.
4. Surveillance for toxicity related to DEC-C/venetoclax to establish RP2D. For patients enrolled in the dose exploration (or dose de-escalation) part of the study, dedicated surveillance including satisfactory assessment of the physical exam and safety labs is required to help detect evidence of past or present DLT as having occurred during the first 28 days of protocol-indicated treatment. Expedited reporting of Dose Limiting Toxicity (DLT) required as outlined in Section 5.2.4. See Section 5.2.4 for definition of DLT and toxicities which, if experienced during the first 28 days after initiating protocol-indicated treatment, shall be considered dose limiting.
5. Hematology includes white blood cell count with differential, hemoglobin, hematocrit, and platelet count. Blood Chemistry to include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase, calcium, albumin, and total protein.
6. One standard 12-lead electrocardiogram (ECG) using local site equipment during screening and EOT visits. Additional ECGs as clinically indicated.
7. For women of childbearing potential: Serum pregnancy test required during screening and either serum or urine pregnancy test required ≤3 days prior to first dose of protocol-indicated treatment and at End-of-Treatment. A woman of childbearing potential is defined as any female who has experienced menarche who has not undergone surgical sterilization (e.g. bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) at least 4 weeks prior to first dose of protocol-indicated treatment, or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.
8. Patients must have at least 2-3 mL of bone marrow aspirate material obtained within 14 days of beginning treatment on this study. Post-enrollment tissue to be collected on Cycle 1 Day 22, Cycle 2 Day 22 (only if C1 Day 22 marrow is

involved), post-remission Cycle 3 Day 1 (acceptable windows up to 3 days before or after); and at End-of-Treatment (≤14 days after treatment was discontinued) or at time of suspected progressive disease.

9. On a day of a bone marrow biopsy, matching peripheral blood pharmacodynamic (PD) blood samples are to be drawn PRIOR to procedure for correlative research. At any time during the study, if additional biopsy is performed as standard-of-care, then a sample of the tissue, if available, may be requested for research purposes. Pharmacodynamic studies will be drawn to assess the impact of DEC-C/venetoclax on immune function/recovery during treatment and correlated with clinical/study outcomes.
10. All patients will have next generation sequencing (NGS) performed on their relapsed marrow and all subsequent marrows performed while on study. If the standard of care NGS report is available prior to enrollment, this should not be repeated. If NGS testing is not indicated per the institutional standard of care, additional bone marrow aspirate may be sent to VUMC and NGS will be performed as a research test.
11. During the first three days of therapy, tumor lysis syndrome (TLS) precautions will include scheduled outpatient visits with TLS laboratory studies. Therapy with a uric acid reducing agent (e.g., allopurinol initiated at least 2-3 days prior to the start of therapy) is required. Laboratory monitoring for TLS (per institution standard of care) will occur prior to the first dose on cycle 1 day 1 and continue for the first three days of cycle 1. Unless contraindicated, allopurinol must be continued through the end of cycle 1. Intravenous fluids should be administered daily during the ramp-up period. Patients with clinical evidence of TLS should be hospitalized.
12. The study will provide decitabine/cedazuridine (DEC-C) to the sites. Treatment with DEC-C will begin on Cycle 1 Day 1 after receiving anti-TLS hydration/prophylaxis. It is intended that patients will receive DEC-C until progression of disease, unacceptable toxicity, revocation of consent, or for up to 12 months of post-remission therapy. DEC-C is to be taken without food at the same time each day. See Section 5.2.1.2.
13. Sites will obtain commercial (standard of care) venetoclax. Venetoclax will begin on Cycle 1 Day 1 after receiving anti-TLS hydration/prophylaxis. Venteoclax dosing is ramped to 400mg/day. It is intended that patients will receive venetoclax until progression of disease, unacceptable toxicity, revocation of consent, or for up to 12 months of maintenance. Venetoclax is taken with food at the same time each day. See Section 5.2.1.1.
14. On Cycle 1, Day 1 only: Physical exam; ECOG performance status; and weight will be obtained unless performed within the prior 7 days. Confirmation of a negative pregnancy test is required in all women of childbearing potential prior to beginning protocol-directed therapies.
15. All patients will undergo bone marrow aspiration and biopsy on cycle 1 day 22 to assess treatment response and for correlative studies. Patients with at least a partial response (PR) to treatment who receive a second cycle of full-intensity therapy will have repeat biopsy at cycle 2 day 22. Aspirate and matching PD blood samples will be sent for correlative studies.

16. Beginning in the post-remission phase: To accommodate scheduling, Day 1 and 15 visits/procedures may occur with flexibility of ± 3 days.
17. Reasonable effort should be made to complete End-of-Treatment (EOT) procedures on the day it is decided a patient will no longer receive protocol-indicated treatment. These procedures must be completed subsequent to and not later than 10 days after investigator decision to permanently discontinue protocol-indicated treatment with DEC-C or venetoclax (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy.
18. At End-of-Treatment: If patient discontinues study treatment for reason other than progressive disease confirmed by biopsy procedure (e.g. due to adverse event), then every effort should be made to obtain fresh biopsy samples to evaluate response and to obtain biospecimens including matching PD blood samples for exploratory research. If progressive disease is suspected between scheduled study biopsies (e.g. due to peripheral blood counts), then fresh biopsy and PD blood samples must be collected in a subsequent procedure to evaluate for progressive disease and to obtain bio specimens for research purposes; if progressive disease is confirmed in that procedure and the patient will terminate the study as a result, then these procedures may be used as the end of treatment procedures.
19. Follow-up clinic visit to be completed within 28 to 35 days after patient's final protocol-indicated treatment with DEC-C or venetoclax (whichever occurs last). Documented attempt(s) must be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained from local and outside facilities. Note: The study may continue to request results of laboratory data conducted outside of the study but related to peripheral blood counts or bone marrow biopsy, until progressive disease is ultimately confirmed.
20. Each patient will be followed for survival every 3 months (± 14 days) after patient's final protocol treatment with DEC-C or venetoclax (whichever occurs last) until death, end of the study, until patient withdraws consent, or for a maximum of 2 years after the patient's final protocol-indicated treatment – whichever comes first. Survival contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

Figure 1: Study Schema – Pre-Remission Phase. All patients will initiate therapy as outlined below. Patients who achieve a leukemia free state on bone marrow biopsy may interrupt therapy and will proceed to the post-remission phase of the study.

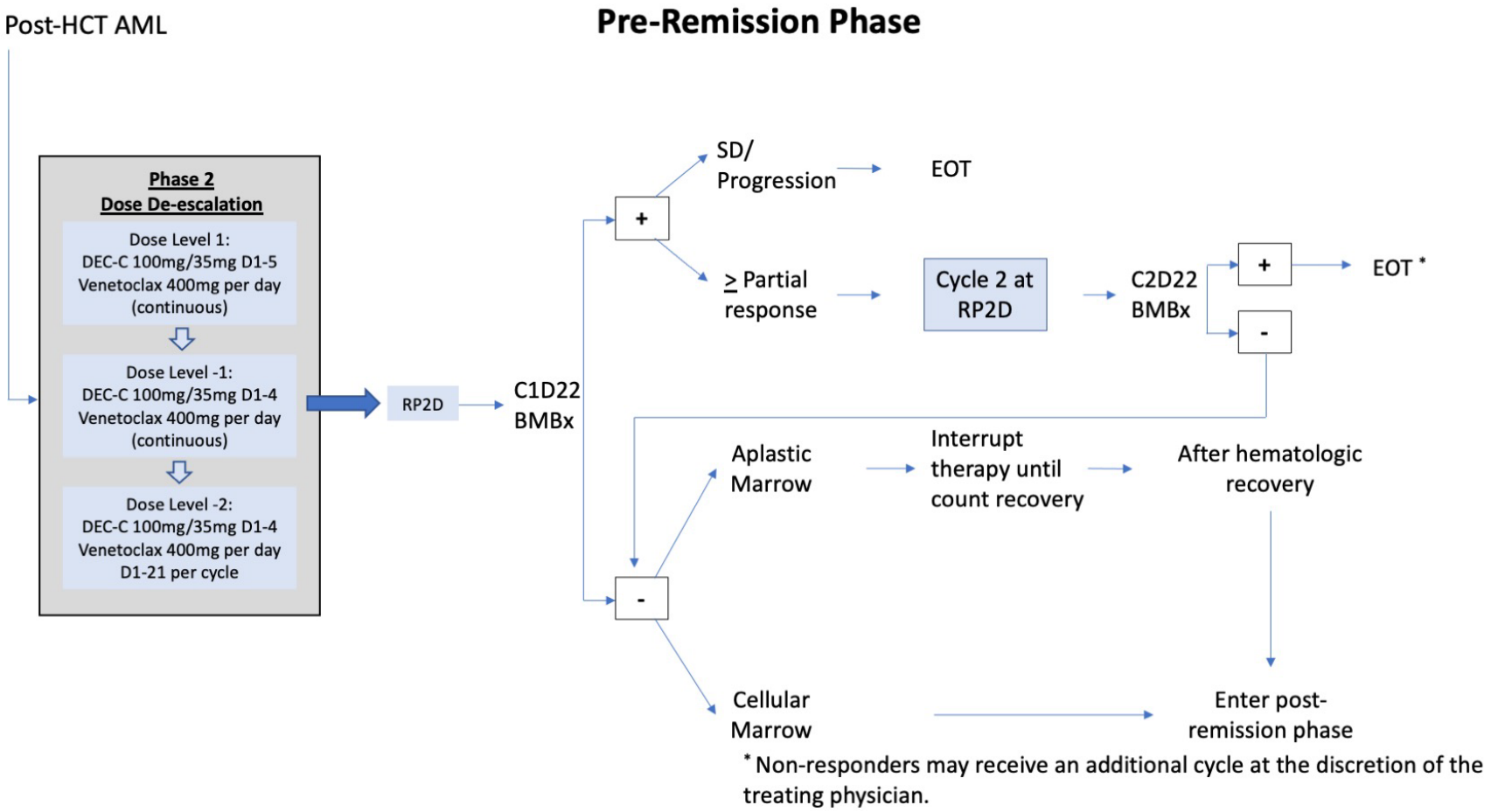
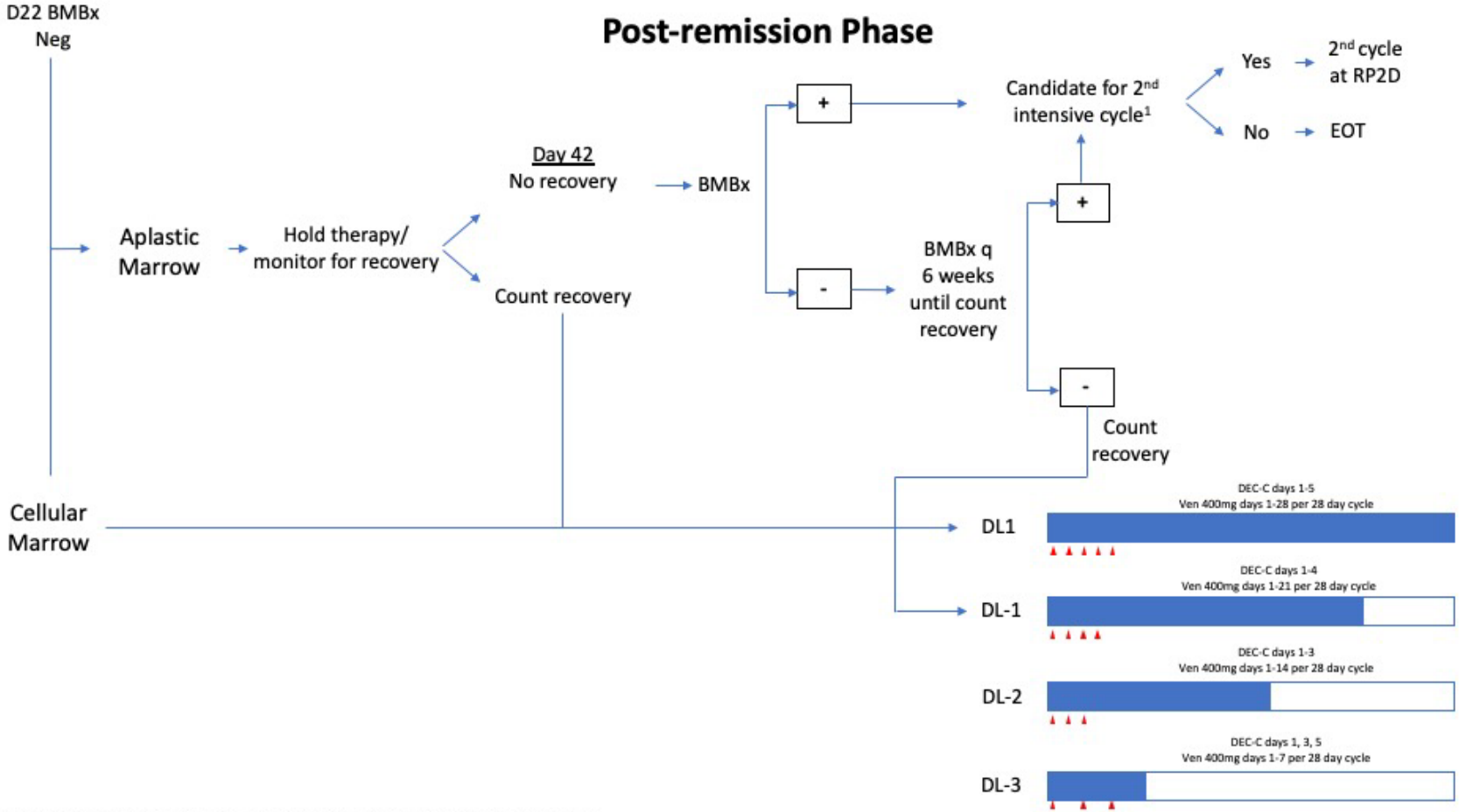


Figure 2: Study Schema – Initiation of post-remission therapy. Post-remission treatment will begin after patients with marrow aplasia recover counts (defined as absolute neutrophil count ≥1,000/μl and platelets ≥50,000/μl). In the setting of bone marrow aplasia and > Grade 2 neutropenia/thrombocytopenia, a BMBx will be performed every six weeks until count recovery or evidence of recurrent disease. If the day 22 bone marrow biopsy is cellular but negative for leukemia, and there is concern for persistent disease, post-remission therapy may begin without interruption.



[1] A 2nd Pre-remission cycle may be administered in patients with one prior cycle

Contents

1 INTRODUCTION

1.1 Background

Acute myeloid leukemia, excluding acute promyelocytic leukemia, is generally associated with poor clinical outcomes. Patients with poor-risk clinical and molecular features experience a shortened survival with a minority surviving beyond 5 years.[1,2,3,4] Similarly, patients with high-grade myeloid malignancies, including myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML), are at risk for leukemic transformation with rates approaching 40%.[5] For poor-risk patients, allogeneic HCT is the only potentially curative therapy, however, post-HCT relapse is common and as many 85% of poor-risk AML patients will experience recurrence of their underlying disease.[6] In a registry analysis, 15% of post-HCT relapsed AML patients achieved a subsequent complete remission (CR). Less than 5% of patients who relapsed within 6 months, and 12% of patients who relapsed 6-24 months after HCT were alive at 3 years.[7]

Dysregulation of anti-apoptotic proteins, including BCL2, is responsible for tumor maintenance and survival. Venetoclax is a selective BCL2 inhibitor that increases cell death/apoptosis in hematologic malignancies. In chronic lymphoid leukemia, a disease heavily reliant on the loss of apoptosis, overall response rates (ORR) exceed 80% with venetoclax.[8] In AML, anti-apoptotic pathways are more heterogeneous. Venetoclax, in combination with DNMTis or low dose cytarabine, results in CR/CRi rates of 60-75% in the treatment naïve (TN) setting.[9,10] Off-label use in the relapsed/refractory (R/R) disease is an emerging treatment paradigm with an ORR of 12-51%. In a series of post-HCT AML patients treated with venetoclax-based salvage therapies at Vanderbilt University Medical Center (16/21 with a DNMTi partner), our group reported that the combination is safe and effective with an ORR of 42.1%.[11] Interrupting therapy in patients with a treatment response improved safety and reduced toxicity after HCT.

Based on our published experience, and other retrospective data in the R/R AML, this phase 2 trial will prospectively assess the ORR of venetoclax/DNMTi salvage therapy after allogeneic HCT.[11,12,13] Partnering venetoclax with DEC-C combines the efficacy of venetoclax/DNMTi therapy with the convenience of an all-oral treatment regimen which will reduce the burden of treatment relative to conventional salvage therapies.

1.1.1 Venetoclax

Venetoclax (also referred to as ABT-199 and GDC-0199) is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics.

Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins like BIM, triggering mitochondrial outer

membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.[14]

Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance, as well as autoimmunity. Overexpression of Bcl-2 is a major contributor to the pathogenesis of some lymphoid malignancies; antagonism of the action of these proteins may enhance response to therapy and overcome resistance, and thus, these proteins are compelling targets for anti-tumor therapy.[15]

Venetoclax was first approved in the United States (US) on 11 April 2016 through accelerated approval for a New Drug Application (NDA) by the Food and Drug Administration (FDA). On 08 June 2018, the US FDA approved venetoclax in combination with rituximab therapy and the venetoclax expanded monotherapy. This approval confirmed the clinical benefit of venetoclax in the relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) population with or without deletion of the p13 locus on chromosome 17 (17p del); thus the initial accelerated approval has been converted to a full approval. On 21 November 2018, venetoclax in the US was granted accelerated approval for the treatment of acute myeloid leukemia AML (in combination with azacitidine/ decitabine or low-dose cytarabine).[9,10,14] On 15 May 2019, the US FDA approved venetoclax in combination with obinutuzumab for treatment of previously untreated patients with CLL or SLL.

In the US, venetoclax is indicated for the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL). In addition, it is approved in combination with azacitidine or decitabine or low dose cytarabine (LDAC) for the treatment of newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

1.1.2 Clinical Experience

As of 28 November 2020, on the basis of data available in the clinical databases for company-sponsored studies with unblinded data, a total of 4599 subjects have been exposed to at least 1 dose of venetoclax across company-sponsored studies. Of these subjects: 4203 oncology subjects, 299 healthy volunteers, 24 subjects with hepatic impairment, and 73 SLE subjects. Of the 4203 oncology subjects, 4101 were adults in the venetoclax oncology program (1199 in monotherapy studies and 2902 in combination therapy studies): 1684 with CLL/SLL, 1011 with AML, 498 with MM, 573 with NHL/MCL, 181 with MDS, and 57 with ALL/LL, and 10 with solid tumors. The remaining oncology subjects included 102 pediatric subjects in the venetoclax program and 74 oncology subjects in studies conducted with other investigational new drug (IND) compounds outside the venetoclax program.

1.1.3 Efficacy

Efficacy data indicates that venetoclax has anti-tumor activity as both monotherapy and in combination with other therapeutic agents and continues to show promising efficacy in oncology subject populations.

The ORR in subjects with CLL/SLL was 74% (IRC-assessed) and 79% (investigator-assessed) for venetoclax monotherapy (Study M12-175 and Study M13-982, respectively), ranged from 29% to 42% for ibrutinib- or idelalisib-resistant CLL subjects in Study M14-032, and was 86% for venetoclax administered in combination with rituximab (Study M13-365). The ORR in subjects with NHL was 18% to 38% for venetoclax monotherapy (Study M12 -175) and 67% for venetoclax in combination with BR (Study M12-630).

In subjects with AML, the ORR was 19% for venetoclax monotherapy (Study M14-212) and was 77% for venetoclax in combination with azacitidine/decitabine (Study M14-358) and 62% for patients treated with venetoclax in combination with low dose cytarabine (M14-387).[9,10] Off-label use in R/R AML, in combinations consistent with the FDA label, is increasing with an ORR of 12-51%.[11]

1.1.4 Safety

As of 28 November 2020, a total of 1011 adult AML subjects treated with venetoclax in the oncology clinical program had open-label or unblinded safety data available, including 32 subjects who received venetoclax monotherapy for R/R AML and 979 subjects who received venetoclax in combination with other therapeutic agents that include the following: dinaciclib, alvocidib, gilteritinib, and AMG 176 in R/R AML; azacitidine and decitabine in AML ineligible for intensive chemotherapy; and hypomethylating agents and LDAC in previously untreated AML ineligible for intensive chemotherapy. Additionally, 10 previously untreated AML subjects in mainland China are known to have received venetoclax in combination with azacitidine in the open-label Chinese safety cohort of the otherwise blinded Study M15-656/VIALE-A, and 431 previously untreated AML subjects with blinded data received either venetoclax in combination with azacitidine or azacitidine with placebo in Study M15-656/VIALE-A.

The safety data in AML and the benefit risk profile of venetoclax, in both monotherapy and combination therapy have been characterized. The safety profile was similar across monotherapy and combination treatment in terms of type and severity of TEAEs, although with some numerical differences, so the safety data for the combination studies have been pooled for the AML indication. Most subjects experienced adverse events, and the most common were nausea, diarrhea, and febrile neutropenia. Approximately 96% of subjects experienced grade ≥ 3 adverse events (87.5% for monotherapy; 96.9% for combination therapy). The most common grade ≥ 3 adverse events for monotherapy were febrile neutropenia, malignant neoplasm progression, pneumonia, and hypokalemia. The most common grade ≥ 3 events for venetoclax combination therapy were febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse events were reported in 79.3% of subjects, and the most common SAE

for both venetoclax monotherapy and combination therapy was febrile neutropenia. Findings from the analysis based on the exposure adjusted incidence rates were consistent with the findings from the analysis based on the subject incidence rates. The reported adverse events were consistent with the natural progression of AML, the known safety profile of venetoclax and any combination therapy and/or any concomitant treatments or coexisting comorbid conditions.

The overall incidence of TLS is 8.9% (4/45) in Study M16-183 and 10.0% (3/30) in Study M16-186. Across the AML venetoclax program, TLS was reported for 21 subjects (3.5%) across all unblinded and open-label AML studies, including 11 events of clinical TLS and 10 events of laboratory TLS (LTLS).

The clinical CTLS events occurred for 5 subjects treated with venetoclax + alvocidib or dinaciclib (2 in Study M16-186, 3 in Study M16-183), 4 subjects treated with venetoclax + LDAC (Study M16-043/VIALE-C), 1 subject treated with venetoclax + gilteritinib (Study M16-802), and after venetoclax discontinuation for 1 subject treated with venetoclax + LDAC (Study M14-387). Two events of CTLS were fatal (Study M16-043/VIALE-C), and 3 additional events of CTLS led to discontinuation of venetoclax (1 in Study M16-043/VIALE-C, 1 in Study M16-183, and 1 in Study M16-186). Of the 2 fatal events, one was in a subject with moderate renal insufficiency; the other was in a subject who was already hospitalized for subconjunctival and periorbital hemorrhage at the time of study drug initiation and in whom additional causes of death were pneumonia and intra-alveolar hemorrhage.

Of the 10 cases of LTLS, 1 event (Study M14-212) occurred after the subject had discontinued venetoclax and started another line of therapy, and 1 event (Study M16-043/VIALE-C) did not meet the Howard criteria but were reported as TLS by the investigator because of kidney injury. The remaining 8 events of LTLS occurred with combination treatments of venetoclax + LDAC (2 in Study M14-387, 3 in Study M16-043/VIALE-C), venetoclax + dinaciclib (1 in Study M16-183), venetoclax + azacitidine (1 in Study M19-072), and venetoclax + alvocidib (1 in Study M16-186). One event led to discontinuation of venetoclax and the other 9 cases resolved without discontinuation of venetoclax. No events of TLS were reported in combination Study M14-358 (venetoclax + hypomethylating agents). Neutropenia and febrile neutropenia are expected in this population. Neutropenia events were generally manageable per standard of care and dose modifications; and no clear relationship with increased rate of infection was found. Serious infections, including sepsis, have been reported in subjects receiving venetoclax treatment, and generally responded to dose interruption and standard management (e.g., antibiotics and supportive care) with few subjects requiring dose reduction. However, serious events with fatal outcome have been reported.

1.2 Oral decitabine and cedazuridine (DEC-C)

DNA methyltransferase inhibitors (DNMTis), such as decitabine and azacitidine, are effective treatment modalities for hematologic cancers and are FDA-approved for higher risk myelodysplastic syndromes (MDS). These agents demonstrate clinical activity in AML. Consecutive daily dosing for a minimum of 5 or 7 days in 28-day cycles is the

labelled schedule and continued monthly treatment for patients who respond is considered the standard of care to delay relapse.[16] Typical intravenous (IV)/subcutaneous (SQ) dosing requires a 1-hour IV infusion or a large-volume SQ injection.

A drug product composed of cedazuridine (E7727), a cytidine deaminase (CDA) inhibitor, and decitabine has improved the convenience associated with DNMTi therapy and is approved for the treatment of patients with MDS. Because cedazuridine inhibits CDA in the gut and liver, the oral decitabine cedazuridine (also referred to as DEC-C or ASTX727) is a fixed-dose combination (FDC) facilitates oral administration of decitabine, achieving exposure and hypomethylation activity similar to IV decitabine at the currently approved dosing schedule of 20 mg/m^2 daily for 5 days. Intra-patient pharmacokinetic (PK) comparison and safety data from the phase 1-2 studies confirm exposure similar to IV decitabine.

DEC-C is the oral FDC of cedazuridine + decitabine. Cedazuridine is a CDA inhibitor and decitabine is a nucleoside hypomethylating agent known to induce demethylation through DNA methyltransferase inhibition. Decitabine is a substrate of CDA. The combination of cedazuridine + decitabine has been shown to increase systemic decitabine exposure (AUC) following oral administration.

1.2.1 Clinical Experience

The ASTX727 clinical program includes a total of 7 clinical trials. Results from ASTX727-01 (Phase 1), ASTX727-01 (Phase 2), ASTX727-02, and ASTX727-04 include analyses of primary PK and/or PD endpoints, efficacy/preliminary efficacy (ASTX727-01 Phase 1, ASTX727-01 Phase 2, and ASTX727-02), and safety.

As of 14 April 2021, a total of 385 subjects have received any dose of cedazuridine. Of these 385, Eight healthy subjects received only cedazuridine in the completed absorption, distribution, metabolism, and excretion (ADME) study E7727-01. Forty-seven subjects with lower risk MDS (low-risk or Int-1 per IPSS) received 100 mg cedazuridine and lower doses of decitabine (≤20mg) in the low-dose ASTX727 clinical program.

In addition to the above studies, ASTX727 is also currently being evaluated in combination with ASTX660 (a novel small molecule nonpeptidomimetic IAP antagonist) in Study ASTX660-02 in subjects with AML as well as several investigator-sponsored trials of ASTX727, including studies in combination with venetoclax.

1.2.2 Efficacy

DEC-C was recently approved for adults with MDS (>INT-1 by IPSS) and CMML-1 following two open-label, randomized (1:1) cross-over studies that compared safety/exposure between oral/IV decitabine. All patients received oral decitabine from cycle 3 onward. In the ASTX727-01-B study, 80 adult patients (MDS with INT-2 or higher disease, CMML) were enrolled. The CR rate was 21%. 60% of patients on study

experienced a clinical benefit and 50% of transfusion dependent patients became transfusion independent. The median time to progression to AML or death was 12.1 months.[17] In the ASTX727-02 study, 133 patients were enrolled and comparability (99%) between IV and PO decitabine. Response rates were similar; 21% of patients achieved a CR with a median CR duration of 7.5 months. 53% of patients achieved transfusion independence, however, treatment was complicated by Gr 3/4 cytopenias in >50% of patients while on study.[18] The recommended dose of DEC-C is 1 tablet (decitabine 35mg and cedazuridine 100mg) daily on days 1-5 per 28 day cycle.

1.2.3 Safety

Subjects in the Dose Escalation Stage of Study ASTX727-01 received oral decitabine alone, cedazuridine alone, and IV decitabine alone on specific days during Cycles 1 and 2. During the remainder of the study, cedazuridine and oral decitabine were administered together for full 5-day cycles.[18] It is difficult to evaluate safety for the single dose of the individual agents, however, based on the large safety margin of cedazuridine alone (no-observed-adverse-effect level is ~40 fold higher than the human therapeutic dose) compared with decitabine, it is believed that the DEC-C safety data primarily reflect the effects of decitabine.

Serious treatment emergent adverse events occurred in up to 69% of patients treated on study. The most common include febrile neutropenia (18.2-26.5%), pneumonia (6.1-13.6%), bacteremia (0-4.5%), sepsis (3.7-13.8%) and cellulitis (4.5-6.1%). Non-serious TEAEs include nausea (34.5%), thrombocytopenia (41.4%), constipation (24.1%), neutropenia (41.4%), and fatigue (31%).

1.3 Study Rationale

Venetoclax/DNMTi combination therapy is an important therapeutic option for elderly and/or unfit patients with treatment naïve AML with CR/CRi rates of 60-75%.[9,10] Off-label use in combination with DNMTi/LDAC is increasing with ORRs in the 12-51% range. In a series from Vanderbilt University Medical Center, we reported the outcomes of 21 post-allogeneic HCT patients who were treated with venetoclax-based salvage therapy (16/21 with a DNMTi partner).[11] Treatment interruptions after achieving a response were associated with improved safety and reduced toxicity. Partnering venetoclax with DEC-C is an extension of this prior work that will combine the efficacy of venetoclax/DNMTi therapy with the convenience of an all-oral treatment regimen that will improve quality of life compared to conventional salvage therapies.

1.3.1 Dose Schedule and Rationale

1.3.1.1 Venetoclax dosing

All patients who initiate therapy on this study will have venetoclax ramped to a dose of 400mg/day. In the dose de-escalation phase of this study, venetoclax will be dosed continuously in 28 day cycles in dose level 1 and dose level -1. In dose level -2,

venetoclax will be dosed 21/28 days. This dosing was selected based on the FDA label in treatment naïve AML. Dose modifications follow the venetoclax US Prescribing Information.

For additional information regarding venetoclax dosing, see Figure 1 and 2.

1.3.1.2 Oral decitabine and cedazuridine dosing

In the dose de-escalation phase of this study, oral decitabine and cedazuridine (DEC-C) will be dosed as 35mg/100 (decitabine 35mg and cedazuridine 100mg) daily on days 1-5 per 28 day cycle in dose level 1. In dose level -1 and dose level -2, DEC-C will be administered on days 1-4. This dosing was selected based on the FDA label in MDS. Dose modifications follow the oral decitabine and cedazuridine US Prescribing Information.

For additional information regarding venetoclax dosing, see Figure 1 and 2.

2 STUDY OBJECTIVES

2.1 Primary Objectives:

1. To assess the effect of DEC-C/venetoclax on the investigator-assessed composite CR rate (CR/CRh/CRi)

2.2 Secondary Objectives:

1. To assess the rate of partial response (PR) and morphologic leukemia free state (MLFS) following treatment with DEC-C/venetoclax
2. To assess the relapse free survival of patients treated with DEC-C/venetoclax
3. To assess overall survival of patients treated with DEC-C/venetoclax
4. To assess the safety and tolerability of DEC-C/venetoclax in the post-HCT setting
5. To assess the rates of measurable residual disease negativity in patients achieving a CR.

3 STUDY DESIGN

3.1 Overall Study Design and Plan

This is an open-label, non-randomized, investigator-sponsored, phase II study of venetoclax in combination with DEC-C in patients with myeloid diseases who relapse with AML after allogeneic HCT.

3.2 Study Duration and Dates

It is estimated that this study will enroll patients from January 2022 through January 2024. Data lock and study closure is expected in January 2025.

4 STUDY POPULATION SELECTION

4.1 Study Population

Adult patients, ≥18 years of age with relapsed/progression to AML after allogeneic HCT, who have not previously progressed while receiving venetoclax or other BCL-2 inhibitor, are eligible. Subjects with active GVHD, acute or uncontrolled infections, or with white blood cell count ≥25,000/μl that cannot be controlled with hydroxyurea are not eligible.

Patients who develop grade 3/4 graft versus host disease while on study will have treatment interrupted. Subjects will be eligible to resume therapy after GVHD returns to ≤ grade 1 after discussion with the study co-chair(s).

4.2 Inclusion Criteria:

1. Age ≥18 years at the time of signing the Informed Consent Form (ICF); must voluntarily sign an ICF and meet all study requirements
2. History of morphologically confirmed AML (per WHO diagnostic criteria) with evidence of disease recurrence (≥5% blasts consistent with prior disease) that occurs after allogeneic HCT. Patients transplanted for another indication (e.g., MDS/CMML) who relapse with AML are eligible to enroll.
3. WBC must be less than 25,000/μl for at least three days prior to C1D1 (hydroxyurea allowed).
4. A bone marrow biopsy must be performed and tissue collected for entrance to the trial.
5. Eastern Cooperative Oncology Group Performance Status of 0 - 2
6. Must have adequate hepatic and renal function as demonstrated by the following: ALT (SGPT) and/or AST (SGOT) less than or equal to 3x upper limit of normal (ULN); total bilirubin < 1.5 x upper limit of normal (ULN). Patients with Gilbert's syndrome (hereditary indirect hyperbilirubinemia) must have a total bilirubin of < 3 x ULN; and calculated creatinine clearance ≥30 ml/min (per the Cockroft-Gault formula).
7. Willingness to abide by all study requirements, including contraception, maintenance of a pill diary, and acceptance of recommended supportive care medications.

4.3 Exclusion Criteria:

1. Prior relapse or progression while receiving venetoclax or other commercially available or investigational BCL-2 inhibitor.
2. Anticancer therapy, including investigational agents ≤2 weeks or ≤5 half-lives of the drug, whichever is shorter, prior to C1D1. (Use of hydroxyurea is permitted).
3. Inadequate recovery from toxicity attributed to prior anti-cancer therapy to ≤Grade 1 (NCI CTCAE v5.0), excluding alopecia or fatigue.
4. History of allogeneic hematopoietic cell transplantation (HCT), or other cellular therapy product, within 3 months of signing consent.
5. Clinically active acute or chronic GVHD. Patients must be off calcineurin inhibitors for at least 4 weeks to be eligible.
6. Radiation therapy or major surgery within 3 weeks of signing consent.
7. Active, uncontrolled infection. Patients with infection under active treatment and controlled with antibiotics are eligible. Prophylaxis is acceptable.
8. Inability to tolerate oral medication, presence of poorly controlled gastrointestinal disease, or dysfunction that could affect study drug absorption.
9. Active documented central nervous system leukemia
10. Concurrent treatment with a non-permitted concomitant medication.
11. Other malignancy IF currently being treated or likely to be treated in next 6 months except for basal or squamous cell carcinoma of the skin or cervical carcinoma in situ.
12. Pregnancy or breastfeeding females
13. Known chronic alcohol or drug abuse
14. Clinically significant cardiovascular disease with major event or cardiac intervention within the past 6 months (e.g. percutaneous intervention, coronary artery bypass graft, documented cardiac heart failure) as determined by the investigator
15. Any other condition deemed by the investigator to make the patient a poor candidate for clinical trial and/or treatment with investigational agents.

5 STUDY TREATMENTS

5.1 Treatments Administered

5.1.1 Tumor Lysis Syndrome Prophylaxis

All patients are required to receive standard tumor lysis prophylaxis. During the ramp-up phase (See Section 5.2.1.1), TLS precautions may include intravenous fluids, uric acid lowering agents, and daily visits with TLS laboratory studies drawn before each dose. Initiation of allopurinol should occur 2-3 days prior to the start of therapy and is continued through the end of Cycle 1 if no clinically significant TLS is observed. If there is clinical or biochemical evidence of TLS as an outpatient, hospitalization should be considered.

At any time, more stringent monitoring and/or prophylaxis may be utilized at the discretion of treating physician based on risk factors such as renal function, tumor burden or other comorbidities.

5.1.2 Study Treatments

5.1.2.1 Venetoclax (venclexta)

Venetoclax (venclexta) is a tan, oval tablet with a “V” debossed on one side and “50” or “100” on the other. The venetoclax 10mg formulation is a tan, round tablet with a “V” debossed on one side and a “10” on the other.

Venetoclax will be obtained as a standard of care therapy by the treating clinician/ treatment team. Venetoclax is not provided by the study.

5.1.2.2 Decitabine cedazuridine (DEC-C or INQOVI)

The DEC-C (INQOVI) tablet is a fixed-dose combination of decitabine 35mg and cedazuridine 100mg for oral administration. The drug product is a red, oval shaped, film-coated, immediate-release tablet. The drug products are either plain faced on both sides or have a debossed marking of “H35” on one side and plain faced on the other.

DEC-C is provided by the study.

5.2 Study Drug Dosing and Administration

5.2.1 Dosing Instructions for Patients

Study medications will be dosed according to the schedules provided below and in Figure 1 and 2. For doses of oral medications to be taken on non-clinic days, patients will be provided with medication to take home.

5.2.1.1 Venetoclax

Venetoclax should be taken with food and water at the same time each day, generally within 30 minutes of a meal. The tablets should be swallowed whole and not crushed or broken. Patients should drink 6-8 glasses of water daily for two days before initiating therapy with venetoclax and during the escalation period. On days that venetoclax is taken with DEC-C, venetoclax should be taken with breakfast at least 2 hours after DEC-C is taken.

Each patient is scheduled to receive oral venetoclax per the dosing schedule in Figure 3, beginning with an initial dose ramp period during Cycle 1. On the first 2 days of initial treatment (e.g. Week 1 of Cycle 1), each patient's daily dose of venetoclax is scheduled to be 100mg and then 200mg. Beginning on day 3, each patient is scheduled to continue oral venetoclax on a continuous schedule of 400mg daily.

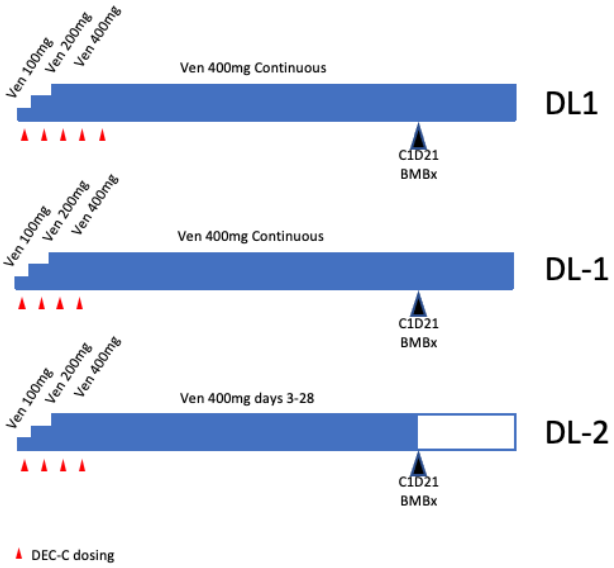


Figure 3. Dose ramp and steady state dosing during cycle 1 of pre-remission phase.

In the absence of unacceptable adverse event requiring dose reduction, it is intended that all patients will receive venetoclax by the same dose and schedule. Patients will take venetoclax tablets 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.

Missed Doses
If a dose is missed within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible. If a dose is missed by more than 8 hours, the subject should not take the missed dose. In either scenario, the subject should resume the usual dosing schedule the next day.

Vomited Doses:
If the subject vomits after dosing, the vomiting episode and the time it occurred should be recorded in the dosing diary. No additional dose should be taken that day. The next prescribed dose should be taken at the usual time. Investigators should consider pre-medicating the subject with antiemetics if vomiting is anticipated to be a recurring issue.

5.2.1.2 Oral Decitabine and cedazudridine

Oral decitabine-cedazuridine (DEC-C) should be taken at the same time each day, typically in the morning. Patients should have an empty stomach with no food for 2 hours before and at least two hours after administration. Anti-acid medications should be taken at night. The tablets should be swallowed whole and not crushed or broken.

Missed Doses
If a dose is missed within 12 hours of the time it is usually taken, the subject should take the missed dose as soon as possible. If a dose is missed by more than 12 hours, the subject should not take the missed dose. In either scenario, the subject should resume the usual dosing schedule the next day and proceed with completing the entire number of planned treatment days per cycle.

Vomited Doses:
If the subject vomits after dosing, the vomiting episode and the time it occurred should be recorded in the dosing diary. No additional dose should be taken that day. The next dose should be taken at the usual time. Investigators should consider pre-medicating the subject with antiemetics if vomiting is anticipated to be a recurring issue.

5.2.1.3 Venetoclax/DEC-C combination therapy:

On days involving dosing of both venetoclax and DEC-C, the DEC-C should be taken orally (PO) daily on an empty stomach (morning before breakfast) with no food for 2 hours before and at least 2 hours after administration. Venetoclax should be taken daily with breakfast at least 2 hours after DEC-C.

In the post-remission phase of the study, patients may take venetoclax with a meal and the DEC-C at bedtime (with an empty stomach). Both agents should be taken at approximately the same time each day.

A dosing diary will be used to enhance compliance.

5.2.2 Dose Schedules for Evaluation (Pre-remission Phase only)

The study will follow a dose de-escalation design. Cycles are 28 days.

Pre-remission phase:

Dose Level 1:	DEC-C 100mg/35mg on days 1-5 Venetoclax 400mg/day x 28 days
Dose Level -1:	DEC-C 100mg/35mg on days 1-4 Venetoclax 400mg/day x 28 days
Dose Level -2:	DEC-C 100mg/35mg on days 1-4 Venetoclax 400mg/day x 21/28 days

Three initial patients will be enrolled at dose level 1 during the pre-remission phase of treatment. If there are 0 dose limiting toxicities (DLTs), then enrollment will proceed at this dose level. If there is 1 DLT, then 3 additional subjects will be enrolled. If ≥2 DLTs in six patients, dose level -1 will be evaluated using a similar approach, followed by dose level -2. See Table 4.

Table 4: Dose De-escalation Rules

Number of Patients with Drug-Related DLT at a Given Dose Level	Dose De-escalation Step
0 of 3	Proceed as RP2D
1 of 3	Treat 3 more patients at the same dose level
≥ 2 of 3	Enrollment at this dose level stops. Proceed to next lower dose level
≤ 1 of 6	Proceed as RP2D
≥ 2 of 6	Proceed to next lower dose level

All patients will be considered evaluable for DLT unless they cannot complete the first cycle of therapy due to withdrawal of consent or disease progression. A patient who is not DLT-evaluable will be replaced. Cohort review discussions will be held between the study chair and other investigator(s) to confirm dose escalation, reductions, and cohort expansions.

5.2.3 Toxicity Grading

The NCI CTCAE version 5.0 will be used for grading the severity of AEs and modifications to the dosing of venetoclax and DEC-C will be made according to this severity grading. If more than 1 type of toxicity occurs concurrently, the most severe grade will determine the modification. For purpose of any necessary definition, “baseline value” is defined as the most immediately known value in place prior to patient’s first receipt of protocol-indicated treatment on Cycle 1, Day 1.

Severity criteria (NCI/CTCAE):
The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious.” Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a patient’s life or functioning.

The severity of the AE will be graded according to the NCI/CTCAE Grading Scale (see the CTCAE web page at http://ctep.cancer.gov for details). For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” or “severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.

5.2.4 Dose-Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as any toxicity that occurs up to day 28 during the dose de-escalation (pre-remission) phase and is at least possibly related to study drug administration. This does not include toxicity with a clear alternative explanation (e.g., disease progression) or transient (≤72 hours) abnormal laboratory values without

associated clinically significant signs or symptoms based on investigator determination. All DLTs will be assessed by the investigator using CTCAE v5.0 criteria.

To be considered evaluable, subjects must fulfill the following minimum criteria:

- All doses of DEC-C.
- 75% of doses of venetoclax during the first cycle (e.g., 21/28 or 16/21 days)

All patients who initiate venetoclax/DEC-C, receive at least one dose of each, and experience a DLT are evaluable regardless of whether the minimum criteria above are met.

Subjects experiencing toxicity that results in dose-holds will remain evaluable provided the minimum criteria outlined above are met. Patients that require dose reductions during the DLT evaluation period (e.g., first 28 days after initiation of the first dose of study treatment/C1D1) will not be considered a DLT so long as they receive the minimum doses at the prescribed dose level outlined above.

Patients who achieve a morphologic remission on C1D22 BMBx, have not experienced a DLT, and have treatment interrupted due to favorable treatment response will be considered evaluable if they complete 75% of protocol-directed doses (i.e., a patient who achieves a remission and is instructed to stop venetoclax on C1D24 is considered evaluable provided they received at least 18/24 venetoclax doses, or 75%) and will not be replaced.

Patients missing >25% of venetoclax doses, or any DEC-C doses due to adverse event(s), will be considered a DLT provided the AEs are considered related. If unrelated, the patient may be replaced as described above.

<u>Definition of Dose-Limiting Toxicity – Non-hematologic</u>

- Grade 3 nausea, vomiting, dehydration, diarrhea, or fatigue lasting > 3 days despite optimal supportive medications. Patients who require tube feeds or total parenteral nutrition will be considered a DLT.
- Any other Grade 3 non-hematological toxicity with the following exceptions:
    - Grade 3 or 4 electrolyte abnormalities that:
        - Improve with supportive care to ≤ Grade 2 within 72 hours
        - Are deemed not medically significant (i.e. hospitalization not indicated or non-life-threatening) by the investigator.
    - Hair loss
    - Grade 3 AST, ALT, or alkaline phosphatase elevations that last <72 hours
- Any other Grade 4 non-hematologic toxicity.
- Patients meeting criteria for Hy's Law as follows:
    - Aminotransferase elevations, often much greater than 3x ULN, with elevation in serum total bilirubin to >2xULN without initial findings of cholestasis (elevated serum alkaline phosphatase).
    - No other reason is identified to explain the combination of increased aminotransferase and total bilirubin, such as viral hepatitis, pre-existing

acute liver disease, or another drug capable of causing the observed injury.

- Any grade 5 non-hematologic toxicity will be considered a DLT.

Definition of Dose-Limiting Toxicity – Hematologic:

- Neutropenia: Progression/development of grade 4 neutropenia and bone marrow aplasia without evidence of disease that extends >2 weeks beyond the end of a treatment cycle.

- Thrombocytopenia: Progression/development of grade 4 thrombocytopenia and bone marrow aplasia without evidence of disease that extends >2 weeks beyond the end of a treatment cycle.

Exceptions

Adverse events that meet the above definitions but that are clearly unrelated to study drug will not be DLTs.

In rare instances, an event may fall within the definition of a DLT, as defined above, but the event may be considered not to be a DLT (e.g., not be clinically meaningful). If this occurs, the study chair and other investigator(s) will review the event and supporting data. The reasons for not considering the event to be a DLT will be clearly documented with supporting rationale.

Patients who have experienced a DLT do not automatically require discontinuation of protocol-indicated treatment, unless the nature or severity of the DLT is also an adverse event that would require permanent discontinuation of study treatment as elsewhere defined by the protocol (e.g. Section 5.2.4). Rather, a patient who has experienced a DLT should be evaluated for consideration of an appropriate dose hold or dose modification which, if consistent with the protocol, would allow continued dosing under revised circumstance.

A dose limiting toxicity (DLT) must be reported by the site using expedited notification procedures. Within 1 business day of investigator awareness of an adverse event meeting DLT criteria, the event must be reported to the sponsor-investigator by both of the following two mechanisms:

1) recorded in the electronic case report form (eCRF) and

2) separate email alert to coordinating.center@vumc.org

If a DLT meets seriousness criteria, such event must also be reported as an SAE (see protocol Section 6.2 and Section 6.3).

For the purpose of ensuring an appropriate opportunity to determine the recommended phase 2 dose (RP2D) of venetoclax/DEC-C, a subject who is withdrawn from the study prior to completing the DLT assessment window (e.g. first 28 days after initiating

protocol-indicated treatment on Cycle 1, Day 1) for reasons other than a DLT will be considered not evaluable for DLT and will be replaced.

Additionally, over the first 28 days after initiating study therapy, if a patient discontinues study treatment for reasons clearly not related to protocol-indicated treatment (in the judgement of the study chair and other investigator(s)) and fails to complete the minimum number of doses of venetoclax/DEC-C, then that patient may be considered not evaluable for response and be replaced with a new patient.

5.2.5 Safety Cohort Review

The study chair, in consultation with the investigator(s), will determine whether the dose will be de-escalated and/or the RP2D dose for the pre-remission therapy phase.

5.2.6 Supportive Care and Dose Reduction Guidelines

5.2.6.1 Infection

Appropriate broad-spectrum IV antibiotics and/or antifungal agents should be started immediately in patients who develop fever or other signs of systemic infection. In patients with minor infections, venetoclax/DEC-C may be continued in parallel with treatment. Venetoclax dosing should be adjusted to reflect drug interactions.

Treatment with venetoclax and DEC-C should be interrupted in any patient with Grade 4 infection, clinical sepsis (in the absence of documented infection), or neutropenic fever.

After the infection is resolved, venetoclax/DEC-C should be restarted at the previous dose level and per the following guidance:

- In patients prior to achieving remission, venetoclax/DEC-C may be restarted after the patient is clinically recovered (e.g., fever is resolved with no evidence of active infection).
- In patients who have achieved a clinical remission, venetoclax/DEC-C may be restarted after the ANC returns to Grade ≤ 2 or baseline, fever has resolved, and patient's condition is stable.

If the neutropenic fever is persistent, or for ≥2 occurrences, consultation with the study chair is recommended.

5.2.6.2 Colony Stimulating Factors:

Colony stimulating factors may be used in patients who achieved a CR and have a duration of neutropenia ≥35 days, develop neutropenic fever, or significant infectious complication at any time, as deemed warranted to maintain safety of the patient per the investigator.

5.2.6.3 Dose Reduction Guidelines

Venetoclax is generally well-tolerated; the most common toxicities observed are fatigue, headache, nausea, diarrhea, hematologic toxicity, and electrolyte abnormalities. Non-hematologic grade 3/4 toxicity is rare. DEC-C is also well-tolerated.

The NCI CTCAE version 5.0 will be used for grading the severity of AEs; the study treatment modifications described below are applied according to this severity grading. Toxicity will be documented as described in Section 5.2.3. If more than one type of toxicity occurs concurrently, the most severe grade will determine the modification. For purpose of any necessary definition, "baseline value" is defined as the most immediately known value in place prior to patient's first receipt of protocol-indicated treatment on Cycle 1, Day 1.

Pre-remission Phase

Treatment interruptions during the pre-remission phase, as well as the reason, must be documented.

Dose reductions are to be avoided for patients during cycle 1 in the dose finding portion of the study. Figure 1 and Table 5 summarizes the starting doses (Dose Level 1) and dose levels. General supportive care guidelines are provided in Section 5.2.6. Outside of the dose finding portion of the study, dose reductions of venetoclax and/or DEC-C for adverse events may take place at any time as otherwise consistent with the protocol.

Table 5: Venetoclax/DEC-C Dose Level Summary (Pre-remission Phase)

DOSE LEVEL	VENETOCLAX	DEC-C
1	400mg once daily Continuous Day 1-28$^{\Delta}$	100mg/35mg once daily Days 1-5
-1	400mg once daily Continuous Day 1-28$^{\Delta}$	100mg/35mg once daily Days 1-4
-2	400mg once daily Continuous Day 1-21$^{\Delta}$	100mg/35mg once daily Days 1-4

* Cycles are every 28 days.

$^{\Delta}$ Venetoclax dosing will be ramped on C1D1 and C1D2 per Figure 3.

During the pre-remission phase, it is intended that venetoclax will be dosed continuously per the dose level summary (Table 5) and will not be interrupted unless the day C1D22 BMBx is negative for leukemia. Missed days of venetoclax due to treatment interruption in a patient with aplastic marrow that is negative for AML, who are otherwise tolerating therapy well and without evidence of a DLT, will not influence evaluability (i.e., required minimum number of venetoclax doses).

Initiating Post-remission Phase (Cycle 1)

Patients will begin the post-remission phase of the study after achieving blast clearance from their marrow. Patients with marrow aplasia must recover peripheral blood counts with ANC of ≥1000/mm^3 / 1 x 10^9/L. Patients with cellular marrows may proceed to the post-remission phase of the study without count recovery if the treating physician believes the cellularity is disease related. Discussion with the study chair is recommended.

Patients with marrow aplasia on C1D22 or C2D22 BMBx will have venetoclax interrupted until the absolute neutrophil count (ANC) recovers to ≥1000/mm^3 / 1 x 10^9/L. If persistent grade 4 cytopenias, repeat BMBx will be performed at D42. If persistent marrow aplasia without disease, patients will be managed expectantly until ≥1000/mm^3 / 1 x 10^9/L. A BMBx will be repeated every 6 weeks until ANC recovery. At that time, patients will enter the post-remission phase (See Figure 2).

To proceed with each cycle of post-remission therapy, platelets/ANC must be improved to grade 2 or higher:

Platelets	≥50,000/mm^3 / 50.0 x 10^9/L
Neutrophils	≥1000/mm^3 / 1 x 10^9/L

Venetoclax and DEC-C are generally intended to be dosed in combination but may be separably dosed for up to 28 consecutive days. The dose levels of venetoclax and DEC-C are indicated in Table 5.

In the event of an adverse event deemed by the study physician as unrelated to protocol-indicated treatment, the study physician may choose to precautionarily interrupt venetoclax and/or DEC-C for up to 28 days, but no dose reduction of either agent should occur.

Venetoclax and/or DEC-C may be delayed for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of DEC-C and/or venetoclax. If either or both drugs are interrupted for >4 weeks for reason other than treatment-related cytopenias, discussion with the study chair is recommended.

Subsequent Post-remission Therapy (Cycle 2+)

Patients without clinical or laboratory evidence of relapse will continue to receive therapy with DEC-C/venetoclax for maintenance of response (See Figure 1 and 2). Subsequent post-remission cycles will be initiated after evidence of count recovery, defined as:

Platelets	≥50,000/mm^3 / 50.0 x 10^9/L
Neutrophils	≥1000/mm^3 / 1 x 10^9/L

In patients who recover counts within 6 weeks of CxD1, and are otherwise tolerating therapy, subsequent post-remission cycles will occur at the same dose level.

If count recovery is delayed >6 weeks beyond CxD1, patients will be reduced by one dose level (e.g., a patient with count recovery lasting 7 weeks after post-remission C1 will dose C2 at dose level -1).

For patients with delayed count recovery (>6 weeks) at dose level -3, discussion with the study chair is recommended.

Table 6: Venetoclax/DEC-C Dose Level Summary (Post-remission Phase)

DOSE LEVEL	VENETOCLAX	DEC-C
1	400mg/day dosed continuously	100mg/35mg Days 1-5
-1	400mg/day 21/28 days	100mg/35mg Days 1-4
-2	400mg/day 14/28 days	100mg/35mg Days 1-3
-3	400mg/day 7/28 days	100mg/35mg Days 1, 3, and 5

* Cycles are every 28 days.

Patients who are experiencing low-grade tolerability symptoms and are deriving clinical benefit from the treatment may have their dose reduced, or subsequent cycle delayed, at the discretion of the PI. Dose reductions should be done in accordance with Table 6. Patients whose dose or schedule is reduced may subsequently be re-escalated to the previous dose upon improvement of the tolerability, at the discretion of the PI. PI may consult with the study chair as necessary.

5.2.7 Dose modifications

Table 7: Toxicity Dose Adjustment Guidelines

Event	Occurrence	Action
Grade 4 neutropenia with or without fever or infection *OR* **Grade 4 thrombocytopenia**	Occurrence prior to achieving remission*	• Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. • In most instances venetoclax and **DEC-C** cycles should not be interrupted due to cytopenias prior to achieving remission
	First occurrence after achieving remission and lasting ≤ 7 days	• Delay subsequent treatment cycle of

		venetoclax and **DEC-C** and monitor blood counts. • Administer G-CSF if clinically indicated (see Section 5.2.6.2) • Once toxicity has resolved to ≤ Grade 2, resume venetoclax/ **DEC-C** at the same dose.
	Subsequent occurrences in cycles after achieving remission and lasting ≥ 7 days.	• Delay subsequent treatment cycle of venetoclax and **DEC-C** and monitor blood counts. • Administer G-CSF if clinically indicated (see Section 5.2.6.2) • Once toxicity has resolved to ≤ Grade 2, resume venetoclax and DEC-C at one dose level lower (see Table 6)

*Consider interim bone marrow biopsy for patients who may have achieved early remission
Table obtained from current venetoclax USPI. Modifications relevant to this study are indicated in underline and bold.

Hematologic Toxicity – Additional Considerations
If after applying the above recommendations for first and subsequent occurrences of hematologic toxicities as outlined and further dose modifications are desired for DEC-C, consider consultation with the study chair. General principles for dose modifications:

1. There will be no dose reduction of either agent based on hematologic toxicity during the pre-remission phase of this study.
2. **Within the post-remission phase, dose reductions of venetoclax and DEC-C should follow Table 6.**

Non-hematologic Toxicity – Additional Considerations
Delay the next cycle for the following non-hematologic adverse reactions and resume at the same or reduced dose of DEC-C and venetoclax upon resolution to patient baseline or ≤ Grade 1.

1. Serum creatinine > 2mg/dl
2. Serum bilirubin > 2x ULN
3. AST or ALT >2x ULN
4. Active or uncontrolled infection

5.2.8 Conditions Not Requiring Dose Reduction

The following conditions are exceptions to the dose-modification guidelines:

- Alopecia of any grade.
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible to the patient's baseline with standard interventions.
- Isolated values of ≥ Grade 3 alkaline phosphatase, defined as asymptomatic elevations in alkaline phosphatase without elevation of other liver function studies (e.g. AST/ALT or bilirubin). Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5' nucleotidase, or other liver enzymes should be performed.

5.2.9 Venetoclax/DEC-C Dose Reduction for Decreased Glomerular Filtration Rate

- If CrCl declines during treatment and is believed to be unrelated to venetoclax/DEC-C, the dosing of these medications may be maintained provided that the patient's condition is closely monitored.
- If CrCl declines to < 30 mL/min, the venetoclax should be held.

5.2.10 Supportive Care Recommendations for TEAEs/potential Adverse Drug Reactions occurring in conjunction with venetoclax

Supportive measures for optimal medical care include prophylaxis against tumor lysis syndrome (TLS) (see Section 5.1.1)

Prophylactic anti-emetic therapy is recommended and will be prescribed at the discretion of the treating clinician.

5.2.11 Concomitant Medication and Treatment

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, and oral herbal preparations taken during the study.

Patients may continue their baseline medication(s) unless otherwise prohibited by the inclusion/exclusion criteria of study protocol and Appendix 1. Any diagnostic, therapeutic, or surgical procedure performed from signing the informed consent form (CF) through 28 day follow-up should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

5.2.11.1 Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as part of standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are permitted.

Appropriate anti-coagulation is allowed during the study (e.g., low molecular weight heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided patients are monitored for INR twice a week during the first two cycles of therapy, then weekly to biweekly thereafter at the discretion of the treating physician.

5.2.11.2 Use of Blood Products

During treatment, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. It is recommended that patients who require repeated transfusion support, in the absence of marrow disease and despite dose reductions, be discussed with the study sponsor.

5.2.12 Contraception requirements

Patients should not become pregnant or father a child while on this study because the study treatments in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female patients of childbearing potential (See Table 1, footnote 7) with male partners able to father children, defined as men without a medical/surgical cause of azoospermia, must agree to use two methods of contraception (one highly effective and one effective) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential.

Highly effective methods include:
- Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)
- Intrauterine device or intrauterine system
- Vasectomy or tubal ligation.

Effective methods include:
- Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

Notes:
No barrier method by itself achieves a highly effective standard of contraception. The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method.

The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception.

When used consistently and correctly, “double barrier” methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. Male and female condoms should not be used together as they can tear or become damaged.

Alternatively, the following fulfill the contraception requirements:

- A sexual partner who is surgically sterilized or post-menopausal as defined in See Table 1, footnote 7.
- Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- The method of acceptable contraception must be explained to both male and female potential patients. In order to be eligible for the study, patients must agree to use to use the methods of birth control described above throughout the study and for 3 months following the last dose of study treatment at the time of consent for the study. Please see Table 1, footnote 7 for additional safety information related to pregnancy.

5.2.13 Off-Treatment Criteria

Participants will be removed from study when any of the following criteria apply:

- Disease progression
- Unacceptable toxicity
- Lost to follow-up
- Withdrawal of consent

5.3 Restrictions and Prohibited Medications

Concurrent Therapies:
Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed. Other investigational agents should not be used during the study.

Diet:
There are no dietary restrictions on this study. Patients should maintain adequate caloric and fluid intake. Grapefruit, starfruit, and Seville oranges should be avoided during the study period given interactions with CYP3A4.

Medications:
Venetoclax should not be used with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole) at initiation, during ramp-up, and pre-remission phase of treatment. Concomitant use of venetoclax with moderate CYP3A inhibitors (e.g. erythromycin, ciprofloxacin, diltiazem, fluconazole, isavuconazole, verapamil), or strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampin, St. John's wort), or moderate CYP3A inducers (e.g. bosentan, efavirenz, etavirine) may be used, if clinically appropriate, during the post-remission phase with appropriate dose adjustments. See Table 8 and Appendix 1 for a list of representative products.

5.3.1 Antifungal prophylaxis

Prophylactic antifungal therapy with CYP3A4 inhibitor activity (eg, fluconazole, posaconazole, and voriconazole) are prohibited 7 days or 5 half-lives, whichever is greater, prior to C1D1and through the pre-remission phase of therapy. Alternative antifungal therapy should be considered per institutional guidelines. During subsequent cycles, investigators may use prophylactic antifungal therapy as guided per local institutional practices. If the therapy of choice is a drug with CYP3A4 inhibitor activity, dose adjustments of venetoclax are required as detailed in Table 8.

Table 8: Drug interaction and dose reduction of venetoclax

Drug Interaction	Dose Reduction of Venetoclax
No CYP3A or P-gp inhibitor activity	No dose reduction (400mg daily)
Posaconazole	Dose reduction to 70mg daily
Other strong CYP3A inhibitor activity (e.g., voriconazole)	Dose reduction to 100mg daily
Moderate CYP3A inhibitor activity (e.g., fluconazole; or drug with P-gp inhibitor activity)	Dose reduction at least by 50% or to 200mg daily.

5.4 Medication Storage

Venetoclax tablets will be obtained by the clinical team as “standard of care.” Venetoclax should be stored in accordance with written instructions provided by the patient’s pharmacy.

DEC-C will be provided by the study sponsor in high-density polyethylene (HDPE) bottle with a child resistant closure. Each bottle contains either 1 or 2 desiccant canisters for moisture absorption. The desiccant canisters should remain in the bottle at all times and must not be ingested. DEC-C is store at controlled room temperature (20 – 25°C) in the original package provided.

5.5 Study Drug Accountability

Venetoclax will be obtained standard of care by the patient’s treatment team.

DEC-C will be provided by the study sponsor. Sites must request study drug by submitting an order form directly to the drug supplier for the study drug to be shipped to

the site pharmacy. The investigator or designee will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

Overall study drug accountability and destruction records (DEC-C only) will be maintained by the Sponsor-Investigator. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of unused material.

DEC-C should not be used for any purpose outside the scope of this protocol, nor may it be transferred or licensed to any party not participating in the clinical study. Data for DEC-C is confidential/proprietary and shall be maintained as such by the investigators.

All drug supplies provided by the drug supplier must be kept in an appropriate, limited access, secure place until used or returned to the drug supplier for destruction. Drug supplies will be counted and reconciled at the site before being returned.

Selection and Timing of Dose for Each Subject
The investigator is responsible for ensuring accountability for DEC-C, including maintenance of adequate drug accountability records.

The investigator or designee will supervise study drug treatment given in the clinic and instruct the patient on study medication self-administration.

Drug accountability records should include an appropriate inventory of DEC-C including:

- Confirmation that DEC-C supplied by the study was delivered to the trial site.
- Record of each dose of DEC-C dispensed.
- Return of unused DEC-C provided by the study to the Sponsor-Investigator or designee, or documentation of destruction at site (if drug destruction by the site is authorized by sponsor-investigator or designee).

Records should specify relevant dates, quantities, batch numbers, use-by dates and patient numbers, as applicable.

The investigator, or designee, should maintain records that adequately document:

- That patients were provided the doses specified by the clinical trial protocol, and
- That all DEC-C provided by the study was fully reconciled, and documentation will be provided to the respective drug supplier upon request.

Treatment Compliance

The Sponsor-Investigator or other study staff will supervise study treatment given in the clinic and instruct the patient on study treatment self-administration. Patients will be given a dosing diary on which to document their dosing compliance.

Patients will be asked to bring their study treatment containers and dosing diary with

them at each visit and compliance with protocol-defined study treatment intake will be checked by pill count and review of the dosing diary.

Compliance to study medication will be recorded by study personnel after discussion with the patient and drug accountability. Compliance to study treatment will be done by the investigator and recorded in source documents. The date will be recorded as per study treatment schedule. The principal investigator or the designee will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the site's internal database and drug accountability logs with the reasons for subsequent verification.

The investigator will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. In case of non-compliance, the patients will be instructed again.

6 STUDY PROCEDURES

6.1 Enrollment Procedures

The Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center will coordinate enrollment in the study.

Prior to registration, a copy of the IRB approval at the site will be requested and kept on file at the Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally at the VICC Coordinating Center. All sites should email the Coordinating Center at coordinating.center@vumc.org to verify slot availability prior to enrollment.

All patients MUST be registered with the VICC prior to the start of protocol treatment. Registration can only be conducted during the business hours of 8AM – 5PM Central Time, Monday through Friday.

1) All sites must email the VICC CTSR Coordinating Center at coordinating.center@vumc.org to notify of upcoming registration and ensure slot availability. The following information should be included in this email:
    - Study number
    - Patient initials
    - Disease type
    - Anticipated consent date
    - Anticipated start date

2) If a subject ID number is required prior to patient enrollment (e.g. at screening due to sample collection requirement), the site must submit the following documents with their email notification to the Coordinating Center:
    - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.

- HIPAA authorization form (if separate from the main consent form)
- VICC Patient Enrollment Form

The Coordinating Center will then provide a subject ID number via email.

3) Email the following documents to the Coordinating Center for eligibility review and patient enrollment (coordinating.center@vumc.org):
    - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
    - HIPAA authorization form (if separate from the main consent form)
    - VICC Patient Enrollment Form
    - Eligibility supporting documents such as pathology reports, laboratory tests, etc. *or* EMR access. Note: all source documents should be de-identified and screening/subject ID number added prior to sending.
    - Signed and completed Eligibility Checklist. To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.

Note: VICC Coordinating Center requires 3 business days to review all documents and confirm eligibility. Registrations will only be accepted with prior notice and discussion with the Lead Institution. Please email the clinical trials office (CTO) if enrollment is needed sooner at coordinating.center@vumc.org.

Upon satisfactory review of eligibility documents submitted, the Coordinating Center will approve enrollment and issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign Subject ID numbers to all patients whose eligibility has been confirmed. Only patients deemed eligible will be registered to investigational treatment. Sequence/study ID numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin study treatment consistent with the protocol no later than 14 days after registration/enrollment by the VICC Coordinating Center. If a participant does not receive protocol therapy following registration within the allowed time period, the participant's registration on the study will be canceled. The Study Contact should be notified of cancellations as soon as possible. Patients being re-screened will need to consent to repeated procedures. As such, the Coordinating Center will require a new, signed Informed Consent document.
Issues that would cause treatment delays should be discussed with the Protocol Chair.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.

6.2 Definitions

6.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

6.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or birth defect; or
- Jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care

6.2.3 Expectedness

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

6.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- 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

6.3 Reporting Procedures

6.3.1 General Considerations

All adverse events will be captured on a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore

Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Specified members at each participating site will submit all regulatory documents to the Coordinating Center.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs, and avoid colloquialisms and abbreviations. If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death.” Deaths that occur during the protocol specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF and not reported as an SAE (See Section 6.2).

A pre-existing medical condition is one that is present prior to initiation of protocol specified treatment. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the

concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure because of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions; or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

6.3.2 Serious Adverse Events

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed (preferred), faxed, or scanned to:

ATTN: VICC CTSR Personnel
EMAIL: coordinating.center@vumc.org

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are unexpected, and is/are believed to be related (e.g., possibly, probably or definitely) to the study device/medication. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

6.3.3 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse

event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

6.3.4 Food and Drug Administration (FDA)

In this trial, unexpected serious adverse events believed to be definitely, probably, or possibly related to study treatment (as determined by the sponsor-investigator) will be reported to the FDA via MedWatch 3500A (currently available at https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf. Submissions by the sponsor can be submitted via fax or email and must be addressed to Regulatory Project Manager in the FDA review division that has responsibility for review of the IND. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

6.3.5 Reporting to Grantor and Funder

The Sponsor/Investigator shall report to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA all Serious Adverse Events (SAEs), and Pregnancy in English via a MedWatch form, in accordance with the Protocol and applicable law. All applicable source document(s) will also be sent to OTSUKA in English. The Sponsor/Investigator shall comply with OTSUKA's reasonable follow-up requests.

The Sponsor/Investigator will provide National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA with details of whom National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA shall address requests for follow up information on SAE and pregnancy cases reported from this Clinical Trial, and further agree to update such contact details as necessary.

Transmission of these reports (initial and follow-up) will be sent electronically via email to ORPreports@nccn.org or fax to 215-358-7699 and Taiho Oncology, Inc via email to Global_Intake@otsuka-us.com within the timelines specified below:

The investigator shall monitor the Clinical Trial Subject for adverse events and fulfill all the reporting requirements to RAs/ECs in accordance with applicable laws. The Investigator shall also inform National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA of serious adverse events:

- Unexpected Fatal or Life Threatening Suspected Adverse Reactions- Complete and send MedWatch to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA within 24 hours of awareness and report to applicable RAs/ECs within 7 calendar days of awareness.
- Serious & Unexpected Suspected Adverse Reactions- Complete and send MedWatch to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA within 24 hours of awareness and report to applicable RAs/ECs within 15 calendar days of awareness.
- All other Serious cases (Expected and Related; Expected and Not related; Unexpected and Not related)- Complete and send MedWatch to National

Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA within 24 hours of awareness.

All serious adverse events need to be sent to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA via a MedWatch Form. For reports from a non-English speaking country, English translations be sent to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA Pharmacovigilance.

MedWatch reports must clearly specify SAE term(s) and corresponding Investigator causality assessment.

Serious AE reports, related or not related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA Pharmacovigilance group within 24 hours of awareness date.

Special Situation Reports:

- Drug Exposure During Pregnancy and Lactation, or Paternal Drug Exposure Reports:
  - The Sponsor/Investigator will report Exposure During Pregnancy and Lactation, or Paternal Drug Exposure on any Clinical Trial Subject while participating in the Clinical Trial, and following exposure to a TAIHO IMP, to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA (as specified below) on a MedWatch Form and within 24 hours from first becoming aware of the pregnancy or exposure. If the partner of a Clinical Trial Subject becomes pregnant, the Sponsor/Investigator may collect information about the pregnancy and birth if the partner agrees.
  - The Subject will also be followed by the Sponsor/Investigator to determine the outcome of the pregnancy (including any premature termination of the pregnancy). Information on the status of the mother and child will be forwarded to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA. The Sponsor/Investigator must provide final outcome of pregnancy to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA. If any SAE(s) is observed in the Subject or fetus/child, then SAE(s) must also be reported to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA.
- Other Special Situation Reports, shall be transmitted to National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA within 24 hours of the awareness date.

The Sponsor/Investigator shall comply with all applicable laws, including those related to data privacy, when undertaking these safety reporting-related obligations. Any SAE/special situations shall only contain anonymous or key coded information so that any individuals' names or other fully identifiable information shall be redacted before being submitted to National Comprehensive Cancer Network (NCCN) and Taiho

Oncology, Inc/OTSUKA. Please note that reporter information is necessary and should not be redacted.

Day 0 for all single case reports (including SUSARs) will be the day National Comprehensive Cancer Network (NCCN) and Taiho Oncology, Inc/OTSUKA is notified by the Sponsor/Investigator and the report meets criteria for reporting.

Each party shall notify the other party within two (2) working days of becoming aware of any of the following urgent safety information: Major safety concerns identified in a clinical trial. Possible teratogenic effects of the Product or other significant hazard to public health. Safety issues published in the scientific and medical literature.

7 STUDY ACTIVITIES

7.1 Description of Procedures

7.1.1 Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

7.1.2 Medical History

During screening, a complete medical history will be obtained from each patient. Medical history will include demographics, baseline symptoms as well as a detailed history of prior therapies and/or procedures for their underlying hematologic malignancy (e.g., chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery), including start and stop dates, best response, disease progression during or after therapy, as well as discontinuations due to intolerability or toxicity.

7.1.3 Physical Examination, Vital Signs, Height/Weight, and ECOG Score

Full physical examinations (PE) will be performed prior to receiving first dose of study drug and at the EoT Visit and should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations. All other PEs during the study should be limited, symptom-directed PEs, including body systems as appropriate.

Information about the PE must be present in the source documentation at the study site. An ECOG Score Assessment will be performed during screening and Day 1 of each cycle.

7.1.4 Concomitant Medications

Review and capture of all concomitant medications will be performed at each visit as indicated in Table 1, 2, and 3. Concomitant medications include prescription medications and over-the-counter preparations (including vitamins, dietary supplements, over-the-counter medications, and herbal preparations) used by a patient within at least 14 days prior to first dose of protocol-defined treatment and continuing through at least the 28-day Follow-Up study visit.

7.1.5 Safety Assessments

All clinical and laboratory adverse events, serious (SAEs) and non-serious (AEs) will be collected as follows: all events, serious and non-serious are collected from the day the patient signed the ICF up to 28-days post EOT. Safety assessments include: vital signs (PE), labs and investigations results – hematology, serum biochemistry, urinalysis.

Adverse events will be collected at each visit along with recording of concomitant medications.

7.1.6 Clinical Laboratory Tests

Table 9: Clinical Laboratory Tests

Hematology (Blood sample: whole blood; ethylenediaminetetraacetic acid [EDTA]) tests including)				
Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration
WBC count	WBC differential[a]	RBC count	Lymphocytes	Monocytes
Neutrophils	Band neutrophils	Eosinophils	Basophils	Platelets
Serum Chemistry (Blood sample: Serum)				
Sodium*	Potassium*	Chloride*	Bicarbonate*	BUN*
Creatinine*	Glucose*	Calcium	Phosphate	Magnesium
ALT*	AST*	Alkaline Phosphatase*	Total bilirubin*	

Total protein	Albumin	Lactate dehydrogenase	Uric acid	
Coagulation				
Prothrombin time (PT)	International normalization ratio (INR)	Partial thromboplastin time (PTT)		

*=Limited serum chemistry

a. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated.

7.1.7 Electrocardiography

A standard 12-lead ECG will be performed during screening. Patients must rest for at least 5 minutes prior to the ECG recording. The investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time the ECG was performed and the following parameters will be recorded: Heart rate, PR interval, QT interval, QRS interval, and QT corrected using Fridericia's formula (preferred) or alternatively by Bazett's formula (if Bazett's is the established site method).

7.1.8 Pregnancy Test

Serum pregnancy test for women of childbearing potential required during Screening. Subsequent pregnancy test – either serum or urine – to be done ≤ 3 days prior to first dose of protocol-indicated treatment (e.g. if prior screening test was done > 3 days before initiating C1D1 treatment, it will need to be repeated), at EOT, and additionally if clinically indicated per study physician.

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche who has not undergone surgical sterilization (e.g. bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) at least 4 weeks prior to first dose of protocol-indicated treatment, or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

7.1.9 Bone marrow aspiration and biopsy

Patients must have at least 2-3 mL of bone marrow aspirate material obtained within 14 days of beginning treatment on this study.

On a day of a fresh biopsy procedure, matching peripheral Pharmacodynamic (PD) blood samples are to be drawn PRIOR to the fresh biopsy procedure (with the PD blood to be drawn ideally coincident with any Hematology and Blood Chemistry specimens – if such safety labs are also scheduled for collection on the day in question).

7.1.10 Pharmacodynamic (PD) Blood Samples

Pharmacodynamic blood samples for research are to be obtained during Screening (any time prior to first dose of study treatment if archival tissue is used to satisfy the requirement of baseline tumor tissue; or if a fresh baseline biopsy is done, then PD blood should be collected on the same-day as the biopsy – PRIOR to the biopsy procedure).

Blood sampling for PD correlative studies will be done as summarized in the Lab Manual.

7.2 Screening (Day -14 to Day -1)

7.2.1 Screening Procedures

Screening will include the screening procedures described below and will be performed within 14 days prior to the start of therapy (e.g., day -14 to day -1). Screening activities are summarized in Table 1.

The Investigator should not repeat procedures that are performed as part of standard of care (SOC), if they are within the screening window and are done prior to signing the ICF. Data from SOC procedures will be part of the patient's medical history and may be used for study purposes.

Prior to performing any study-based procedures, patient informed consent must be obtained. Screening may be divided into two (or more) clinic visits at the discretion of the Investigator. The procedures to be performed during screening are listed below:

- Informed consent and baseline characteristics
- Physical Exam
- ECOG performance status
- Height and weight
- Vital signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and adverse event review.
- CBC with differential
- Blood chemistry including magnesium, phosphorus, LDH, and uric acid
- Coagulation testing (PT/INR, PTT)
- Electrocardiogram (ECG)
- Serum or urine pregnancy test in women of childbearing potential
- Bone marrow aspiration/biopsy with additional aspirate sent for correlative science
- Next generation sequencing (locally done/myeloid focused)
- PD studies (blood)
- Anti-TLS hydration / prophylaxis Allopurinol must be initiated at least 2-3 days prior to the start of therapy.

7.2.2 Screen Failures

A patient found not eligible for the trial after giving informed consent is considered a screen-failure. The enrollment form must be completed and sent to the sponsor-investigator or designee to confirm the outcome of the screening process.

Re-screening and re-enrollment of a subject who has discontinued the study as a pre-treatment failure (e.g. subject has not received protocol-indicated treatment) is permitted.

A consented patient previously reported to the coordinating center as pre-treatment failure must be re-consented prior to undergoing re-screening.

7.3 Cycle 1 (Pre-remission Therapy)

7.3.1 Cycle 1, Day 1

On Cycle 1, Day 1, the following procedures must be completed, unless previously completed ≤ 3 days prior to a patient's first dose of protocol-indicated treatment:

- Physical Exam
- ECOG performance status
- CBC with differential
- Blood chemistry including magnesium, phosphorus, LDH, and uric acid
- Serum or urine pregnancy test in women of childbearing potential
- Weight.
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 for DLT definition.
- Anti-TLS hydration / prophylaxis
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.3.2 Cycle 1, Day 2, 3, & 5

- CBC with differential
- Blood chemistry including magnesium, phosphorus, LDH, and uric acid
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 for DLT definition.
- Anti-TLS hydration / prophylaxis
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.3.3 Cycle 1, Day 8

- CBC with differential

- Blood chemistry including magnesium, phosphorus, LDH, and uric acid
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 for DLT definition.
- Anti-TLS hydration / prophylaxis
- Dose venetoclax as outlined in Table 5 and Table 6.

7.3.4 Cycle 1, Day 15

- CBC with differential
- Blood chemistry
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 for DLT definition.
- Anti-TLS hydration / prophylaxis
- Dose venetoclax as outlined in Table 5 and Table 6.

7.3.5 Cycle 1, Day 22

- CBC with differential
- Blood chemistry
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 for DLT definition.
- Anti-TLS hydration / prophylaxis
- Dose venetoclax as outlined in Table 5 and Table 6.
- Bone marrow aspiration/biopsy with additional aspirate sent for correlative science
- Next generation sequencing (Central/VUMC)
- PD studies (blood)

7.4 Cycle 2 (Pre-remission Therapy; only if C1D22 marrow is involved)

7.4.1 Cycle 2, Day 1

- Physical Exam
- ECOG performance status
- Weight.
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry

- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 for DLT definition.
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.4.2 Cycle 2, Day 8

- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax as outlined in Table 5 and Table 6.

7.4.3 Cycle 2, Day 15

- Physical Exam
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax as outlined in Table 5 and Table 6.

7.4.4 Cycle 2, Day 22

- Physical Exam
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax as outlined in Table 5 and Table 6.
- Bone marrow aspiration/biopsy with additional aspirate sent for correlative science
- Next generation sequencing (Central/VUMC)
- PD studies (blood)

7.5 Post-remission Cycle 1 (if remission confirmed/counts recovered)

7.5.1 Post-remission Cycle 1, Day 1

- Physical Exam
- ECOG performance status
- Weight.
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 for DLT definition (**only in patients who received one pre-remission cycle**)

- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.5.2 Post-remission Cycle 1, Day 5

- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.5.3 Post-remission Cycle 1, Day 15

- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax as outlined in Table 5 and Table 6.

7.6 Post-remission Cycle 2 (if remission confirmed/counts recovered)

7.6.1 Post-remission Cycle 2, Day 1

- Physical Exam
- ECOG performance status
- Weight.
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Surveillance for and expedited reporting of Dose Limiting Toxicity (DLT) – see Section 5.2.4 or DLT definition (**only in patients who received one pre-remission cycle**)
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.6.2 Post-remission Cycle 2, Day 5

- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.6.3 Post-remission Cycle 2, Day 15

- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential

- Blood chemistry
- Dose venetoclax as outlined in Table 5 and Table 6.

7.7 Post-remission Cycle 3 (only if remission confirmed/counts recovered)

7.7.1 Post-remission Cycle 3, Day 1

- Physical Exam
- ECOG performance status
- Weight.
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.
- Bone marrow aspiration/biopsy with additional aspirate sent for correlative science
- Next generation sequencing (Central/VUMC)

7.8 Post-remission Cycle 4+ (if remission confirmed/counts recovered)

7.8.1 Post-remission Cycle 4+, Day 1

- Physical Exam
- ECOG performance status
- Weight.
- Vital Signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and Adverse Event review.
- CBC with differential
- Blood chemistry
- Dose venetoclax/DEC-C as outlined in Table 5 and Table 6.

7.8.2 End of Treatment (≤ 10 days after last dose of study treatment)

Reasonable effort should be made to complete End-of-Treatment (EOT) / Withdrawal procedures on the day it is decided that a patient will no longer receive protocol-indicated treatment.

The following EOT procedures must be completed subsequent to and not later than 10 days after the patient's last dose of protocol-indicated treatment with venetoclax/DEC-C (whichever treatment occurs last) and prior to any subsequent anti-cancer therapy:

- Physical Exam
- ECOG performance status
- Weight
- Vital signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and adverse event review.

- CBC with differential
- Blood chemistry including magnesium, phosphorus, LDH, and uric acid
- Coagulation testing (PT/INR, PTT)
- Electrocardiogram (ECG)
- Serum or urine pregnancy test in women of childbearing potential
- Bone marrow aspiration/biopsy with additional aspirate sent for correlative science
- Next generation sequencing (Central/VUMC)
- PD studies (blood)

7.9 28 Day Follow-up Visit Assessments

Documented attempt(s) must be made for patient return to the study clinic. It will not be considered a protocol deviation if the patient is physically unable to return for the follow-up visit; such circumstance should be recorded in the study documents, and as much of the follow-up information as possible should be obtained via feasible patient contact and from local and outside facilities.

A Follow-up clinic visit is to be completed 28 days (+7 days) after patient's final protocol-indicated treatment venetoclax or DEC-C (whichever occurs last), in order to undergo the following assessments:

- Physical Exam
- ECOG performance status
- Weight
- Vital signs: Blood pressure (BP), heart rate (HR) and temperature.
- Concomitant medication and adverse event review.
- CBC with differential
- Blood chemistry

For patients who discontinue study treatment for reason other than progressive disease confirmed by bone marrow aspiration and biopsy (e.g. suspicious peripheral blood counts), please note the study may continue to request results of laboratory data conducted outside of the study but related to peripheral blood counts or bone marrow examination, until progressive disease following venetoclax/DEC-C is ultimately confirmed by marrow procedure.

7.10 Survival Follow-up

Each patient will be followed for survival every 3 months (± 14 days) after patient's final protocol treatment with DEC-C or venetoclax (whichever occurs last) until death, end of the study, until patient withdraws consent, or for a maximum of 2 years after the patient's final protocol-indicated treatment – whichever comes first. Survival contact can be made via clinic visit, chart review, obituary or similar observation (e.g. Social Security death index), or by telephone.

8 CORRELATIVE STUDIES

8.1 Specific Aims

- Assess the phenotypic and functional changes of post-HCT DEC-C/venetoclax therapy on B and T cell subsets.
- Correlate changes in B and T cell subsets with clinical data, including DEC-C/ venetoclax dosing schedules and patient characteristics.

8.2 Study methods:

We will assess the effect of DEC-C/venetoclax on immune subsets in post-HCT AML. Using B- and T-cell mass cytometry (CyTOF) panels in stimulated/unstimulated peripheral blood mononuclear cell (PBMC) samples, we will perform immunophenotyping prior to treatment, following pre-remission therapy, during post-remission therapy, and at the end of treatment (EOT). Specimens that will be collected are described in Table 1. Correlative data interpreted in the context of clinical data and study outcomes.

8.2.1 Assess the phenotypic and functional changes of post-HCT DEC-C/ venetoclax therapy on B and T cell subsets

Immunophenotyping will be performed to identify quatitative and functional changes in B-cell and T-cell subsets with the intent of furthering our understanding of the mechanism(s) of immune-related adverse events. These assays will include flow cytometry/CyTOF and cytokine analysis.

Sample	Timepoint			
	Pre-Tx	On Treatment		EOT
		Intense C1D22	Intense C2D22	
Blood- PBMC isolation	X	X	X	X
Blood- serum/plasma isolation	X	X	X	X

Figure 4. Time points for clinical correlates

We will interrogate T and B cell signaling, and immune function/ composition, by flow cytometry or single cell mass cytometry (CyTOF) using cryopreserved PBMCs isolated from patients pre-treatment and at serial timepoints post-treatment. The Cytec Aurora, will allow up to 20 spectra at one time without compensation issues. Using a 15-20 antibody immune oncology panels and standard operating procedures for the staining of clinical and preclinical samples to define the immune phenotype. Specific lymphocyte subsets can also be characterized with intracellular cytokines as well as cell surface markers of activation or polarization. For more highly multiplexed analyses a Helios mass cytometer (CyToF) will be employed to measure up to 35-40 protein parameters on a per cell basis. We will utilize validated anti-human T-cell and B-cell antibodies for a comprehensive immune cell analysis.

Modulation of cytokines will also be monitored by Luminex leveraging serum or plasma isolated from whole blood from patients pre-DEC-C/venetoclax treatment and at serial timepoints post-treatment. The Luminex system (Millipore/Thermo-Fisher) will be used with Millipore plates and beads on biospecimens collected from patients. Standard manufacturer-recommended protocols will be used, and MAGPIX/xPONENT will be used for readout of cytokine levels. Standard curves generated from positive controls will be used to quantitate the concentration of the cytokines.

Immunological data generated from these assays will be integrated and correlated with patient outcomes (infection vs. no infection and response vs. no response).

8.2.2 Correlate changes in B and T cell subsets with clinical data, including DEC-C/venetoclax dosing schedules and patient characteristics.

As DEC-C/venetoclax combination therapy is evaluated in the corresponding phase II trial, the study data will be analyzed in combination with the immune subset data from SA1. Combining these datasets will provide important clinical context in an immunocompromised population. Clinical features, including time from HCT to relapse, dosing of DEC-C/venetoclax, immunosuppression, infectious complications, and non-relapse mortality events will be correlated with immune subset data. Body surface area (BSA) and body mass index (BMI) after HCT will be correlated with the depth and duration of cytopenias, including absolute lymphocyte count. This approach will extend SA1, identify clinical populations at-risk for toxicity, and inform study design and dosing in future DEC-C/venetoclax studies.

9 PLANNED STATISTICAL METHODS:

9.1 General Considerations

Statistical support for this study will be provided by the Department of Biostatistics at Vanderbilt University Medical Center with analyses being performed by or under the direction of a faculty member in biostatistics.

9.2 Disease Assessments

For the purposes of this analysis, responses will be assessed in accordance with the International Working Group (IWG) response criteria in acute myeloid leukemia.[19]

9.3 Dose De-escalation Design

Assuming a historical ORR of 15%, per the phase II efficacy trial, Simon's optimal two-stage design calls for a total of 34 patients. A preliminary efficacy assessment will be performed following enrollment of the first 20 patients. If $\geq$3/20 enrolled patients achieve a CR, this is sufficient to continue enrollment for the remainder of the study.

If ≥9/34 patients respond, we will reject ($p<0.05$) the null hypothesis that the true response rate of the regimen is less than or equal to 15%. If the true response rate is 35% or greater, this study design has 80% probability of rejecting the null hypothesis. If the true response rate is low at 15%, the probability of early termination is 60% with an expected sample size of 19 patients.

The maximum number of patients enrolled (n=51) reflects an anticipated drop out of 15% (n=5) and enrollment of 6-12 additional patients if dose level 0 is deemed toxic.

9.3.1 General Analysis Considerations

Continuous variables (e.g., age) will be summarized using the minimum, 25th, 50th (median), 75th, and maximum values along with the mean and standard deviation, as appropriate. Generally, rank based nonparametric tests will be used to compare continuous variables among patient subgroups. Categorical variables (e.g., objective response) will be summarized in frequency tables and compared among patient subgroups using the chi-square test. Linear regression and logistic (or ordinal logistic) regression will be used to construct multivariable models for continuous, binary, and ordinal variables, as appropriate. In addition to ORR, the distributions of progression-free and overall survival will be estimated using the Kaplan-Meier method. We will consider statistical comparisons statistically, but not necessarily clinically, significant for $p<0.05$.

Dose limiting toxicity (see Section 5.2.4) will be monitored in this phase II clinical trial using a Bayesian approach. A maximum of 34 patients will be enrolled and toxicity monitoring will begin when the 6th patient is evaluable for toxicity. It is expected that the toxicity rate is maintained at approximately 20% (maximum probability of DLT of 0.2, prior distribution (1,1), cohort size 1, and posterior probability > 80%). Pursuant to this rule, patients will be monitored according to the stopping boundaries outlined in Table 10. For example, the protocol will pause for review due to excessive toxicity if 2 or more DLTs are experienced by the first 6 patients treated. 9 DLTs will be allowed among 34 patients treated.

Number of DLTs	Of total number of patients treated
2	6
3	10
4	14
5	19
6	23
7	27
8	31
9	34

Table 10. Toxicity stopping rules. The expansion phase will be paused for review if DLT rate exceeds above.

9.3.2 Adverse Events

Adverse Events (AEs) will be coded using the MedDRA dictionary and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Analyses of AEs will be performed for those events that are considered to be treatment emergent AEs (TEAEs), defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 28 days following last dose or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

AEs will be summarized by patient incidence rates. In all tabulations, a patient may contribute only once to the count for a given AE preferred term.
The number and percentage of patients with TEAEs will be summarized, as well as the number and percentage of patients with TEAEs assessed by the Investigator as at least possibly related to treatment. The number and percentage of patients with any Grade ≥ 3 TEAE will be tabulated in the same manner. In the event a patient experiences repeated episodes of the same TEAE, the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations. Serious AEs (SAEs) will also be tabulated.

No formal hypothesis-testing analysis of AE incidence rates will be performed.
All AEs (treatment emergent and post-treatment) will be listed in patient data listings. Separate by-patient listings will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

9.3.3 Laboratory Data

The actual value and change from baseline for each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, by arm, and for all study patients combined. In the event of repeat values, the last non-missing value per study day/time will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades ≥ 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

9.3.4 Vital Signs and Physical Examinations

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs for all study patients combined. By-patient listings of vital sign measurements will be presented in data listings.
Physical examination results at screening will be summarized; all other abnormal physical examination data will be recorded. All examination findings will be presented in a data listing.

10 REGULATORY AND ETHICAL COMPLIANCE

10.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to IRB per current institutional standards.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by the study chair and the local IRB prior to local implementation. All amendments will also be submitted as necessary to the FDA by the study chair (or designee).

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB; and the study chair (or designee), who will communicate as appropriate with the FDA.

The study chair (or designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

10.2 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent form (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

10.3 Ethics and Good Clinical Practice

This study will be carried out in compliance with the protocol and Good Clinical Practice (GCP), as described within:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 199639
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described within the above and thereby to adhere to the principles of Good Clinical Practice with which the above conform.

10.4 Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier, which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly assisting with the trial.

10.5 Study Termination

The study chair reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Decision by suppliers to modify or discontinue the availability, development or manufacture of DEC-C.
- A request to discontinue the study by the IRB or FDA.

The study chair will promptly notify investigators, the IRB and FDA if the study is terminated for any reason.

10.6 Multi-Center Guidelines

10.6.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the IRB per the current institutional standards of each participating center.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to local implementation.

The study chair (or designee) is responsible for the coordination and development of all protocol amendments. Once approved by the study chair, Vanderbilt will disseminate this information to the participating centers.

10.6.2 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the coordinating center. The required documents include, but are not limited to the following: local IRB approvals (e.g., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The coordinating center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the coordinating center.

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information inclusive of:

- Source documents (patient registration list, CRF info, toxicity assessments, tumor measurements / responses, etc.) are required to be provided within 30 days of visit or 10 days in advance of a monitoring visit or audit.
- Essential Documents (IRB approval documents, financial disclosure forms, 1572, delegation of authority log, protocol training, etc.) are required to be provided within one week of receiving the updated documents.

Personnel from the VICC Clinical Trial Shared Resource (CTSR) will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

10.6.3 Records Retention

United States (US) FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the US FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The coordinating center will inform the investigator at each site at such time that the records may be destroyed.

10.6.4 Publication

It is understood that any manuscript or releases resulting from the collaborative research must be approved by the Study Chair and will be circulated to applicable participating sites/investigators prior to submission for publication or presentation.

10.6.5 Administrative and Regulatory Requirements

This is an investigator-initiated study. The Study Chair and sponsor-investigator, Sanjay Mohan, is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the Study Chair include both those of a sponsor and those of a principal investigator.

10.6.6 Auditing and Monitoring:

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of the VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through onsite and/or remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

During scheduled monitoring visits, investigators and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests, provide required regulatory documents, and respond to any other trial-related inquiries of the monitor.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

10.6.7 Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, each site investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

Queries resulting from review of the eCRFs will be generated for the site and corrections will be made by the study site personnel. This will be done on an ongoing basis.

10.6.8 Data Verification

Data will be collected via eCRFs and entered into the database per Coordinating Center guidelines. The Coordinating Center will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. This will be conducted remotely, with the possibility of on-site verification periodically. Discrepancies in the data will be brought to the attention of the investigator and/or the investigator's staff. Any necessary corrections will be made directly to the eCRFs or via queries by the investigator and/or the investigator's staff.

10.6.9 Study Closure

The Coordinating Center reserves the right to discontinue a site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

10.6.10 Protocol Deviations

The Coordinating Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the investigator, or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

10.6.11 Changes to Protocol and Informed Consent Document

Any change to the protocol or informed consent document must be reviewed and approved by the Coordinating Center before being submitted to the Institutional Review Board/Independent Ethics Committee at participating institutions. Amendments should not be implemented until all necessary approvals have been obtained, except when necessary to eliminate an immediate hazard to study subjects.

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APPENDIX 1: EXCLUDED AND CAUTIONARY MEDICATIONS AND DIETARY RESTRICTIONS

Excluded throughout the study:
• Grapefruit and grapefruit products. • Seville Oranges (including marmalade containing Seville oranges) • Starfruit. • Concurrent therapy with any other approved or investigative anticancer therapeutics. • Other investigational agents.
Excluded during venetoclax ramp-up phase; and **Cautionary when receiving venetoclax at the steady state dose:**
• Strong CYP3A inhibitors. • Strong CYP3A inducers. • Moderate CYP3A inhibitors — Exclude during the first cycle and consider alternative medications. — If a subject requires use of these medications at the venetoclax plateau dose, use with caution and reduce the venetoclax dose by 50% for moderate inhibitors. After discontinuation of a moderate CYP3A inhibitor, wait for 3 days before the venetoclax dose is increased back to the initial target dose. • Moderate CYP3A inducers — Exclude during the ramp-up phase and consider alternative medications.
Cautionary throughout the study:
• Warfarin (closely monitor the international normalized ratio, INR). • P-gp substrates • BCRP substrates • OATP1B1/1B3 substrates • P-gp inhibitors • BCRP inhibitors