ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA9152

A Phase Ib/II Study of Venetoclax (ABT-199) in Combination with Liposomal Vincristine or Vincristine Sulfate in Patients with Relapsed or Refractory T-cell or B-cell Acute Lymphoblastic Leukemia

Rev. Add11

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Version Date: July 20, 2022

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STUDY PARTICIPANTS	***ACTIVATION DATE***
Phase I – Limited Institutions:	April 26, 2018
PA121 / Thomas Jefferson University (ECOG-ACRIN)	***ADDENDA***
Rev. Add3 **NY016 /** Memorial Sloan Kettering Cancer Center (ECOG-ACRIN)	Addendum #1 – Prior to Activation
PA075 / University of Pennsylvania/Abramson Cancer Center (ECOG-ACRIN)	Addendum #2
PA042 / Penn State Cancer Institute (ECOG-ACRIN)	Addendum #3
CT018 / Yale University (ECOG-ACRIN)	Addendum #4
WI013 / Medical College of Wisconsin (ECOG-ACRIN)	Addendum #5
MN026 / Mayo Clinic (ECOG-ACRIN)	Addendum #6
Rev. Add4 **NJ066** / Rutgers University (ECOG-ACRIN)	Addendum #7
Rev. Add4 **IL036** / Northwestern University (ECOG-ACRIN)	Addendum #8
Rev. Add6 **MD017** /Johns Hopkins University (ECOG-ACRIN)	Addendum #9
Phase II – **US Sites only:**	Addendum #10
ALLIANCE / Alliance for Clinical Trials in Oncology	Addendum #11
NRG / NRG Oncology	
SWOG / SWOG	

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Agents	**NSC#**	**Supply**
ABT-199	766270	AbbVie
Vincristine sulfate liposomes injection (Marqibo) **NOTE:** Liposomal Vincristine is no longer being manufactured as of April, 2022.	748728	Commercial
Vincristine Sulfate	67574	Commercial

IND #: Study Exempt from IND Requirements per 21 CFR 312.2(b)

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com..	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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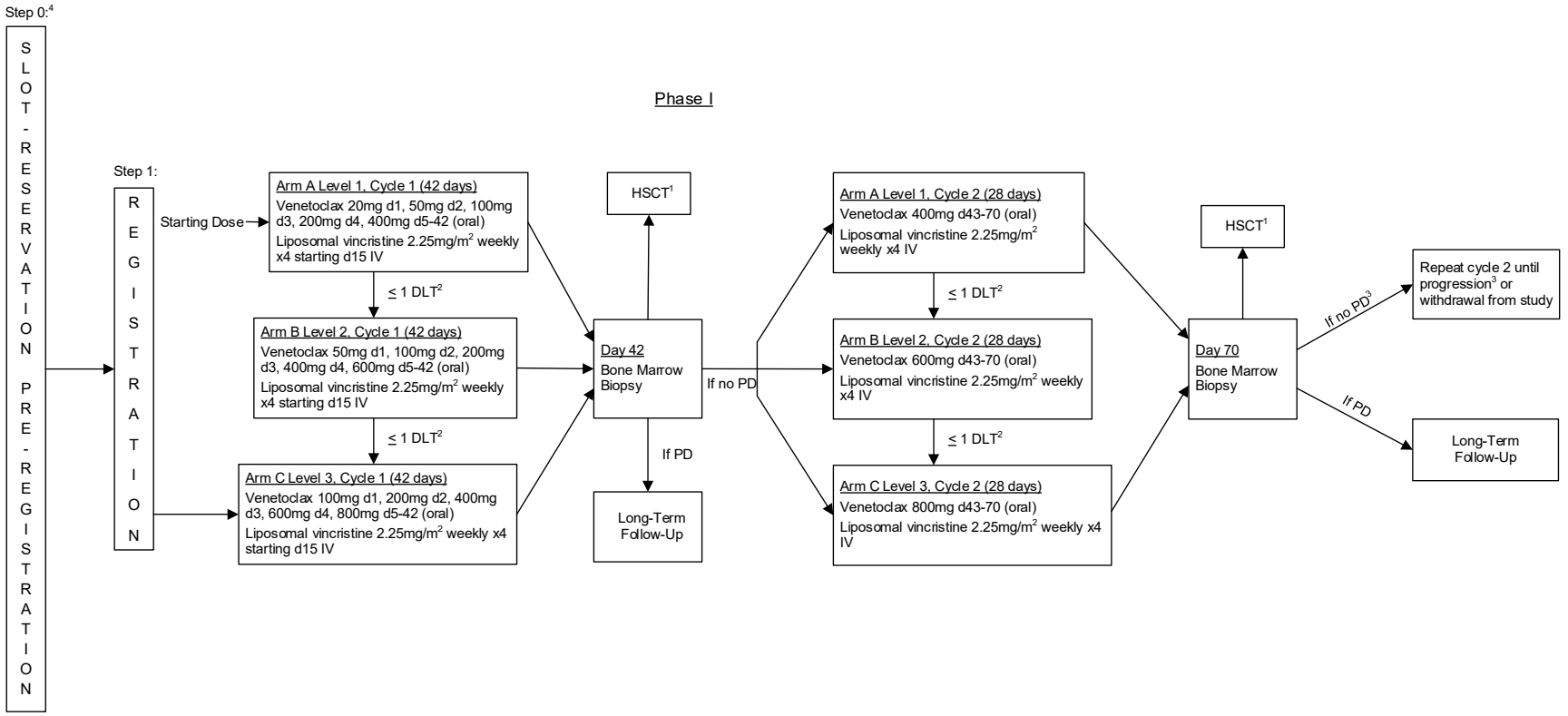
Schema



Phase I Dose Escalation Accrual Goal: 3 - 18 patients

1. If patient demonstrates CR or CRi at the day 42 or 70 bone marrow biopsies, they may continue on combination therapy or proceed to HSCT if deemed fit for transplant and advised by treating physician. Patient may proceed to HSCT at any point at treating physician's discretion (if not at day 42 or 70).
2. Subsequent arm will open for accrual only if ≤ 1 DLT is observed in prior cohort. DLTs will be monitored days 1-42.
3. If patient does not demonstrate any signs of progression, they may continue on combination therapy as long as they are receiving benefit per treating physician. Patients, if in CR/CRi by the end of cycle 2 may continue on combination or single agent at the discretion of treating physician.
4. Bone marrow and peripheral blood specimens must be submitted for mandatory central review.

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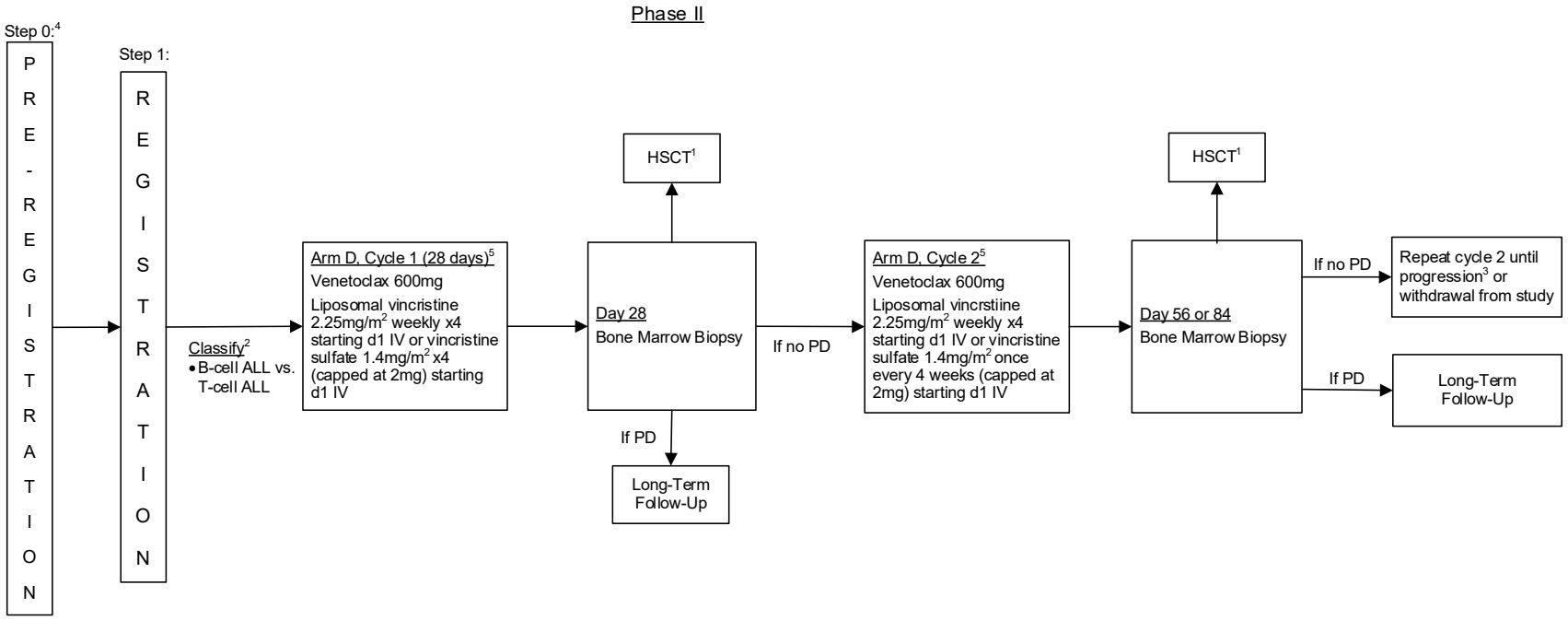
Schema



Phase II Accrual Goal: 56 patients

1. If patient demonstrates CR or CRi at day 28 or day 56 bone marrow biopsies, they may continue on combination therapy or proceed to HSCT if deemed fit for transplant and advised by treating physician. Patient may proceed to HSCT at any point at treating physician's discretion (if not day 28 or 56).
2. Patients will be classified by immunophenotype: B-cell ALL vs. T-cell ALL, with 28 patients as the accrual goal for each cohort..
3. If patient does not demonstrate any signs of progression, they may continue on combination therapy as long as they are receiving benefit per treating physician. Patients, if in CR/Cri by the end of cycle 2 may continue on combination or single agent venetoclax at the discretion of the treating physician.
4. Bone marrow and peripheral blood specimens collected for the purpose of banking.
5. In the event of liposomal vincristine shortage or discontinuation, patients actively undergoing treatment will be switched permanently to vincristine sulfate.
   NOTE: Liposomal Vincristine is no longer being manufactured

1. Introduction

1.1 Current Therapy for Relapsed or Refractory Acute Lymphoblastic Leukemia

Despite the fact that multi-agent chemotherapy regimens like Hyper-CVAD induce remissions in greater than 90% of adults with acute lymphoblastic leukemia, only a minority of patients are cured of their disease.[1-3] Five year survival rates of all comers approach 40%, and when patients are refractory to primary treatment or for those unable to proceed to allogeneic hematopoietic stem cell transplant (allo-HSCT) after relapse, the prognosis is dismal.[1] For fit patients after relapse, therapy directed toward inducing a complete remission so that an allogeneic stem cell transplant can performed currently offers the best chance of long-term disease control or cure. However, traditional re-induction strategies, like liposomal vincristine or other combination chemotherapies, achieve a complete remission only 20-30% of the time, leaving many fit patients without the option of transplant.[4, 5]

Recently, blinatumomab, a bi-specific T-cell engager antibody targeted towards CD19 and CD3, and inotuzumab ozogamicin, an anti-CD22 monoclonal antibody linked to a calicheamicin-family antibiotic, have been developed for use in relapsed B-cell ALL. In this setting, blinatumomab demonstrates significant activity with CR or CRh rates approaching 70% of patients.[6] However, its difficult administration schedule (continuous infusion for 4 weeks) along with significant neurotoxic side effects and a still-short overall survival of 9.8 months argue for alternate strategies. Inotuzumab reported the results of its phase 3 three trial, and again, while CR rates were high 81%, overall survival remained poor (average overall survival of 7.7 months). The study failed to meet its CR co-primary endpoint, though it did allow for significantly more (41% vs 11%) patients to proceed to allo-HSCT. Chimeric antigen receptor therapy has been recently approved by the FDA, however, is only available in specialized centers and limited to treat those under the age of 25.[7]

While new therapies are being developed for relapsed B-cell ALL, relapsed T-cell disease remains with few treatment options.[8, 9] Currently, nelarabine, a pro-drug analogue of deoxygaunosine causing impairment of DNA synthesis, is the only T-ALL specific therapy approved by the FDA. The drug's activity was demonstrated in a phase II open label trial and showed CR or CRi rates of 31%, but with dose-limiting neurotoxicity seen in 1/3 of patients. Though these new regimens are encouraging, better therapies are still clearly needed for this disease.

1.2 BCL-2 and Apoptosis

One of the several hallmarks of cancers is the ability to evade programmed cell death. The careful organization of upstream regulators and downstream effectors of apoptosis allows for the precise dismantling of a cell in response to a wide variety of stimuli including external signaling via the FAS or TNF pathways, and internal signals in response to DNA damage or cytokine deprivation. This later pathway, or the intrinsic pathway, is tightly regulated by BCL-2 superfamily of proteins and culminates in the release of cytochrome-C from "stressed" cells' mitochondria by the creation of pores in its outer membrane, a process denoted as mitochondrial outer membrane permeabilization (MOMP). (Please see references 10-12 for excellent review).

The BCL-2 family of proteins regulates MOMP through inhibitory and promotional interactions between different members of the superfamily. Members share BCL-2-like homology domains 1-4 (BH1-BH4) which help govern their interactions and function. The supergroup can be divided by each protein's effect on the fate of the cell: sensitizers, activators, suppressors and effectors of apoptosis. In resting state, suppressors of apoptosis (BCL-2, BCL-xL, MCL1, BCL-W) bind to the effectors (BAX or BAK) and activators (BID and BIM) and suppress their activity. In response to cell damage, the production of sensitizers and activators is induced. Sensitizers bind directly to anti-apoptotic proteins which causes their disassociation from effector and activator proteins. In turn, activators bind to effectors, inducing a conformational change in effectors that allows for their oligomerization. This oligomerization creates pores in mitochondria that are responsible for MOMP and the release of cytochrome-C. In turn, cyctochrome-C complexes with Apaf-1 which itself oligomerizes into a heptamer known as the apoptosome and recruits and activates caspase 9. Caspase 9 in turn activates other subsequent effector caspases to proteolytically dismantle the cell.[10, 11]

Upstream of the intrinsic pathway, the central tumor suppressor p53 helps orchestrates the cell signals leading to apoptosis. For example, the release of p53 from MDM-2 by DNA damage initiates a broad cascade including the rapid translocation of p53 to the mitochondria. Evidence suggests that p53 can interact directly with Bak among others in the BCL-2 family, causing a release of inhibitory proteins BCL-2/BCL-xL and can complex with BCL-2/BCL-xL which functionally sequesters them. Additionally, p53 acts as a transcription factor for the initiator proteins including PUMA and NOXA, which bind to BCL-xL and allow for the release of Bax to form its effector oligomers. It is postulated that through these downstream effects, p53-deficient cells are rendered chemotherapy-resistant. Cytokine withdrawal can also upregulate initiators of apoptosis, namely Bim and PUMA via Forkhead Box O (FOXO) transcription factors.[10-12]

The relative expression of BCL-2 family proteins is temporally and geographically regulated in non-malignant cells during growth and differentiation. This program in lymphocytes demonstrates the complex interactions that can exist between superfamily members. BCL-2 expression in critical for development of B and T lymphoid progenitors from hematopoietic stem cells.[13] Early T-cells demonstrate high levels of expression of BCL-2 relative to BCL-xL at CD4-CD8- (double negative stage) but down regulates BCL-2 in favor of BCL-xL during CD4+CD8+ stage[14-18] BCL-2 expression rises as T-cells further differentiate into single positive thymocytes (CD4+CD8- or CD4-CD+)[15, 18] and then is maintained in memory T-cells.[19] On antigen binding, co-stimulation of the T-cell receptor with CD28 upregulates BCL-xL.[20] Similarly during b-cell ontogenesis, high levels of BCL-2 are seen early only (pro-B stage), are markedly lower in intermediate stages of differential and again are upregulated in the memory b-cell.[21, 22]

Proof for a central role of the BCL-2 superfamily in malignancies, and especially hematologic malignancies has been provided by decades of basic science research. BCL-2 was first discovered in the late 1970's as part of the translocation 14:18 that is a hallmark of follicular lymphoma. Seminal studies demonstrated that cell lines that have upregulated anti-apoptosis protein like BCL-2 or MCL-1 do not themselves become cancerous, but, allow otherwise lethal mutations in the cell cycle to propagate. Additionally, upregulation of these

inhibitory proteins by various means in a wide variety of tumor subtypes renders them relatively chemotherapy resistant.[11]

1.3 Venetoclax

1.3.1 Mechanism of action

Venetoclax (ABT-199) is a highly-selective, orally-bioavailable BCL-2 inhibitor rationally designed from prior anti-BCL-2 drugs to spare the inhibition of BCL-xL.[23] Previous compounds in the family, like navitoclax, induced apoptosis in circulating platelets in an on target fashion (ie, sequestering BCL-xL) which resulted in dose-limiting and dose-dependent thrombocytopenia.[24] Using time-resolved fluorescence resonance energy transfer (TR-FRET) binding assays, the affinity of venetoclax for BCL-2 was found to be sub-nanomolar (Ki < 0.010 nM) and between 2,000-20,000 times less avid for BCL-xL and BCL-W, with essentially no affinity for MCL-1 (Ki>444).[23] In vitro testing of venetoclax has demonstrated remarkable sensitivity of patient chronic lymphocytic leukemia samples, with a LC50 10.0 ± 3.2 nM compared to healthy donor T-cells and granulocytes (2.5 ± 2.8 μM and >4 μM) respectively. Researchers have shown sensitivity to a wide variety of other dependent cell lines including, diffuse large b-cell lymphomas, acute myeloid leukemias, acute lymphoblastic leukemias, and multiple myelomas.[25-27]

The Letai group has pioneered an approach to determine the mitochondrial priming of a cell line for apoptosis and therefore predict its sensitivity to BCL-2 inhibitors like venetoclax.

This technique, termed BH3 profiling, is a multifaceted interrogation of the relative state of the BCL-2 superfamily proteins of a particular cell sample by utilizing the principle that groups of activator, sensitizers and suppressor BH3 proteins bind preferentially to each other.[25, 28-31]. Cells are made permeable exposed systematically to synthetic BH3 domains derived from various activating and sensitizing classes of proteins. Fundamentally, the greater the amount of these synthetic proteins needed to achieve MOMP, the less well “primed” a cell is to undergo cell death. Several classes of priming have been described, ranging from those incapable of apoptosis (i.e., cells that lack BAX and/or BAK through mutation or otherwise) to those nearly on the verge of cell death (i.e., highly primed). Importantly, these assays can also determine the anti-apoptotic proteins that a cell sample depends on for survival. For instance, cells that display increased MOMP in response to NOXA, a sensitizer BH3 protein which binds only to MCL-1, are thought to be dependent on MCL-1 for survival. This addiction can be confirmed by exposure to anti-MCL-1 drugs causing apoptosis but not anti-BCL-2 drugs. In another example, the Letai group investigated the priming of a variety primary AML samples by exposing them to a fixed concentration of BAD, which preferentially binds to and overwhelms BCL-2-mediated inhibition of apoptosis, and also a fixed dose of venetoclax. A very close correlation of cytochrome C release by BAD and venetoclax was seen (Spearman r =0.935, p<0.0001), demonstrating the on target effects of the drug. In those lines that were primarily blocked from apoptosis by BCL-2,

venetoclax demonstrated significantly greater sensitivity than those blocked from apoptosis with BCL-xL or MCL-1.

Recently, dynamic BH3 profiling, which predicts response to chemotherapy drugs, has also been described. Here, samples are exposed to a test drug and then treated similarly with exogenous BH3 peptides. Results are compared to untreated samples. Cells who become significantly more primed (i.e., require less BH3 peptide to initiate apoptosis) are considered sensitive to the agent. For example, lung cancer cell lines with EGFR exon 19 mutations sensitive to gefitinib and with a T790M mutation which renders resistant to gefitinib but sensitive to a WZ4002 were examined using this method. As expected, the exon 19 EGFR cell lines demonstrated a significant increase in priming with both gefitinib and WZ4002, while the T790F lines showed only an increase in priming with response to WZ4002. The correlation between increase in priming at 16 hours and cell death at 72 hours as measured by annexin V/PI was impressively strong (Spearman r 0.82 95%CI:0.46-0.95). [32]

1.3.2 Clinical Efficacy in Hematologic Malignancies

Early clinical experience in various hematologic malignancies with venetoclax has been published.[33-38] Escalating doses of venetoclax (50mg-600mg) in combination with rituximab in patients with relapsed/refractory CLL have shown to be well-tolerated and to have impressive preliminary activity.[35] Of the 18 evaluable patients reported in a phase I study, 78% of subjects had at least a PR, with 38% having a CR/CRi. Toxicity was acceptable, with hematologic toxicities and nausea predominating. Grade 3/4 neutropenia, thrombocytopenia and anemia were found in 43%,16%, and 11% respectively. One death occurred during dose escalation of ABT-199 (at 50mg) on account of uncontrolled tumor lysis (due to hyperkalemia), prompting more aggressive monitoring as well as a lower starting dose (20mg). In a subsequent study with more intense TLS-mitigating measures, venetoclax (20mg to 600mg) was given with bendamustine and rituximab in patients with relapsed/refractory CLL with none developing clinical or laboratory signs of TLS [36]. Patients experienced similar rates of hematologic and non-hematologic toxicity as the prior study. As a single agent (dose rage 20mg-1200mg) in relapsed/refractory AML or as frontline therapy for pts unfit for intensive therapy, ABT-199 was again well tolerated with the most common treatment-emergent AEs being nausea (14/32, 44%), diarrhea (12/32, 38%), fatigue (9/32, 28%), neutropenia 8/32, 25%). and vomiting (8/32, 25%).[34] Grade 3/4 AEs (in ≥3 pts) were limited to febrile neutropenia (8/32, 25%), anemia (3/32, 9%) and pneumonia (3/32, 9%). There were no reported events of clinical or laboratory tumor lysis syndrome and no AEs leading to death. CR/CRi was seen in 15.5% (5/32) of those tested. The largest study reported to date demonstrated the efficacy of venetoclax in patients with relapsed or refractory deletion 17p CLL.[38] 107 patients were enrolled across 31 centers world-wide in this single arm study using a graduated dosing schedule to mitigate the risk of tumor lysis syndrome. Analysis of the primary outcome measure, response at 36

weeks by International Workshop for Chronic Lymphocytic Leukemia (IWCLL) criteria, showed that 77% of patients achieved at least a partial remission of disease, with 10% attaining a complete response. As seen in previous studies, neutropenia (43 of 107[40%], anemia (19 [18%]), and infection (21 [20%]) were the most common grade 3-4 adverse events. Few (9%) experienced dose interruption or dose reduction for neutropenia. No deaths or serious adverse events related to tumor lysis were seen. The outcomes of this study led to accelerated FDA approval for venetoclax in deletion 17p CLL.

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1.4 Rationale for Study

The use of ABT-199 in combination with cytotoxic agents in ALL is attractive mechanistically, as BCL-2 upregulation is thought to induce chemotherapy resistance and BCL-2 inhibition may lower the apoptotic threshold of a cell.[10] In addition, work to date with BH3 profiling of primary B-ALL and ETP-cells has demonstrated the BCL2 dependence of these subtypes [30, 39]. Preclinical synergy data with other BH3-mimetics in T-ALL and B-ALL has been demonstrated with an array of agents including steroids, anthracyclines, asparaginase, TKIs and vincristine.[39-42] The combination of vincristine and ABT-737, for example, demonstrated strong to very strong synergy with median combination indices ranging from 0.09-0.9, among both T and B ALL cell lines.[42] Mice xenografted with MLL patient samples and treated with venetoclax and a combination of vincristine, peg-asparginase and dexamethasone showed marked synergy.[44] In this model, ABT-199 alone and VXR alone had minimal effect on circulating blasts, however, the combination reduced leukemia burden by more than 70%. In one patient sample tested, the combination eradicated ALL in mice below the level of detection.

Diverse T-ALL cell lines treated with ABT-199 demonstrated significant response with IC50 values ranging from 13.9nM – 10uM, with cells line expressing immature phenotypes more sensitive to the drug. This work was extended to patient samples, where again, cells expressing immature T-cell markers (i.e., lacking CD4 and CD8) demonstrated cell kill with lower IC50 concentrations and higher caspase activity after exposure to a fixed dose of ABT-199.[30, 41] In B-cell ALL, BCL-2 may be more uniformly expressed, with B- ALL samples being inhibited at low concentrations of ABT-199 (IC50 0.1-3.0 nM).[40] In vivo, treatment of mice xenografted with LOUCY cell lines, B-cell precursor ALL, early pre-T-cell ALL and MLL-rearranged, patient-derived ALL samples with ABT-199 results significantly reduced tumor burden when compared to controls.[45-47] Recently, Bourquin et al published their investigation of BCL-2 inhibition in vitro and in vivo testing of a wide variety of ALL samples.[48] They interrogated 68 ALL samples, many from highly resistant patients in co-culture with bone marrow stromal cells with the intent of determining the feasibility of real-time drug-response profiling. In vitro testing demonstrated strong sensitivity to single agent venetoclax across early pre-T ALL, T-ALL and a variety of b-cell precursor ALL. In vivo, venetoclax demonstrated significant synergy with vincristine and dexamethasone, significantly delaying disease progression for multiple samples over either agent alone.

The study of venetoclax alone and in combination in acute myeloid leukemia has helped inform the dose and schedule proposed in this clinical trial. In order to mitigate the risk of tumor lysis, fixed, intra-patient dose escalation designs have

been utilized.[34, 49, 50] In a single agent phase II study, venetoclax 800mg was found to be safe, with no toxicity related deaths, and no reports of clinical tumor lysis syndrome. An elderly, upfront phase Ib/II trial found the recommended phase II dose of the combination of venetoclax and low-dose cytarabine to be 600mg, with prolonged (> 42 days), grade 4 thrombocytopenia being the predominant dose limiting toxicity.[49] However, another group studying venetoclax in combination with azacitidine, did not see dose-limiting thrombocytopenia at up to 800mg.[50] Of note, no trial in AML has reported significant TLS.

Liposomal Vincristine, Marqibo®, is a lipid-encapsulated nanoparticle formulation of vincristine, and was developed to have improved pharmacokinetic and side-effect profile over naked vincristine.[51] The drug gained FDA approval for ALL in second relapse after a phase II trial demonstrated significant activity.[4] In this study, sixty-five heavily pre-treated patients were treated with 2.25mg/m2 of liposomal vincristine weekly.Thirteen (20%) achieved a CR/CRi, and an additional 15% had either a partial response or bone marrow blast response (defined as morphologic response with incomplete platelet and neutrophil recovery). The formulation demonstrated response in patients who notably had all previously been exposed to vincristine in prior treatment regimens. The majority of serious adverse events where related to neuropathy and constipation, occurring in 25% and 12% of subjects respectively.

Especially in patients with relapsed disease, the combination of venetoclax and liposomal vincristine is a promising treatment strategy as these agents have non-overlapping toxicity profiles. Given this tolerability along with the significant pre-clinical data supporting the potential synergy of BCL-2 inhibition with vincristine, we propose a phase Ib/II clinical trial to explore the safety and preliminary efficacy of the combination in B- and T-ALL.

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Please note: As of April 2022, the removal of liposomal vincristine from the market in the US necessitates substitution of vincristine sulfate for liposomal vincristine. Section 5.2 of this protocol details the administration differences for vincristine sulfate. Section 9.2 documents additional toxicity monitoring instituted to ensure patients' safety in the phase II portion of this trial.

2. Objectives

2.1 Primary Endpoints

2.1.1 Phase I:

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2.1.1.1 To determine the maximum tolerated dose of venetoclax in combination with liposomal vincristine/vincristine sulfate in patients with relapsed or refractory T-cell and B-cell ALL.

NOTE: Liposomal Vincristine is no longer being manufactured.

2.1.1.2 Safety assessment and toxicity characterization after treatment of venetoclax in combination with liposomal vincristine in patients with relapsed or refractory T-cell and B-cell ALL.

2.1.2 Phase II:

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2.1.2.1 To determine the preliminary efficacy of venetoclax in combination with liposomal vincristine/vincristine sulfate to induce CR+CRi in patients with relapsed or refractory T-cell and B-cell ALL.

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2.2 Secondary Endpoints

2.2.1 Phase II:

2.2.1.1 To determine the progression free survival, overall survival and toxicity after the combination treatment in patients with relapsed or refractory T-cell and B-cell ALL.

2.2.1.2 To determine the rate of MRD negativity rate of the combination

2.3 Exploratory/Correlative Studies

2.3.1 Phase II:

2.3.1.1 To determine if genetic signature as determined by next generation sequencing can predict response to combination.

2.3.1.2 To determine if immunophenotype of ALL is associated with response to combination.

2.3.1.3 To determine if the BH3 profile is associated with response to combination.

2.3.1.4 To determine if relative expression of BCL-2 measure by flow cytometry is associated with response to combination.

NOTE: Exploratory biomarker testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

Rev. Add5 **3. Selection of Patients**

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

Rev. Add8 3.1 Eligibility Criteria – Phase I (Arms A, B, C) – Step 0

Rev. Add2 _____ 3.1.1 Patient must be considered a potential candidate for the trial.

NOTE: Enrollment to Step 0 may occur prior to or following completion of the assessments to verify patient eligibility for Step 1 registration. Bone marrow and/or peripheral blood specimens collected during Step 0 or prior to treatment on Step 1 must be submitted for central review in order for the patient to be considered evaluable. Results will not be reported to the site and will not impact patient participation in the trial.

Rev. Add8 3.2 Eligibility Criteria – Phase I (Arms A, B, C) – Step 1

Rev. Add2
Rev. Add10 _____ 3.2.1 Patients must have a diagnosis of:

A) Relapsed or refractory B-cell or T-cell ALL after multi-agent chemotherapy.

B) Patients with < 5% blasts may enroll on trial in phase I portion provided that minimal residual disease (MRD) is present at > 10^{-3} as tested on an assay with minimum sensitivity of 10^{-4}.

Rev. Add6 OR

C) Relapsed lymphoblastic lymphoma

_____ 3.2.2 Age ≥ 18 years

_____ 3.2.3 ECOG performance status 0-2

Rev. Add6 _____ 3.2.4 Adequate liver function with AST/ALT less than 3X upper limit of normal and total bilirubin less than 2 mg/dL within 10 days prior to first dose of study agent.

Rev. Add3 _____ 3.2.5 Circulating WBC count must not be above 25 x10^9/L at the time of registration.

Rev. Add4
Rev. Add5

3.2.5.1 Patients with WBC count above 25 x10^9/L are eligible if they have started steroids or hydroxyurea per institutional guidelines. Please see Section 5.6.2 for additional details.

Rev. Add5 _____ 3.2.6 Glomerular filtration rate (GFR) of at least 40 mL/min within 7 days prior to first dose of study agent.

_____ 3.2.7 Patients of childbearing potential must not be pregnant or breast-feeding due to risk of fetal harm by the chemotherapeutic agents prescribed in this protocol.

Rev. Add3 _____ 3.2.8 All patients of childbearing potential must have a blood test or urine study with a minimum sensitivity 25 IU/L or equivalent units of HCG within 2 weeks prior to registration to rule out pregnancy.
Rev. Add6

A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of childbearing potential? _____ (Yes or No)

Date of blood or urine test: _____

_____ 3.2.9 Patients must not expect to conceive or father children by using accepted and highly effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and for 30 days after the last dose of venetoclax.

Should a patient or a partner of a patient become pregnant or suspect they are pregnant while participating in this study, the treating physician should be notified immediately.

Rev. Add8 _____ 3.2.10 No evidence of prior solid malignancy except adequately treated non-melanoma skin cancer, in situ cervical carcinoma, or any surgically- or radiation-cured malignancy continuously disease free for ≥ 2 years so as not to interfere with interpretation of radiographic response.

_____3.2.11 Patients with isolated testicular or CNS relapsed disease are not eligible.

_____ 3.2.12 Patients must not have Burkitt's lymphoma/leukemia based on the WHO criteria.

Rev. Add5 _____ 3.2.13 Patients must not have active central nervous system (CNS) leukemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF) or the use of CNS-directed local treatment for active disease within the prior 28 days. Prophylactic intrathecal chemotherapy is allowed. Previously treated CNS disease with documented clearance of the CSF will be allowed.

Rev. Add4

_____ 3.2.14 Patients will not be enrolled if they received prior chemotherapy within 2 weeks before registration to step 1with the following exceptions: to reduce the circulating lymphoblast count or palliation or for ALL maintenance (mercaptopurine, methotrexate, vincristine, thioguanine, and/or tyrosine kinase inhibitors).

Rev. Add4 _____ 3.2.15 Patients may be enrolled with a prior allogeneic hematopoietic stem cell transplant (HSCT) but the transplant date must be at least 90 days before date of registration to step 1. Patient must be off immunosuppression and without active GVHD prior to registration to step 1 if previous HSCT.

Rev. Add4 _____ 3.2.16 Patients cannot have poorly controlled chronic viral infections including Hepatitis B, C, or HIV. HIV positive patients are allowed on this study if they have a CD4 count ≥ 400, and are on a stable antiviral regimen.

_____ 3.2.17 Patients with NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia may not be enrolled.

_____ 3.2.18 Patients with serious medical or psychiatric illness that in the opinion of the primary investigator is likely to interfere with study participation may not be enrolled.

Rev. Add6 _____ 3.2.19 Patients must not be taking any other experimental medications within 21 days prior to registration. Clinical trial medications that are FDA approved will be allowed within 14 days prior to registration.

Rev. Add3 _____ 3.2.20 Patients should not have received the following **within 7 days** prior to the first dose of study drug:

- Strong and Moderate CYP3A inhibitors (see Appendix V for details);
- Strong and Moderate CYP3A inducers (see Appendix V for details)

See Section 5.6.3 for discussion of the use of azole anti-fungals.

Rev. Add3 _____ 3.2.21 Patients must not have grade 3 or higher peripheral neuropathy or history of grade 3 or higher peripheral neuropathy. Patients with familial demyelinating disease like Charcot-Marie-Tooth disease are also excluded.

Rev. Add4

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add2 3.3 Eligibility Criteria – Phase II (Arm D) – Step 0

Rev. Add2 _____ 3.3.1 Patient must be considered a potential candidate for the trial.

Rev. Add8
Rev. Add10 **NOTE:** Enrollment to Step 0 may occur prior to or following completion of the assessments to verify patient eligibility for Step 1 registration.

Rev. Add8
Rev. Add9 3.4 Eligibility Criteria – Phase II (Arm D) – Step 1

_____ 3.4.1 Relapsed or refractory B-cell or T-cell ALL, including lymphoblastic lymphoma, after at least one line of chemotherapy.

_____ 3.4.2 Patients with prior venetoclax treatment for ALL will be excluded.

_____ 3.4.3 Age ≥ 18 years.

_____ 3.4.4 ECOG performance status 0-2.

Rev. Add6 _____ 3.4.5 Adequate liver function with AST/ALT less than 3X upper limit of normal and total bilirubin less than 2 mg/dL within 10 days prior to first dose of study agent.

Rev. Add3
Rev. Add4
Rev. Add5 _____ 3.4.6 Circulating WBC count must not be above 25 $x10^9$/L at the time of registration to step 1.

3.4.6.1 Patients with WBC count above 25 $x10^9$/L are eligible if they have started steroids or hydroxyurea per institutional guidelines. Please see Section 5.6.2 for additional details.

Rev. Add5 _____ 3.4.7 GFR of at least 40 mL/min within 7 days prior to first dose of study agent.

_____ 3.4.8 Patients must not be pregnant or breast-feeding due to risk of fetal harm by the chemotherapeutic agents prescribed in this protocol.

Rev. Add3
Rev. Add6 _____ 3.4.9 All patients of childbearing potential must have a blood test or urine study with a minimum sensitivity 25 IU/L or equivalent units of HCG within 2 weeks prior to registration to rule out pregnancy.

A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Patient of childbearing potential? _____ (Yes or No)

Date of blood or urine test: _____

_____ 3.4.10 Patients must not expect to conceive or father children by using accepted and highly effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and for 30 days after the last dose of venetoclax.

Should a patient or partner of a patient become pregnant or suspect she is pregnant while participating in this study, the treating physician should be informed immediately.

Rev. Add9 _____ 3.4.11 No evidence of prior malignancy except adequately treated non-melanoma skin cancer, in situ cervical or breast carcinoma, or chemotherapy-surgically- or radiation-cured malignancy continuously disease free for ≥ 2 years.

Rev. Add5 _____ 3.4.12 Patients with isolated testicular or CNS relapsed disease are not eligible.

_____ 3.4.13 Patients must not have Burkitt's lymphoma/leukemia based on the WHO criteria.

Rev. Add5
Rev. Add9 _____ 3.4.14 Patients must not have active central nervous system (CNS) leukemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF) or the use of CNS-directed local treatment for active disease within the prior 28 days. Prophylactic intrathecal chemotherapy is allowed. Previously treated CNS disease with documented clearance of the CSF will be allowed and once cleared, prophylactic intrathecal chemotherapy can be continued.

_____ 3.4.15 Patients will not be enrolled if they received prior chemotherapy within 2 weeks before enrollment with the following exceptions: to reduce the circulating lymphoblast count or palliation (i.e., steroids or hydroxyurea), for ALL maintenance (mercaptopurine, methotrexate, vincristine, thioguanine, and/or tyrosine kinase inhibitors).

Rev. Add10 _____ 3.4.16 Patients may be enrolled with a prior allogeneic hematopoietic stem cell transplant (HSCT) but the transplant date must be at least 90 days before date of enrollment. Patient must be off immunosuppression and without active GVHD prior to enrollment if previous HSCT. Low-dose steroids (10mg or less) are allowed.

Rev. Add4
Rev. Add10 _____ 3.4.17 Patients cannot have poorly controlled chronic viral infections including Hepatitis B, C, or HIV. HIV positive patients with undetectable viral load are allowed.

_____ 3.4.18 Patients with NYHA Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia may not be enrolled.

_____ 3.4.19 Patients with serious medical or psychiatric illness that in the opinion of the primary investigator is likely to interfere with study participation may not be enrolled.

_____ 3.4.20 Patients must not be participating in any other clinical trial or taking any other experimental medications within 21 days prior to registration.

Rev. Add11 _____ 3.4.21 Patients must not have received the following **within 7 days** prior to the first dose of study drug or while on study treatment:

Rev. Add3

- Strong and Moderate CYP3A inhibitors (see Appendix V for details);
- Strong and Moderate CYP3A inducers (see Appendix V for details)

See Section 5.6.3 for discussion of the use of azole anti-fungals.

Rev. Add3

_____ 3.4.22 Patients must not have grade 3 or higher peripheral neuropathy or history of grade 3 peripheral neuropathy. Patients with familial demyelinating diseases like Charcot-Marie-Tooth disease also excluded.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add5
Rev. Add9

4. Registration Procedures

CTEP Registration Procedures

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

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

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

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

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorresources/default.htm. For questions, please contact the RCR *Help Desk* by email at RCRHelpDesk@nih.gov.

CTSU Registration Procedures

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

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

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

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol. Site registration forms may be downloaded from the EA9152 protocol page located on the CTSU members' website.

- Log on to the CTSU members' website Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA9152
- Click on Documents, select the Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents

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

To access the Regulatory Submission Portal log on to the CTSU members' website Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory → Regulatory Submission

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

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number

- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

Checking Your Site's Registration Status:

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

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

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

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Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within seven days after registration.

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

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in the Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. Once a slot- reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;

Rev. Add7

- Have an approved site registration for a protocol prior to patient enrollment.

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

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

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

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

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

Rev. Add7
Rev. Add10

4.1 Preregistration to Phase I (Arms A, B, C) – Step 0

NOTE: Patients who are only preregistered must not begin treatment.

Rev. Add6

4.1.1 Protocol Number

4.1.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

Rev. Add6
Rev. Add7

4.1.5.2 Bone marrow and/or peripheral blood specimens **must be submitted** for central review as outlined in Section 10.

4.1.5.3 Biological specimens are to be submitted for defined laboratory research studies and/or future undefined research per patient consent as outlined in Section 10.

Rev. Add10

4.2 Registration to Phase I (Arms A, B, C) – Step 1

4.2.1 Protocol Number

4.2.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.2.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

4.2.5 Additional Requirements

4.2.5.1 Patients must provide a signed and dated, written informed consent form.

Rev. Add7

4.2.5.2 Biological specimens are to be submitted for defined laboratory research studies and/or future undefined research per patient consent as outlined in Section 10.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.2.5.3 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata, site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and assigned one of the following Rave roles on the relevant

Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. To hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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

Rev. Add3

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

Rev. Add10

4.3 Preregistration to Phase II (Arm D) – Step 0

NOTE: Patients who are only preregistered must not begin treatment.

4.3.1 Protocol Number

4.3.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator

- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.3.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.3.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.3.

4.3.5 Additional Requirements

4.3.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

Rev. Add7

4.3.5.2 Biological specimens are to be submitted for defined laboratory research studies and/or future undefined research per patient consent as outlined in Section 10.

Rev. Add10

4.4 Registration to Phase II (Arm D) – Step 1

4.4.1 Protocol Number

4.4.2 Site/Investigator Identification

- Institution CTEP ID
- Treating Investigator
- Consenting Person
- Site Registrar
- Network Group Credit
- Credit Investigator

4.4.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics

- Gender
- Birth date (mm/yyyy)
- Race
- Ethnicity
- Nine-digit ZIP code
- Method of payment
- Country of residence

4.4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.4.

Rev. Add10

4.4.5 Classification Factor

4.4.5.1 Patient will be classified by immunophenotype: B-cell vs. T-cell.

4.4.6 Additional Requirements

4.4.6.1 Patients must provide a signed and dated, written informed consent form.

Rev. Add7

4.4.6.2 Biological specimens are to be submitted for defined laboratory research studies and/or future undefined research per patient consent as outlined in Section 10.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.4.6.3 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata, site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. To hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the

"accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

4.5 Data Query Portal

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

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

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

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

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

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA9152 Forms Completion Guidelines.

Rev. Add5 **5. Treatment Plan**

Rev. Add4 5.1 Administration Schedule – Phase I

NOTE: Liposomal Vincristine is no longer being manufactured.

In the phase I portion of this trial, venetoclax will be given orally in a tablet formulation once daily in 3 dose arms with a fixed, standard dose of intravenous (IV) liposomal vincristine 2.25mg/m^2 weekly starting after a 2 week lead-in phase of venetoclax.

Venetoclax will be dosed as follows:

- Cohort 1 (Arm A) – 20, 50, 100, 200 mg on Days 1, 2, 3, 4 and 400 mg on Days 5 – 70
- Cohort 2 (Arm B) – 50, 100, 200, 400 mg on Days 1, 2, 3, 4 and 600 mg on Days 5 – 70
- Cohort 3 (Arm C) – 100, 200, 400, 600 mg on Days 1, 2, 3, 4 and 800 mg on Days 5 – 70

In order to mitigate the risk of tumor lysis syndrome (TLS), fixed intra-patient dose escalation (per company standards) will be employed, as well as TLS prophylaxis starting 3 days prior to venetoclax dosing. Patients will be admitted to the hospital for TLS monitoring during dose escalation (days 1-6). See Section 5.6.2.

Three (3) patients will be enrolled in the initial dose arm (Arm A). If none of the initial three (3) patients experience a dose limiting toxicity (DLT), then an additional three (3) patients will be enrolled at the next dose arm (Arm B). If for any dose arm, one (1) patient experiences a DLT, then an additional three (3) patients will be enrolled at that dose arm. Escalation will continue until > 33% of a particular dose arm experiences a DLT. The next lower dose arm to that which caused the DLTs will be considered the recommended phase II dosing schema (RP2D) and implemented for Arm D. If < two (2) patients experience a DLT in dosing arm C, then dosing arm C will be used in the phase II portion of this trial. The table below illustrates the dose escalation plan based on observed DLTs for any given group of patients on the same treatment arm.

Number of Observed DLTs	Action
0/3 patients	Escalate to the next dose arm
1/3 patients	Add 3 more patients at current dose arm
>1/3 patients	Dose in previous arm is **MTD***
1/6 patients	Escalate to the next dose arm
≥2/6 patients	Dose in previous arm is **MTD***

*Discontinue the trial if occurs at the initial dose level. MTD refers to maximum tolerated dose.

The maximum tolerated dose (MTD) must be confirmed with six (6) patients. If only 0/3 patients with DLT in the MTD, three (3) additional patients will be enrolled into this dose level to better characterize the safety of this phase I portion dose. The MTD of venetoclax determined in the phase I portion will be the recommended dose for venetoclax used in combination with liposomal

vincristine in the phase II portion of this study. A minimum of three (3) patients and a maximum of eighteen (18) patients will be treated in the phase I portion of the study.

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Patients will receive venetoclax per their assigned dose arm schedule, Arm A, B, or C below. After a two-week lead-in phase, patients will also be initiated on weekly liposomal vincristine 2.25mg/m^2 IV x 4 weeks (Cycle 1 = 42 days). A bone marrow biopsy will be performed on Day 42 +/- 2 days. Cycle 2 may be held up to two weeks (14 days) for results of day 42 bone marrow biopsy, and should this occur, oral venetoclax should be continued. All patients will continue onto a second 28-day cycle of the combination therapy (Cycle 2 = 28 days). Patients with progressive disease will be off treatment. A bone marrow biopsy will be performed at day 70 +/- 2 days. Patients who achieve at least a stable disease response can remain on a 28-day cycle of combination therapy until disease progression, or withdrawal from trial. If patients achieve CR/CRi, patient may continue on combination therapy or single agent venetoclax therapy after the completion of cycle 2 at the discretion of the treating physician. All subsequent cycles will follow the cycle 2 regimen for combination therapy over 28 days. At the discretion of the treating physician, a patient who achieves CR or CRi may proceed to HSCT at any time. Dose modifications occurs per Section 5.5 are allowed starting in Cycle 2 (i.e., after day 42 of DLT monitoring window). The 4th weekly dose (day 36) of liposomal vincristine may be held for treatment emergent adverse events in cycle 1, at the discretion of the site investigator. This should be discussed with the study chair prior to liposomal vincristine dose being held. Patients must have taken at least 75% of venetoclax doses and 75% of liposomal vincristine doses during the DLT period to be considered evaluable for MTD. Those patents not meeting this requirement and not showing any DLT will need to be replaced for MTD determination.

The provided medication diary should be distributed to patients to document venetoclax administration schedules (see Appendix II).

NOTE: Marqibo (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vinCRIStine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage.

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5.1.1 **Arm A**

Cycle 1:

Venetoclax: orally in a tablet formulation once daily at 20, 50, 100, 200 mg on Days 1, 2, 3, 4 and 400 mg on Days 5 – 42.

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Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4 starting Day 15. The 4th weekly dose (day 36) may be held at the discretion of the site investigator in the first cycle.

NOTE: All patients should proceed to Cycle 2 receiving combination therapy unless they have progressive disease or they achieve CR or CRi and proceed to HSCT. Patients may continue on combination therapy until HSCT can be arranged.

NOTE: Liposomal Vincristine is no longer being manufactured.

Cycle 2:

Venetoclax: orally in a tablet formulation once daily at 400 mg on Days 43 – 70.

Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4.

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NOTE: Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition.

If patients achieve CR/CRi, patient may continue on combination therapy or single agent venetoclax therapy after the completion of cycle 2 at the discretion of the treating physician.

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NOTE: Dose reduction of liposomal vincristine is allowed during cycle two per package insert guidelines at investigator's discretion.

NOTE: Liposomal Vincristine is no longer being manufactured.

5.1.2 **Arm B**

Cycle 1:

Venetoclax: orally in a tablet formulation once daily at 50, 100, 200, 400 mg on Days 1, 2, 3, 4 and 600 mg on Days 5 – 42.

Rev. Add6
Rev. Add8

Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4 starting Day 15. The 4th weekly dose (day 36) may be held at the discretion of the site investigator in the first cycle.

NOTE: All patients should proceed to Cycle 2 receiving combination therapy unless they have progressive disease or they achieve CR or CRi and proceed to HSCT. Patients may continue on combination therapy until HSCT can be arranged.

NOTE: Liposomal Vincristine is no longer being manufactured.

Cycle 2:

Venetoclax: orally in a tablet formulation once daily at 600 mg on Days 43 – 70.

Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4.

NOTE: Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition.

If patients achieve CR/CRi, patient may continue on combination therapy or single agent venetoclax therapy after the completion of cycle 2 at the discretion of the treating physician

NOTE: Dose reduction of liposomal vincristine is allowed during cycle two per package insert guidelines at investigator's discretion.

NOTE: Liposomal Vincristine is no longer being manufactured.

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5.1.3 **Arm C**

Rev. Add2

Cycle 1:

Venetoclax: orally in a tablet formulation once daily at 100, 200, 400, 600 mg on Days 1, 2, 3, 4 and 800 mg on Days 5 – 42.

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Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4 starting Day 15. The 4th weekly dose (day 36) may be held at the discretion of the site investigator in the first cycle.

NOTE: All patients should proceed to Cycle 2 receiving combination therapy unless they have progressive disease or they achieve CR or CRi and proceed to HSCT. Patients may continue on combination therapy until HSCT can be arranged.

NOTE: Liposomal Vincristine is no longer being manufactured.

Cycle 2:

Venetoclax: orally in a tablet formulation once daily at 800 mg on Days 43 – 70.

Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4.

NOTE: Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition.

If patients achieve CR/CRi, patient may continue on combination therapy or single agent venetoclax therapy after the completion of cycle 2 at the discretion of the treating physician.

NOTE: Dose reduction of liposomal vincristine is allowed during cycle two per package insert at investigator's discretion.

NOTE: Liposomal Vincristine is no longer being manufactured.

Rev. Add4

5.1.4 Dose Limiting Toxicity (DLT)

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Prior trials have shown serious, non-hematologic adverse events for venetoclax to be grade 3/4 tumor lysis syndrome, grade 3/4 nausea, and grade 3/4 diarrhea. Grade 3/4 peripheral neuropathy and constipation have been seen in administration of liposomal vincristine. For the purposes of this trial, any adverse event occurring ≤ 42 days of first dose of study drug that meets the following qualifications and is potentially related to study medication or combination will be considered a dose limiting toxicity:

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- Non-hematologic Grade 3 adverse events that do not resolve to ≤ Grade 2 within 7 days. Optimal medical therapy for nausea, vomiting, and diarrhea must be employed before these would be considered a DLT. Alopecia of any grade will not be considered a DLT. Recurrent (i.e., if venetoclax was held and restarted) non-hematologic grade 3 AEs will be considered a DLT with the exception of electrolyte abnormalities.

- Grade 3 or 4 electrolyte abnormalities that do not result in clinical sequelae and that resolve to ≤Grade 2 with optimal medical management within 72 hours will not be considered DLTs.
- Non-hematologic Grade 4 adverse events.
- Any type of grade 3-4 hypersensitivity reaction (i.e.: allergic reaction, anaphylaxis, serum sickness, skin disorders, etc.), that necessitates discontinuation of study drug.

Rev. Add2

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Rev. Add2

- Hematologic:

  Prolonged myelosuppression defined as persistence of ≥Grade 4 neutropenia or thrombocytopenia AND marrow cellularity of 5% or less in the absence of persistent ALL (i.e. >5% of nucleated cells are leukemic blasts in bone marrow) that persists at least 42 days after the initiation of Cycle 1 of therapy. Persistent cytopenias that were present at cycle 1, day 1 that persist until day 42 in the absence of active disease will not be considered a DLT (i.e., cytopenia must be treatment-emergent). Infections will not be considered DLTs (including neutropenic fever), unless the investigator determines that the infection or neutropenic fever resulted from the degree or duration of myelosuppression **in the absence of persistent leukemia**

Rev. Add3

- Grade 3 or greater peripheral neuropathy not present at study entry that does not resolve to ≤ Grade 2 within 7 days with the 4th dose of vincristine held on day 36.

Rev. Add6

While the phase I portion is ongoing, the study team will meet weekly via teleconference to review and discuss DLTs and the overall trial conduct. Toxicities will be assessed and graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE). No patients can be enrolled in a subsequent dose cohort until all patients of the previous cohort have completed the 42 days of cycle 1. If a patient never starts the study drug, withdraws prior to Day 42 (of cycle 1) for non-DLT reasons, is lost to follow up prior to Day 42, or does not receive 75% of study medications, this slot will be made available for replacement.

Dose modifications are not allowed during cycle 1 of the phase I portion of this trial. If study drugs are felt required to be held (for non-hematologic grade 3 treatment emergent adverse events), the study chair will be notified prior to doses being held. Patients must take at least 75% of venetoclax doses and 75% of liposomal vincristine doses to be considered evaluable for MTD decision.

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Rev. Add8

5.2 Administration Schedule – Phase II

NOTE: Liposomal Vincristine is no longer being manufactured.

The phase II portion of this trial will be a single arm, open-label trial of the combination of the RP2D of venetoclax and vincristine sulfate. As of amendment 11, no new patients should be started on liposomal vincristine on trial, and any patient currently receiving liposomal vincristine should be switched to vincristine sulfate at the beginning of their next cycle or as the drug supply requires, whichever comes first.

Rev. Add3

Rev. Add11

No lead-in phase of venetoclax will be required. Patients will be initiated on daily venetoclax at the MTD (600mg) and vincristine sulfate 1.4mg/m^2 (capped at 2mg) weekly x 4 weeks to substitute for liposomal vincristine 2.25mg/m^2 x 4 weeks (Cycle 1 = 28 days). A bone marrow biopsy will be performed on Day 28 +/- 2 days. Subsequent cycles may be held up to 2 weeks (14 days) to allow for peripheral blood count recovery and bone marrow interpretation (see Section 5.5 for additional dose modification guidelines).Patients who achieve at least a stable disease response will continue onto a second 28-day cycle of the combination therapy (Cycle 2 = 28 days). Patients with progressive disease will be taken off treatment. A bone marrow biopsy will be performed at day 56 +/- 2 days (note: if cycle 2 is held for blood count recovery, the first day of cycle 2 should be considered day 29 for purposes of second bone marrow biopsy). Patients who achieve at least a stable disease response can remain on combination therapy until disease progression or withdrawal from trial. All subsequent cycles will follow the cycle 2 regimen for combination therapy over 28 days, unless a dose modification occurs per Section 5.5. At the discretion of the treating physician, a patient who achieves CR or CRi may proceed to HSCT at any time. Dose reductions for cytopenias in patients during cycle 1 are strongly discouraged. Study treatment may be held for up to 14 continuous days in the event of an adverse event. The dose of liposomal vincristine or conventional vincristine sulfate may be given up to 2 days after scheduled date in order to accommodate infusion center holidays or patient preference.

Patients will be classified according to ALL phenotype (B-cell vs T-cell) based on the immunophenotyping provided by enrolling sites.

The provided medication diary should be distributed to patients to document venetoclax administration schedules (see Appendix II).

NOTE: Liposomal vincristine has different dosage recommendations than vincristine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage.

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5.2.1 **Arm D**

Cycle 1:

Venetoclax 600mg: orally in a tablet formulation once daily, Days 1-28.

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Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4 starting on Day 1.

OR,

Conventional vincristine sulfate 1.4mg/m^2 IV weekly x 4 (capped at 2mg).

NOTE: All patients should proceed to Cycle 2 unless they have progressive disease or they achieve CR or CRi and proceed to HSCT.

Dose modifications for venetoclax and liposomal vincristine or conventional vincristine sulfate per Section 5.5.2 are allowed during Cycle 1.

Patients may switch from liposomal vincristine to conventional vincristine sulfate in the middle of a cycle (including cycle 1). Once a patient switches, patients must

continue with conventional vincristine sulfate for the duration of trial.

NOTE: Liposomal Vincristine is no longer being manufactured.

Rev. Add11

Cycle 2 and Beyond:

Venetoclax 600mg: orally in a tablet formulation once daily 1-28 per cycle.

Liposomal Vincristine: 2.25mg/m^2 IV weekly x 4 starting on Day 1 of each cycle.

OR,

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Conventional vincristine sulfate 1.4mg/m^2 IV (capped at 2mg) every 4 weeks (C1D1). Please note change in frequency from cycle 1 and phase I dosing with liposomal vincristine.

NOTE: Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition.

If patients achieve CR/CRi, patient may continue on combination therapy or single agent venetoclax therapy after the completion of cycle 2 at the discretion of the treating physician.

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Dose reduction or elimination of liposomal vincristine or vincristine sulfate is allowed during cycle two per package insert guidelines at investigator's discretion.

Patients may switch from liposomal to conventional vincristine sulfate in the middle of a cycle (including cycle 1). Once a patient switches, patients must continue with conventional vincristine sulfate for the duration of trial.

NOTE: Liposomal Vincristine is no longer being manufactured.

Rev. Add10

5.3 Adverse Event Reporting Requirements

Rev. Add3

All toxicity grades described in this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.3.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.3.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA9152 forms packet for instructions on where, when and what adverse events are to be reported routinely on this protocol.

5.3.3 Expedited Reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be also reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting.

5.3.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to protocol treatment.
Unlikely	The AE is *doubtfully related* to protocol treatment.
Possible	The AE *may be related* to protocol treatment.
Probable	The AE is *likely related* to protocol treatment.
Definite	The AE is *clearly related* to protocol treatment.

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- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

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- **Dose Limiting Toxicity (DLT):** The appearance of side effects occurring ≤ 42 days of the first dose of study agent that are possibly severe enough to prevent further increase in dosage or strength of treatment agent, or to prevent continuation of treatment at any dosage level. Any adverse event occurring on the phase I portion of the study that meets the E9152 definition of DLT must be reported via CTEP-AERS

- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Rev. Add3

5.3.5 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov., so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2990)
- the FDA (1-800-FDA-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

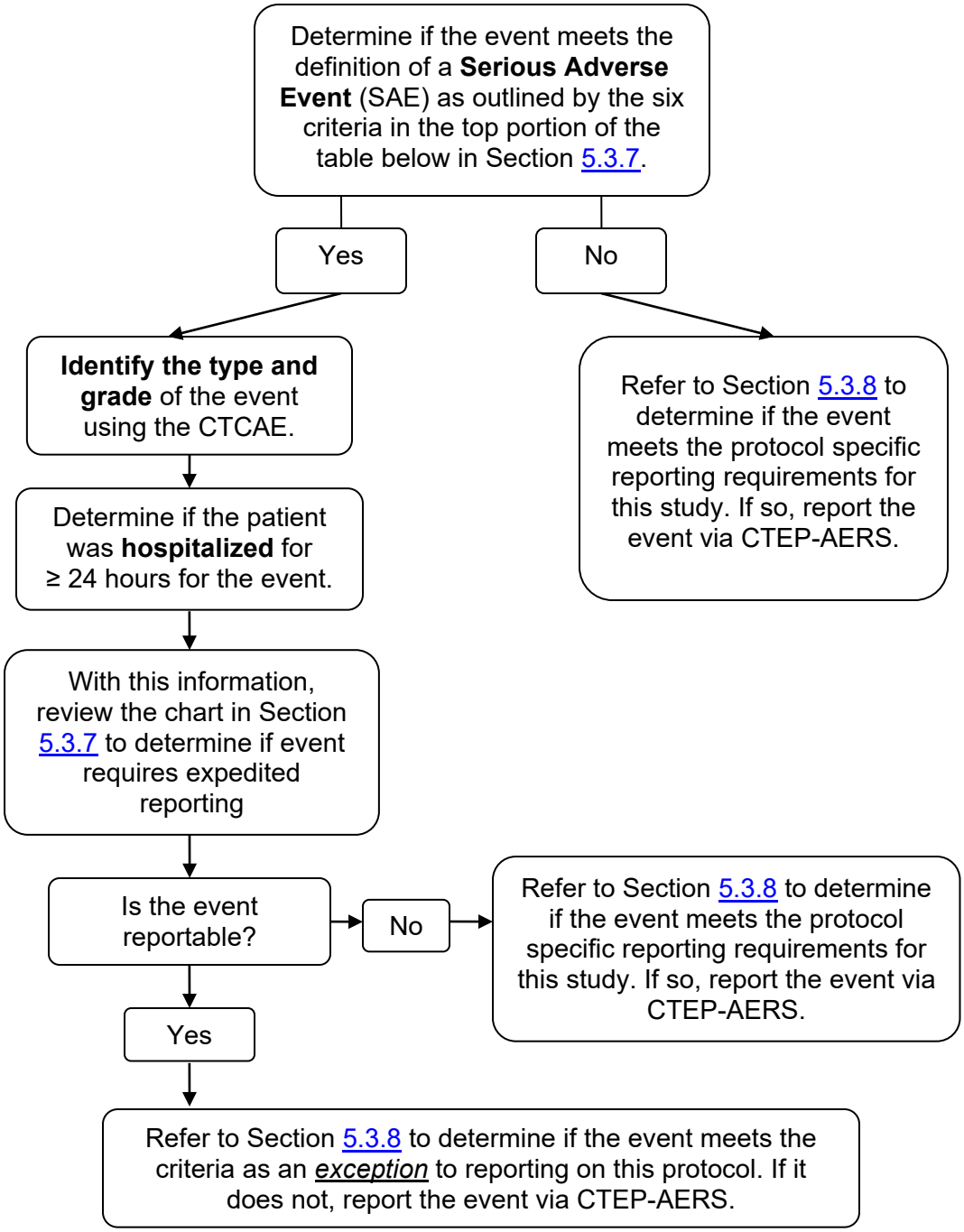
Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and

tables in the following sections have been customized for protocol EA9152 and outline the specific expedited adverse event reporting requirements for study EA9152.

5.3.6 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A, B, C, and D

Rev. Add10

5.3.6.1 Guidelines for reporting adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent/IND exempt.



Rev. Add6

5.3.6.2 Guidelines for reporting adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational/IND exempt agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.3.7, AND has an attribution of possible, probably or definite, OR meets the protocol specific requirements in Section 5.3.8, the following events require reporting as follows:

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

- All Grade 3, 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational/IND exempt agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

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

5.3.7 Expedited Reporting Requirements for protocol EA9152

Investigational/IND exempt Agents: Venetoclax

Commercial Agents: Liposomal vincristine, Vincristine sulfate

Rev. Add11

NOTE: Liposomal Vincristine is no longer being manufactured.

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational/IND Exempt Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational/IND exempt agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational/IND exempt agent(s)/intervention (21 CFR 312.64)

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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5.3.8 Additional instructions, requirements and exceptions for protocol EA9152

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study**: A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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EA9152 specific expedited reporting requirements:

- **Dose Limiting Toxicities (Phase I arms only – Arms A, B, and C)**

  For the purposes of this trial, any adverse event (per NCI Common Terminology Criteria for Adverse Events (CTCAE)) occurring within 42 days of first dose of study agent that meets the following qualifications and is potentially related to study medication or combination will be considered a dose limiting toxicity and must be reported initially via CTEP-AERS within 24 hours, followed by a complete report via CTEP-AERS within 5 calendar days, including the following:

  - Non-hematologic Grade 3 adverse events that do not resolve to ≤ Grade 2 within 7 days. Optimal medical therapy for nausea, vomiting, and diarrhea must be employed before these would be considered a DLT. Alopecia of any grade will not be considered a DLT. Recurrent (i.e. if venetoclax was held and restarted) non-hematologic grade 3 AEs will be considered a DLT with the exception of electrolyte abnormalities.
  - Grade 3 or 4 electrolyte abnormalities that do not result in clinical sequelae and that resolve ≤ Grade 2 with optimal medical management within 72 hours will not be considered DLTs.

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  - Non-hematologic Grade 4 adverse events.
  - Any type of Grade 3-4 hypersensitivity reaction (i.e.: allergic

reaction, anaphylaxis, serum sickness, skin disorders, etc.), that necessitate discontinuation of study drug.

- Prolonged myelosuppression defined as persistence of ≥ Grade 4 neutropenia or thrombocytopenia AND marrow cellularity of 5% or less in the absence of persistent ALL (i.e. > 5% of nucleated cells are leukemic blasts in bone marrow) that persists at least 42 days after the initiation of Cycle 1 of therapy. Persistent cytopenias that were present at cycle 1, day 1 that persist until day 42 in the absence of active disease will not be considered a DLT (i.e., cytopenia must be treatment-emergent). Infections will not be considered a DLT (including neutropenic fever), unless the investigator determines that the infection or neutropenic fever resulted from the degree or duration of myelosuppression **in the absence of persistent leukemia**

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- Grade 3 or greater peripheral neuropathy not present at study entry that does not resolve to < grade 2 within 7 days with the 4th dose of vincristine held on day 36.

- **Pregnancies (All Arms – A, B, C, and D):** Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on venetoclax, or within 28 days of the female patient's last dose of venetoclax, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix IV for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EA9152 specific expedited reporting exceptions:

For study, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- Myelosuppression that causes a delay of < 14 days in initiating cycle 2

Rev. Add2

- Grade 4 neutropenia that is attributable to underlying disease or persisting < 6 weeks from the start of a cycle that is not attributable to the underlying disease
- Any hematologic toxicities not meeting definition for dose-limiting toxicity

5.3.9 Other recipients of adverse event reports and supplemental data

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company.

ECOG-ACRIN may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by ECOG-ACRIN MUST be uploaded to the Supplemental Data Folder in Medidata Rave.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.3.10 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows:

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

     NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).
  3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
  4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

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Rev. Add5

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for more information. *Frequency is provided based on 1298 patients*. Below is the CAEPR for Venetoclax (ABT-199).

Version 2.1, May 8, 2019[1]

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

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Hemolysis; Thrombotic thrombocytopenic purpura

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (coronary artery disease); Heart failure; Myocardial infarction; Sinus tachycardia; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo

GASTROINTESTINAL DISORDERS - Abdominal pain; Belching; Dry mouth; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (Crohn's disease); Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Flu like symptoms; General disorders and administration site conditions - Other (general physical heath deterioration); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); Injection site reaction; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatic function abnormal)

IMMUNE SYSTEM DISORDERS - Cytokine release syndrome

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction; Injury, poisoning and procedural complications - Other (laceration)

INVESTIGATIONS - Aspartate aminotransferase increased; Blood bilirubin increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain

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

NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Intracranial hemorrhage; Ischemia cerebrovascular; Nervous system disorders - Other (neuropathy peripheral); Peripheral sensory neuropathy; Syncope

PSYCHIATRIC DISORDERS - Confusion; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Ovarian rupture

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Dyspnea; Epistaxis; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asphyxia)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Pruritus; Rash acneiform; Rash maculo-papular

VASCULAR DISORDERS - Hypotension; Thromboembolic event

NOTE: Venetoclax (ABT-199) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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Rev. Add10

5.5 Dose Modifications

Dose modifications during cycle 1 of the phase I portion of this trial are not allowed.

5.5.1 Venetoclax

Rev. Add6

During cycle 1 of the phase I portion of this trial, venetoclax should not be held for hematologic toxicities unless meeting DLT criteria. Venetoclax may be held for non-hematologic grade 3 adverse events which will be considered a DLT if they do not resolve within 7 days (see Section 5.1.4). Any temporary or permanent discontinuation of study drug should be discussed with study chair in real time if possible. After cycle one of the phase I portion, venetoclax may be reduced for toxicity at the discretion of the investigator with the following guidelines.

During the phase II portion of the trial, venetoclax may be reduced for toxicity at the discretion of the investigator. The following table may serve as a guideline for suggested dose reduction:

Dose Modification Guidelines for Adverse Events		
Adverse Event	**Occurrence**	**Dosage Modification**
Grade 4 neutropenia with or without infection; or grade 4 thrombocytopenia	Prior to achieving remission or clinically significant response	In most instances, do not interrupt venetoclax
	First occurrence after achieving remission or clinically significant response	Delay subsequent cycle of combination up to 2 weeks prior to initiation of subsequent cycle
	Subsequent occurrence after achieving remission or clinically significant response	Reduce venetoclax duration by 7 days during each of the subsequent cycles, such as D1- 14 or D1-21 days instead of D1-28 days.
Grade 3 or 4 nonhematologic toxicities	Any occurrence	Interrupt venetoclax if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, may resume venetoclax at the same dose.

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5.5.2 Liposomal Vincristine

NOTE: Liposomal Vincristine is no longer being manufactured.

Liposomal vincristine will be administered to patients weekly. Starting from cycle 2 of the phase 1 portion and cycle 1 of the phase II portion, liposomal vincristine will be dose modified *at the discretion of the treating physician* with the following prescribing information as a guideline.

- For Grade 3 or 4 (severe symptoms; limiting self-care activities of daily living [ADL]) or persistent Grade 2 (moderate symptoms;

limiting instrumental ADLs) peripheral neuropathy: interrupt liposomal vincristine.

- If the peripheral neuropathy remains at Grade 3 or 4: discontinue liposomal vincristine.
- If the peripheral neuropathy recovers to Grade 1 or 2: reduce liposomal vincristine dose to 2 mg/m^2.

- If the patient has persistent Grade 2 peripheral neuropathy after the first dose reduction to 2 mg/m^2: interrupt liposomal vincristine for up to 7 days.
  - If the peripheral neuropathy increases to Grade 3 or 4: discontinue liposomal vincristine.
  - If the peripheral neuropathy recovers to Grade 1: reduce liposomal vincristine dose to 1.825 mg/m^2.
- If the patient has persistent Grade 2 peripheral neuropathy after the second dose reduction to 1.825 mg/m^2: interrupt liposomal vincristine for up to 7 days.
  - If the peripheral neuropathy increases to Grade 3 or 4: discontinue liposomal vincristine.
  - If the peripheral neuropathy recovers to Grade 1: reduce liposomal vincristine dose to 1.5 mg/m^2.

Rev. Add11

5.5.3 Vincristine sulfate (conventional)

Vincristine sulfate will be dose modified at the discretion of the treating physician with the following prescribing information as a guideline.

- For neurotoxicity characterized as areflexia only, give 100% of the vincristine sulfate dose. For grade 1 motor neuropathy including abnormal ability to button or write, give 100% of the vincristine sulfate dose. For grade 2 motor neuropathy, hold until recovery and then reduce dose of vincristine sulfate to 50% of planned dose. For grade 3 motor neuropathy, hold until recover to < grade 2.
- For other Grade 3 related nonhematological/organ toxicity, hold vincristine sulfate until resolution.
- Grade 4 other related nonhematological/organ toxicity, discontinue vincristine sulfate.

5.6 Supportive Care

5.6.1 All supportive measures consistent with optimal patient care will be given throughout the study.

Please reference Appendix V for a list of CYP3A Inhibitors and Inducers and medications affecting P-Glycoprotein (PGP). If the treating physician and patient decide that any of the medications listed here are to be used for best patient care, please consult the study chair.

Rev. Add5

5.6.2 Tumor Lysis Prophylaxis and Monitoring

In previous clinical trials, venetoclax has been associated with life threating tumor lysis. Careful monitoring for tumor lysis based on tumor burden will be instituted. Prior to initiation of study drug, circulating WBC count must not be above 25 $x10^9$/L. Patients with leukocyte count above 25 $x10^9$/L should start steroids or hydroxyurea per institutional guidelines, and these medications should be discontinued before Day 1 of study drug if possible. If at least 4 days hydroxyurea or dexamethasone has been utilized without reduction in blasts, patient may start trial after discussion with the study chair. Hydrea or steroids may be reinstituted if deemed necessary by treating physician to control counts after Day 6.

Phase I:

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Given the high risk of tumor lysis inherent to ALL, patients should be monitored as inpatients for intensive laboratory monitoring during the intrapatient dose escalation of venetoclax (days 1-6). Serum chemistries, uric acid, LD (TLS labs) should be drawn within 4 hours pre-dose as well as every 8 hours (+/- 2 hours) during hospitalization. Additionally, tumor lysis labs should be drawn prior to first dose of combination and then every 24 hours for 3 days afterwards (i.e. days 15-18) only if patient remains at risk for tumor lysis per treating physician. Three days prior to initiation of study drug, patients should start uric acid lowering therapy with allopurinol unless prior allergic reaction or intolerance prevents its use. Oral hydration with at least 2L of fluids should be encouraged for all patients daily during administration of drug. If appropriate oral hydration cannot be ensured, IV fluids should be administered at the discretion of the treating provider. Documentation of the review of tumor lysis labs required in study procedures must occur before the patient is instructed to take subsequent doses of venetoclax by clinical research staff during the first week of single agent venetoclax and the first cycle of combination of drugs. Sites that utilize a day hospital may monitor patients in this setting as opposed to traditional inpatient provided that all laboratory measures and evaluations can be completed in the timeframes listed within this protocol.

Phase II:

Given low rates of tumor lysis syndrome (TLS) seen in phase I portion of this trial and in acute leukemias in general treated with venetoclax, inpatient administration will NOT be required unless WBC >20 at C1D1. Daily tumor lysis labs should be drawn on D1-3 and institutional protocol for TLS prophylaxis and management should be followed. Oral hydration with at least 2L of fluids should be encouraged for all patients daily during administration of drug. If appropriate oral hydration cannot be ensured, IV fluids should be administered at the discretion of the treating provider. Documentation of the review of tumor lysis labs required in study procedures must occur before the patient is instructed to take subsequent doses of venetoclax by clinical research staff during the first week of cycle 1.

5.6.2.1 If laboratory TLS, please reference the venetoclax package insert for supportive care guidelines:

Withhold the next day's dose of venetoclax. If resolved within 24-48 hours of last dose, resume at the same dose.

- For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose of venetoclax.
- For any events of clinical TLS, resume at a reduced dose of venetoclax following resolution.

Rev. Add11

5.6.3 Use of Anti-fungal Azoles

Many patients with ALL are prescribed azole anti-fungal medications (i.e., fluconazole, vorinconazole, posaconazole, isavuconazonium sulfate) as prophylaxis or treatment for invasive fungal infections. Standard dose reductions for use of azole antifungals per venetoclax PI are strongly recommended.

Rev. Add5

5.6.4 Drug Interactions

Rev. Add11

Please see Section 8.1.11 and for potential drug interactions involving venetoclax and liposomal or conventional vincristine sulfate.

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event, submit forms according to the instructions in the EA9152 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Progression of disease.

Rev. Add4

5.8 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration to step 1. All patients must also be followed through completion of all protocol therapy if it exceeds 5 years of treatment.

6. Measurement of Effect

Response to combination therapy will be determined by patient bone marrow samples that will be locally analyzed [54].

6.1 Complete Remission (CR)

Requires that all of the following be present for at least 4 weeks.

- Peripheral Blood Counts
  - Neutrophil count ≥ 1.0 x 10^9/L.
  - Platelet count ≥ 100 x 10^9/L.
  - Reduced hemoglobin concentration or hematocrit has no bearing on remission status.
  - Leukemic blasts must not be present in the peripheral blood.
- Bone Marrow Aspirate and Biopsy
  - Cellularity of bone marrow biopsy must be > 20% with maturation of all cell lines.
  - ≤ 5% blasts.
- Extramedullary leukemia, such as CNS or soft tissue involvement, must not be present.

Rev. Add5

- An MRD negative response must meet the criteria for CR or CRi and have any residual disease <0.01% based on original testing technique.

6.2 Complete Remission incomplete (CRi)

Requires that all the same response criteria in peripheral blood and bone marrow as CR with the exception of one of the following

- Incomplete platelet recovery (platelets > 75 but < 100 x 10^9/L (> 75,000 but < 100,000/mm^3) independent of platelet transfusions)
- Incomplete neutrophil count recovery > .75 but < 1 x 10^9/L (> 750 but < 1000/mm^3).

6.3 Partial Remission (PR)

Requires that all of the criteria for complete remission be satisfied except that the bone marrow may contain > 5% blasts but < 25% blasts.

6.4 Stable Disease (SD)

Failure to achieve at least a PR, but with no evidence of progression as defined as an increase of peripheral blood or bone marrow blasts of more than 10% from nadir during study.

6.5 Relapse

Relapse following complete remission (CR) and complete remission incomplete (CRi) is defined as:

- Peripheral Blood Counts
  - Reappearance of blasts in the blood.
- Bone Marrow Aspirate and Biopsy

- Presence of > 5% blasts, not attributable to another cause (e.g., bone marrow regeneration).
- If there are no circulating blasts and the bone marrow contains 5% to 20% blasts, then a repeat bone marrow performed ≥ 1 week later documenting more than 5% blasts is necessary to meet the criteria for relapse.

6.6 Progressive Disease (PD)

Progressive disease is defined as a 50% increase in blasts in the marrow, depending on blast percentage at baseline:

- For patients with < 5% blasts at baseline, there must be an increase to ≥ 10% blasts.
- For patients with 5% to 10% blasts at baseline, there must be a ≥ 50% increase to > 10% blasts.
- For patients with 10% to 20% blasts at baseline, there must be a ≥ 50% increase to ≥ 20% blasts.

Rev. Add5

6.7 Response Criteria for Lymphomatous Extramedullary Disease, Lymphoblastic Lymphoma[55]

A PET/CT that includes the neck, chest, abdomen and pelvis is the preferred method of evaluation at diagnosis and after two cycles of combination therapy. If a patient at enrollment has a negative bone marrow and only extramedullary disease, i.e. lymphoblastic lymphoma, then response will be assessed by PET CT by day 84. A bone marrow biopsy to look for MRD will be required at this time point.

Rev. Add10

Complete Response: Complete resolution of lymphomatous enlargement by CT. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.

Partial Response: > 50% decrease in the sum of the product of the great perpendicular diameters (SPD) of the largest site of involvement (usually mediastinum). For patients with a previous positive PET scan, a post treatment residual mass must be positive in at least one previously involved site.

Progressive disease: > 25% increase in the SPD of the largest site of involvement. For patients with a previous positive PET scan, a post treatment residual mass must be positive in at least one previously involved site.

No Response/Stable disease: Fits criteria for neither PR nor PD.

Rev. Add5

7. Study Parameters

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7.1 Phase I Therapeutic Parameters

1. Prestudy CBC with differential, LFTs, and Tumor Lysis Labs must be done ≤ 10 days before first dose of study medication.
2. All required prestudy chemistries should be done ≤ 10 days before first dose of study medication - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours before first dose of study medication.
3. Pre-study bone marrow biopsy and aspirate must be completed ≤ 2 weeks prior to registration to step 0. If more than 14 days have elapsed from bone marrow and aspirate to cycle 1, day 1, these studies would need to be repeated only if necessary in the opinion of the investigator.

Test and Observations	Prior to Cycle 1	Treatment					Off-Treatment Visit[k]	Follow-Up[m]
		Cycle 1, Day 1	Cycle 1, Days 15-18	Cycle 2, Day 1	Cycle 2, Days 2-28	Cycle X, Day 1[l]		
Physical Exam	X	X		X		X	X	
Peripheral Neuropathy Assessment	X	X		X		X	X	
CBC with Differential[a,b]	X	X[o]	X	X[p]	X[p]	X[p]	X	X
Serum or Urine Pregnancy Test[g],	X							
Rev. Add3 Comprehensive Metabolic Panel[b,c]	X	X[o]	X	X	X[q]	X[q]		
Urinalysis[d]	X							
Tumor Lysis Labs [b,e, f]	X	X[o]	X[e]	X	X[q]	X[q]		
HIV, HBC, HCV[b,h]	X							
Rev. Add5 PET CT/CT Chest/Abdomen/Pelvis[i]	X					X		
CSF Sampling[j]	X[j]							
Bone Marrow Biopsy and Aspirate	X			X[n]		X[n]	X	X[m]

Rev. Add4 a. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the first dose of venetoclax in each treatment cycle.

Rev. Add6 b. All study procedures and blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 10 days prior to dosing. Chemistry results must be reviewed and confirm that subject's liver function tests and other safety labs still meet inclusion criteria prior to

administration of venetoclax dose. They should be seen and evaluated more often if clinically indicated for the management of toxicities, at the discretion of the treating physician investigator.

Rev. Add3 c. Chemistry laboratory analysis includes albumin, urea or BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3 (CO2; venous blood), calcium, phosphorous. Once disease progression occurs, these labs are no longer required to be completed.

d. Urinalysis will be done as clinically indicated. Urinalysis tests to include gross examination including specific gravity, protein, glucose and blood. A microscopic evaluation will also be performed, as clinically indicated, to include WBC/HPF, RBC/HPF and any additional findings.

Rev. Add3 e. Tumor lysis labs include LDH, uric acid, fibrinogen and coagulation studies in addition to chemistries. TLS labs on days 17 and 18 are required only if evidence of TLS on day 15 and 16 labs. If the patient has already undergone tumor lysis with single agent venetoclax in the opinion of the investigator, days 16-18 TLS labs are optional.

f. Please see tumor lysis monitoring guidelines in Section 5.6.2.

g. Patients of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 2 weeks prior to Step 1 registration.

h. At screening, testing should be performed for HIV antibody, hepatitis C antibody, and HBs antigen utilizing local standard informed consent procedures prior to this laboratory collection. These tests could be repeated later during the course of the study, if clinically indicated.

Rev. Add5 i. As clinically indicated and if solid disease at time of study entry. Patients with LBL at registration would need to have response assessment before starting cycle three. PET-CT imaging is strongly preferred, but CT C/A/P will be an acceptable alternative if PET-CT is not feasible.
Rev. Add4

j. As clinically indicated after initial screening to Lumbar Puncture. CNS sampling to document no active CNS disease should be done within 28 days of enrollment.

k. End of Study Assessment will be done within 6 weeks (+/- 1 week) of the last dose of study treatment.

l. If patient continues receiving study drug after cycle 2, the cycle length will remain 28 days for each additional cycle and indicated tests should be completed on day 1 of each consecutive treatment cycle.

Rev. Add4 m. Patient will be followed for survival every 6 months until 5 years after study registration to step 1. Follow-up bone marrow biopsies should also be performed at relapse, unless the patient received HSCT. If the patient comes off treatment for a reason other than progression, they will be followed for response until progression, for which bone marrow biopsy and aspirate will be performed on the follow up schedule of q6 months. Biopsies - other than those done prior to start of Cycle 1 and at relapse - do not need to be submitted to the EA LTB, per Section 7.2.

n. Bone marrow biopsies may be performed at +/- 2 days of designated schedule.

Rev. Add6 o. Inpatient admission for tumor lysis monitoring is required for days 1-6 of cycle 1. Please see Section 5.6.2 for additional details and requirements.

p. Complete blood counts should be monitored at least twice weekly if patient is requiring transfusion therapy as outpatient.

q. Subsequent monitoring of serum chemistries tumor lysis labs should be at least weekly for cycle 2, and then afterwards at the discretion of the treating physician.

7.2 Phase II Therapeutic Parameters

1. Prestudy CBC with differential, LFTs, and Tumor Lysis Labs must be done ≤ 10 days before first dose of study medication.
2. All required prestudy chemistries should be done ≤ 10 days before first dose of study medication - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours before first dose of study medication.
3. Pre-study bone marrow biopsy and aspirate must be completed ≤ 2 weeks prior to registration to step 0. If more than 14 days have elapsed from bone marrow and aspirate to cycle 1, day 1, these studies would need to be repeated only if necessary in the opinion of the investigator.

Rev. Add11

Test and Observations	Prior to Cycle 1	Treatment					Off-Treatment Visit[k]	Follow-Up[m]
		Cycle 1, Day 1	Cycle 1, Days 15	Cycle 2, Day 1	Cycle 2, Days 2-28	Cycle X, Day 1[l]		
Physical Exam	X	X		X		X	X	
Peripheral Neuropathy Assessment	X	X		X		X	X	
CBC with Differential[a,b]	X	X[o]	X	X[p]	X[p]	X[p]	X	X
Serum or Urine Pregnancy Test[g],	X							
Comprehensive Metabolic Panel[b,c]	X	X[o]	X	X	X[q]	X[q]		
Urinalysis[d]	X							
Tumor Lysis Labs [b,e, f]	X	X[o]	X	X	X[q]	X[q]		
HIV, HBC, HCV[b,h]	X							
PET CT/CT Chest/Abdomen/Pelvis[i]	X					X		
CSF Sampling[j]	X[j]							
Bone Marrow Biopsy and Aspirate	X			X[n]			X	X[m]

a. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct required for protocol therapy must be done < 24 hours prior to the first dose of venetoclax in each treatment cycle.

b. All study procedures and blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 10 days prior to dosing. Chemistry results must be reviewed and confirm that subject's liver function tests and other safety labs still meet inclusion criteria prior to administration of venetoclax dose. They should be seen and evaluated more often if clinically indicated for the management of toxicities, at the discretion of the treating physician investigator.

c. Chemistry laboratory analysis includes albumin, urea or BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3 (CO2; venous blood), calcium, phosphorous. Once disease progression occurs, these labs are no longer required to be completed.

d. Urinalysis will be done as clinically indicated. Urinalysis tests to include gross examination including specific gravity, protein, glucose and blood. A microscopic evaluation will also be performed, as clinically indicated, to include WBC/HPF, RBC/HPF and any additional findings.

e. Tumor lysis labs include LDH, uric acid, fibrinogen and coagulation studies in addition to chemistries. TLS labs on days 17 and 18 are required only if evidence of TLS on day 15 and 16 labs. If the patient has already undergone tumor lysis with single agent venetoclax in the opinion of the investigator, days 16-18 TLS labs are optional.

f. Please see tumor lysis monitoring guidelines in Section 5.6.2.

g. Patients of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 2 weeks prior to Step 1 registration.

h. At screening, testing should be performed for HIV antibody, hepatitis C antibody, and HBs antigen utilizing local standard informed consent procedures prior to this laboratory collection. These tests could be repeated later during the course of the study, if clinically indicated.

Rev. Add5 Rev. Add4 i. As clinically indicated and if solid disease at time of study entry. Patients with LBL at registration would need to have response assessment before starting cycle three. PET-CT imaging is strongly preferred, but CT C/A/P will be an acceptable alternative if PET-CT is not feasible.

j. As clinically indicated after initial screening to Lumbar Puncture. CNS sampling to document no active CNS disease should be done within 28 days of enrollment.

k. End of Study Assessment will be done within 6 weeks (+/- 1 week) of the last dose of study treatment.

l. If patient continues receiving study drug after cycle 2, the cycle length will remain 28 days for each additional cycle and indicated tests should be completed on day 1 of each consecutive treatment cycle.

Rev. Add4 m. Patient will be followed for survival every 6 months until 5 years after study registration to step 1. Follow-up bone marrow biopsies should also be performed at relapse, unless the patient received HSCT. If the patient comes off treatment for a reason other than progression, they will be followed for response until progression, for which bone marrow biopsy and aspirate will be performed on the follow up schedule of q6 months. Biopsies - other than those done prior to start of Cycle 1 and at relapse - do not need to be submitted to the EA LTB, per Section 7.2.

n. Bone marrow biopsies may be performed at +/- 2 days of designated schedule.

Rev. Add6 o. TLS should be monitored on C1D1-3 with TLS labs as above.

p. Complete blood counts should be monitored at least twice weekly if patient is requiring transfusion therapy as outpatient.

q. Subsequent monitoring of serum chemistries tumor lysis labs should be at least weekly for cycle 2, and then afterwards at the discretion of the treating physician

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7.3 Biological Specimen Submissions

Specimens are to be submitted as outlined in Section 10.

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

Biological Materials[6]	Prior to Start of Treatment[1,2]	Relapse
PHASE I ONLY: MANDATORY for Central Review		
Bone Marrow Aspirate (heparin, first pull)	X	
Peripheral Blood (heparin, green or purple, EDTA top tubes, 30-40mL)	X	
Bone Marrow/Peripheral Blood Smears (Wright-Giesma stained)	X	
Submit from patients who answer 'Yes' to 'I agree to have my samples collected and I agree that my samples and related information may be used for laboratory studies.'		
Bone Marrow Aspirate (heparin, first pull)[4,5]	X (Phase II)	X
Peripheral Blood (heparin, green or purple, EDTA top tubes, 30-40mL)[5]	X (Phase II)	X
Submit from patients who answer 'Yes' to 'I agree to provide additional samples for research.'		
Peripheral Blood (red top tubes, 15-20mL)	X	
Buccal Rinse[2]	X	

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1. Preregistration bone marrow and/or peripheral blood specimens are to be submitted for defined laboratory research studies and undefined future research per patient consent.
2. Buccal rinse is strongly encouraged to be collected at baseline, but can be collected at any other time during the study if necessary.

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3. The laboratory will accept any amount of bone marrow as long as it represents the first pull. Ideally, 2-3-mL of aspirate from a separate aspiration site should be submitted. If bone marrow at the time of relapse is not collected, then peripheral blood collection is sufficient as long as circulating absolute blast count is >1000.
4. Leftover specimens from the defined laboratory research studies will be stored for future undefined research studies from patients who answer 'Yes' to 'My samples and related information may be kept in a Biobank for use in future health research.'

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5. Specimens are to be submitted to the ECOG-ACRIN Leukemia Laboratory at MD Anderson Cancer Center.

Rev. Add11 **8. Drug Formulation and Procurement**

8.1 Venetoclax (ABT-199) NSC 766270

8.1.1 Other Names

Venclexta, Venclyxto, ABT-199.

8.1.2 Classification

Antineoplastic Agent, BCL-2 Inhibitor.

8.1.3 Mode of Action

Venetoclax selectively inhibits the anti-apoptotic protein BCL-2, which mediates tumor cell survival and has been associated with chemotherapy resistance. Venetoclax binds directly to the BCL-2 protein, displacing pro-apoptotic proteins and restoring the apoptotic process.

8.1.4 Storage and Stability

The clinical supply should be stored at 15° to 25°C (59° to 77°F).

Rev. Add2 8.1.5 Dose Specifics

Arm A: 20, 50, 100, 200 mg on Days 1, 2, 3, 4 and 400 mg on Days 5 – 70+

Arm B: 50, 100, 200, 400 mg on Days 1, 2, 3, 4 and 600 mg on Days 5 – 70+

Arm C: 100, 200, 400, 600 mg on Days 1, 2, 3, 4 and 800 mg on Days 5 – 70+

Arm D: 600mg Day 1 until study completion

8.1.6 Preparation

Venetoclax is available in a tablet formulation.

Excipients:

Copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, calcium phosphate dibasic

Coating Composition:

10 mg and 100 mg tablet coating contains iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium oxide.

50 mg tablet coating contains iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.

8.1.7 Route of Administration

Venetoclax should be taken orally with food and water. Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition.

8.1.8 Incompatibilities

Not applicable.

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8.1.9 Availability

Venetoclax is provided free of charge by AbbVie and will be distributed by Patwell.

Phase I Drug Orders:

Venetoclax will be supplied in the following configurations:

- 2x8 blister card of 10mg tablets (16 tablets total)
- 1x8 blister card of 50mg tablets (8 tablets total)
- 1 bottle with 120 100mg tablets (120 tablets total)

Different configurations should be ordered depending on the arm to which the patient is assigned. Suggested orders based on arm assignment may be found on the EA9152 Venetoclax Drug Request Form.

Phase I Initial Orders: Following submission of the required regulatory documents and patient registration to Step 1, Arm A, B or C, a supply of venetoclax may be ordered from the ECOG-ACRIN Drug Team. Institutions must email the completed EA9152 Venetoclax Phase I Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. A copy of the EA9152 Venetoclax Phase I Drug Request Form is available for download from the EA9152 Study Specific Tools section on the website (www.ecog.org). Please see Appendix VI for instructions on how to download this document.

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Phase I Reorders:

Institutions should keep in mind that shipments take 3 business days from the date the drug request is received by Patwell. Reorders using the EA9152 Venetoclax Phase I Drug Request Form should be emailed to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. Once the reorder is approved, the drug will be received on site within 2-3 business days. Shipments will be made from Patwell on business days only. **There will be no weekend or holiday delivery of drugs.**

Phase II Drug Orders:

3 x 120-ct bottles of Venetoclax 100mg = 2 cycles of treatment will be dispensed to a site as per drug order form

Phase II Initial Orders: Following submission of the required regulatory documents and patient registration to Step 1, Arm D, a supply of venetoclax may be ordered from the ECOG-ACRIN Drug Team. Institutions must email the completed EA9152 Venetoclax Phase II Drug Request Form to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. A copy of the EA9152 Venetoclax Phase II Drug Request Form is available for download from the EA9152 Study Specific Tools section on the website (www.ecog.org) and the CTSU website under the study specific Pharmacy Tab. Please see Appendix VI for instructions on how to download this document.

Phase II Reorders:

Institutions should keep in mind that shipments take 3 business days from the date the drug request is received by Patwell. Reorders using the EA9152 Venetoclax Phase II Drug Request Form should be emailed to the ECOG-ACRIN Drug Team at DrugOrder@ecog-acrin.org. Once the reorder is approved, the drug will be received on site within 2-3 business days. Shipments will be made from Patwell on business days only. **There will be no weekend or holiday delivery of drugs.**

Drug Inventory Records:

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Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational production disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines. The EA9152 Investigational Product Destruction Record must be submitted to document any unused venetoclax at the completion of the study. Please see Appendix VI for instructions on how to download this document.

Drug Destruction and Return:

At the completion of each patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

8.1.9.1 Drug Accountability:

All NCI studies using an oral agent must maintain Oral Drug Accountability Record Forms (DARF) to track study-supplied agents. The NCI Investigational Agent Accountability Record Form for Oral Agents should be utilized to track the disposition of venetoclax. This form is available on the CTEP website at http://ctep.cancer.gov/forms.

8.1.10 Side Effects

See Section 5.4 for side effects.

8.1.11 Potential Interactions

Venetoclax is metabolized primarily by CYP3A4 and is a substrate of P-glycoprotein. CYP3A4 inhibitors should not be used during days 1-21 of cycle 1 until patients begin receiving final venetoclax dose with no evidence of TLS. Medications that are moderate/strong inhibitors or inducers of 3A4 are contraindicated on this study, and may require removal from study if necessary to initiate these medications. See Appendix V for a list of these medications. See Section 5.6.3 for institution of azole anti-fungals. Alternative agents with weak or no CYP3A4 effects should be considered. Due to venetoclax being a substrate of P-glycoprotein, medications affecting P-glycoprotein are

also contraindicated (this medication list is also included in Appendix V). A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/. This website is continually revised and should be checked frequently for updates.

8.1.12 Nursing/Patient Implications

Instruct patients to take venetoclax tablets with a meal and water at approximately the same time each day. The tablets should be swallowed whole and not chewed, crushed, or broken. At least 8.5 cups of water (2 L) should be consumed every day starting 2 days before the first dose and throughout the ramp-up phase, especially the first day of each dose increase. Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment. If a patient misses a dose within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day. If a patient vomits following dosing, no additional dose should be taken that day and the next prescribed dose should be taken at the usual time.

8.2 Liposomal Vincristine (Marqibo) NSC 748728

NOTE: Liposomal Vincristine is no longer being manufactured.

8.2.1 Other Names

Marqibo, Vincristine sulfate liposome injection.

8.2.2 Classification

Antineoplastic agent, Vinca Alkaloid.

8.2.3 Mode of Action

Vincristine is a cell cycle specific agent that binds to tubulin, leading to microtubule depolymerization and cellular apoptosis. The liposomal formulation increases the half-life, allowing for enhanced activity.

8.2.4 Storage and Stability

Store intact kit (containing vincristine vial, sphingomyelin/cholesterol liposome vial, and sodium phosphate vial) refrigerated at 2 degrees C to 8 degrees C; do not freeze. Once prepared and diluted, liposomal vincristine is stable for no more than 12 hours at room temperature.

8.2.5 Dose Specifics

Arm A: 2.25mg/m^2 IV weekly starting Day 15

Arm B: 2.25mg/m^2 IV weekly starting Day 15

Arm C: 2.25mg/m^2 IV weekly starting Day 15

Arm D: 2.25mg/m^2 IV weekly starting Day 1

8.2.6 Preparation

Marqibo (vinCRIStine sulfate LIPOSOME injection) is vincristine encapsulated in sphingomyelin/cholesterol liposomes for intravenous

administration. Marqibo is prepared from the components in the Marqibo Kit. Liposomal vincristine takes approximately 60 to 90 minutes to prepare. The preparer should have dedicated uninterrupted time to prepare the medication due to the extensive monitoring of temperature and time required for the preparation.

Refer to the FDA-approved package insert for complete preparation information. Below is a list of items required by the pharmacy to prepare Marqibo:

- Marqibo Kit
- Water bath
- Calibrated thermometer (0°C to 100°C)
- Calibrated electronic timer
- Sterile venting needle or other suitable device equipped with a sterile 0.2 micron filter
- 1 mL or 3 mL sterile syringe with needle, and
- 5 mL sterile syringe with needle.

The manufacturer will provide the water bath, calibrated thermometer, and calibrated electronic timer to the medical facility at the initial order of Marqibo and will replace them every 2 years. All syringes and needles should be used from the preparing pharmacy's standard supply.

After preparation, each single-dose vial of Marqibo (vinCRIStine sulfate LIPOSOME injection) contains 5 mg/31 mL (0.16 mg/mL) vincristine sulfate

8.2.7 Route of Administration

Intravenous infusion over 1 hour

8.2.8 Incompatibilities

Do not use with in-line filters. Do not mix with other drugs.

8.2.9 Availability

Commercially available supply

8.2.10 Side Effects

Below are the most commonly reported adverse events related to vinCRIStine sulfate LIPOSOME injection. Please refer to the package insert for the comprehensive list of adverse events.

The most common adverse reactions (>30%) from previous clinical trials were:

- Constipation (57%)
- Nausea (52%)
- Pyrexia (43%)
- Fatigue (41%)
- Peripheral neuropathy (39%)
- Febrile neutropenia (38%)
- Diarrhea (37%)
- Anemia (34%)
- Decreased appetite (33%)
- Insomnia (32%)

The most common grade 3 or higher toxicities reported:

- Febrile Neutropenia (31%)
- Anemia (17%)
- Pneumonia (8%)
- Staphylococcal bacteremia (6%)
- Constipation (5%)
- Asthenia (5%)
- Respiratory failure (5%)
- Fatigue (12%)
- Abdominal pain (8%)
- Hypotension (6%)
- Cardiac arrest (6%)
- Musculoskeletal and connective tissue disorders (8%)
- Neutropenia (18%)
- Thrombocytopenia (17%)
- Septic shock (6%)
- Peripheral sensory and motor neuropathy (17%)
- Ileus (6%)
- Respiratory distress (6%)
- Pyrexia (15%)
- Pain (8%)
- Aspartate aminotransferase increased (7%)
- Mental status changes (4%)
- Renal and urinary disorders (7%)

8.2.11 Potential Interactions

Liposomal vincristine is metabolized primarily by CYP3A4. Medications that are moderate/strong inhibitors or inducers of 3A4 are contraindicated on this study, and will require removal of patient from study if necessary to initiate these medications. See Appendix V for a list of these medications. Alternative agents with weak or no CYP3A4 effects should be considered.

8.2.12 Nursing/Patient Implications

Liposomal vincristine is NOT to be given intrathecally, and could result in death.

NOTE: Marqibo (vinCRIStine sulfate LIPOSOME injection) has different dosage recommendations than vinCRIStine sulfate injection. Verify drug name and dose prior to preparation and administration to avoid overdosage.

8.2.13 References

Marqibo (vincristine liposomal) [prescribing information]. Rockford, IL: Talon Therapeutics Inc; April 2017.

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8.3 Vincristine Sulfate NSC 67574

8.3.1 Other names

Oncovin R, Vincasar PFS R, vincristine sulfate, VCR, leucocristine, LCR.

8.3.2 Classification

Vinca alkaloid (tubulin inhibitor).

8.3.3 Mode of Action

Vincristine binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and causing cessation of cellular mitosis.

8.3.4 Storage and Stability

Store refrigerated between 2°–8°C (36°–46°F). Discard unused solution. Protect from light. Store Upright.

Rev. Add11 8.3.5 Dose Specifics

For Cycle 1, 1.4 mg/m^2 (capped at 2 mg) IV on day 1 given weekly for 4 doses.. For Cycle 2, 1.4 mg/m2 (capped at 2 mg) IV on day 1 given every 4 weeks. Dose modifications are necessary in patients with hepatic insufficiency. Please refer to Section 5.5.3 for dose modification information.

Rev. Add11 8.3.6 Preparation

Please refer to institutional SOP or package insert for preparation and BUD (beyond use dating).

Rev. Add11 8.3.7 Administration

Please refer to institutional SOP or package insert for administration guidelines. Please note that this drug is a VESICANT and should ONLY be given by intravenous route. May be FATAL if given by other routes.

Rev. Add11 8.3.8 Compatibilities

This drug is compatible in NSS and D5W. Refer to institutional policies or package insert for VCR and compatible solutions.

8.3.9 Availability

Vincristine is commercially available as 1 mg (1mg/mL) single-use vial or 2 mg (2mg/2mL) single-use vial.

8.3.10 Side Effects

1. Hematologic: Leukopenia (mild and rare), thrombocytopenia (rare), anemia.
2. Dermatologic: Alopecia; skin and soft tissue damage if extravasated (the manufacturer recommends subcutaneous injection of hyaluronidase and application of heat to help disperse the drug); rash.
3. Gastrointestinal: Nausea, vomiting (rare); constipation (see neurological side effects); abdominal pain (cramps); anorexia; diarrhea. Fatal ascending paralysis follows intrathecal administration.
4. Hepatic: Elevations of SGOT and SGPT (mild and transient).
5. Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis); autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis); ataxia; myalgias; cortical blindness; headache; seizures.

6. Pulmonary: Bronchospasm (acute shortness of breath), more common when administered with mitomycin.
7. Ocular: Diplopia; ptosis; photophobia; cortical blindness (see neurologic); optic atrophy.
8. Other: Severe pain in the jaw, pharynx, bones, back and limbs following injection; syndrome of inappropriate antidiuretic hormone (SIADH); fever; pancreatitis (rare).

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8.3.11 Nursing Implications

1. Vesicant - Refer to extravasation protocol if inadvertent infiltration occurs. The manufacturer recommends local injection of hyaluranidase and warm compress to the area of leakage if extravasation occurs.
2. Monitor for neurotoxicities - numbness, tingling, ataxia, loss of deep tendon reflexes, etc.
3. Monitor for constipation and treat promptly. May require prophylactic stool softeners and/or laxatives.
4. Precautions must be taken to prevent inadvertent intrathecal administration. ISMP recommends preparing vincristine in a mini bag to ensure safety.

   NOTE: Please refer to the commercially-available package labeling for more information.

8.3.12 References

Byrd RA, Rohrbaugh TM, Raney RB, Norris DG. Transient cortical blindness secondary to vincristine therapy in childhood malignancies. Cancer 47:37-40, 1981.

Drug Package Insert

McRae MP, King JC. Compatibilities of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. Am J Hosp Pharm 33:1010-1013, 1976.

Chauncey TR, Shanel JL, Fox JH. Vincristine neurotoxicity. JAMA 254:507, 1985. ECOG 2/91

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9. Statistical Considerations

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9.1 Phase I

The primary objective of the phase I portion of this trial is to determine the maximum tolerated dose (MTD), safety and toxicity of venetoclax that can be administered in combination with liposomal vincristine during the phase II portion in patients with relapsed or refractory T-cell and B-cell ALL. The venetoclax dose cohorts examined are described as follows:

- Cohort 1 (Arm A): 20, 50, 100, 200 mg on Days 1, 2, 3, 4 and 400 mg on Days 5 – 70
- Cohort 2 (Arm B): 50, 100, 200, 400 mg on Days 1, 2, 3, 4 and 600 mg on Days 5 – 70
- Cohort 3 (Arm C): 100, 200, 400, 600 mg on Days 1, 2, 3, 4 and 800 mg on Days 5 – 70

Venetoclax will be first given to the patients based on an intra-patient dose escalation scheme (as described above) in a 2-week lead-in phase, then in combination with a fixed, standard dose of intravenous liposomal vincristine for 28 days. A bone marrow biopsy will be performed at day 42 +/- 2 days. All patients should proceed to Cycle 2 (28-day of combination therapy) unless they have progressive disease or they achieve CR or CRi and proceed to HSCT. A second bone marrow biopsy will be performed at day 70 +/- 2 days (the end of Cycle 2). Patients who achieve at least a stable disease response can remain on a 28-day cycle of combination therapy until disease progression or withdrawal from trial. At the discretion of the treating physician, a patient who achieves CR or CRi may proceed to HSCT at any time. In addition, patients who enter CR/CRi who develop side effects thought related to liposomal vincristine may continue on single agent venetoclax therapy at the discretion of treating physician after cycle 2.

9.1.1 Statistical Analysis Plan

The phase I portion of this study will use a standard 3+3 design according to the rules outlined below, with patients enrolled in cohorts of 3.

Number of Observed DLTs	Action
0/3	Escalate to the next dose cohort
1/3	Add 3 more patients at current dose cohort
> 1/3	Dose in previous cohort is MTD*
1/6	Escalate to the next dose cohort
≥ 2/6	Dose in previous cohort is MTD*

* Discontinue the trial if occurs at the initial dose level

Dose limiting toxicities (DLT) are defined in Section 5.1.4 of this protocol document. The table below summarizes the probabilities of dose escalation (that is, of 0/3 DLTs or of 1/3 + 0/3 DLTs) for a range of true DLT rates.

True DLT Rate	10%	20%	30%	40%	50%
Probably of Dose Escalation	91%	71%	49%	31%	17%

Upon completion of the trial, frequency of patients experiencing toxicities will be summarized by dose level, among patients who receive at least one dose of study drug. The DLTs will also be reviewed and tabulated by dose level, among patients evaluable for DLTs. Toxicities will be assessed and graded according to the CTCAE version 5.0.

9.1.2 Sample Size

A minimum of 3 patients and maximum of 18 patients will be treated in the phase I portion of this trial.

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9.1.3 Projected Accrual and Duration

The accrual rate is expected to be 38 patients per year. Consequently, the accrual of 3 patients per cohort is projected to take approximately 1 month. Given the 3 patients in a cohort need to be followed for 42 days and toxicity data need to be reviewed before the next cohort can be opened, this evaluation can be up to 2 months. It is, thus, expected that the accrual together with evaluation for each cohort of 3 patients will be up to 3 months. With the maximum of 18 patients enrolled into the phase I part, the duration of the phase I part might take up to 18 months

9.1.4 Monitoring Plan

While the phase I study is ongoing, the study team will meet weekly via teleconference to review and discuss DLTs and the overall trial conduct.

9.2 Phase II

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The phase II portion of this trial will be a single arm, open-label trial of the combination of the venetoclax and liposomal vincristine or vincristine sulfate.

As conventional vincristine sulfate will be substituted for liposomal vincristine due to discontinuation of the latter, the grades 3-4 motor and sensory neuropathy will be closely monitored at each interim analysis for patients who starts protocol treatment with conventional vincristine sulfate. Frequency and percentage will be used to report combined grade 3-4 motor and sensory neuropathy events. A 90% binomial confidence interval will be estimated for these events combined as well. It is expected that the target combined rate would be 35% If the lower limit of the 90% confidence interval is above the expected rate of 35% the results will be discussed with the study team and NCI for accrual suspension. Should this threshold be reached, subsequent amendment of the protocol will be considered to decrease the dose of venetoclax.

Patients will be classified in phase II according to ALL phenotype (B-cell vs T-cell) tested by the site. The primary endpoint of this phase II portion is CR+CRi rate (with respect to the best response) by the end of Cycle 3. Secondary endpoints include progression-free survival, overall survival, and toxicity. Correlative markers are also going to be explored for their association with response; currently, studies of genetic signature, intracellular BCL-2 expression, BH3 profiling and immunophenotype of ALL are planned.

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9.2.1 Statistical Analysis Plan

As the dose schedule is different between Phase I and Phase II, all analyses (except for the toxicity analysis) on Phase II will be performed on enrolled, eligible patients who started the phase II combination therapy (i.e., excluding those to be treated at the MTD on the phase I portion of the trial) and had phenotype (B-cell vs T-cell) information available. All patients starting phase II treatment will be included in the toxicity analysis regardless of eligibility.

A 90% confidence interval will be computed for the CR+CRi rate (the primary endpoint, defined in Section 6) achieved by the end of Cycle 3 for each patient cohort (B-cell or T-cell).

Progression-free survival (PFS) is defined as the time from study registration (to step 1) to documented disease progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date of last disease evaluation showing they are progression-free. Overall survival (OS) is defined as the time from study registration (to step 1) to death from any cause. Patients who have not experienced death at the time of final analysis will be censored at the date of last contact. For each patient cohort (B-cell or T-cell), PFS and OS distributions will be estimated using the Kaplan-Meier method, and the median OS and PFS along with its corresponding 90% confidence interval will be reported.

Toxicity incidences assessed and graded according to the CTCAE version 5.0, will be tabulated by patient cohort.

In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned because we do not anticipate an excess of missing data.

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9.2.2 Sample Size

For each stratum (B-cell or T-cell ALL, tested by the sites), a sample size of 25 eligible patients achieves a 87% power to detect a difference of 25% between historical complete response rate of liposomal vincristine alone by 90 days (20%, O'Brien et al. (2013)) and the complete response rate in our phase II portion receiving the combination treatment by the end of Cycle 3 (45%), using a one-sided binomial test with the type I error of 5%. The null hypothesis will be rejected if >/= 9 patients in either stratum are found to have achieved a CR or a CRi by the end of Cycle 3.

Assuming a total of 10% of patients will be ineligible or never start the combination treatment of the phase II portion, the number of patients needed for the phase II portion is inflated to 28 patients per stratum, making the total accrual goal of the phase II study 56 patients.

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9.2.3 Projected Accrual and Duration

With 28 patients planned for each cohort and a yearly accrual of 24 patients for the B-cell and 8 patients for the T-cell ALL, it is projected

that the phase II accrual duration takes approximately 14 months and 42 months, respectively, for the B-cell and the T-cell cohorts.

9.2.4 Monitoring Plan

9.2.4.1 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.3.

9.2.5 Correlative Studies

Correlative markers are going to be explored for their association with efficacy measures; currently, studies of intracellular BCL-2 expression, immunophenotype of ALL, and genetic signature are planned. Correlative analyses will be performed on all patients included in the phase II efficacy analysis, and have the lab data available.

Intracellular BCL-2 expression by flow cytometry will be dichotomized into two groups by the median (low vs. high). Univariate Cox proportional hazards (PH) models will be used to evaluate the association of the BCL-2 expression at baseline and immunophenotype (B-cell and T-cell ALL) with OS and PFS, separately. Logistic regression models will be used to investigate the association of the BCL-2 expression at baseline and immunophenotype with response (CR/CRi/PR vs. others by the end of Cycle 3). Multivariable Cox PH modelling and logistic regression modelling will also be used to adjust for the effect of covariates that are possibly associated with these efficacy outcomes.

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As to the association of genetic signature and response to the combination therapy, data analysis will be performed by the Ferrando Lab (as described in Section 11.2). For BH3 profiling, the statistical analysis will be performed by a team to be determined, and the analysis plan (as described in Section 11.3) is subject to change depending on the methodology used by the team.

NOTE: An amendment for any correlative science studies to be performed on biological specimens will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked bone marrow or peripheral blood specimens will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Specimens for testing will not be released until the appropriate NCI approvals have been obtained.

9.2.6 Gender and Ethnicity

Both men and women of all races and ethnic groups are eligible for this study. The anticipated accrual in subgroups defined by gender, race, and ethnicity is:

Racial Categories	Ethnic Categories				Total
	Hispanic or Latino		Non Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	1	1
Black or African American	1	0	2	2	5
White	3	4	19	23	49
Total	4	4	22	26	56

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

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10. Specimen Submissions

PHASE I ONLY: Bone marrow aspirates and/or peripheral blood must be submitted at preregistration for the centralized review described in Section 11.1.

Bone marrow aspirates and peripheral blood are to be submitted from consenting patients for the defined laboratory research studies described in Section 11.2.

Peripheral blood and buccal rinse are to be submitted from consenting patients for future undefined research studies.

It is required that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS) (see Section 10.3). An STS shipping manifest form is to be included with every submission.

All specimens must be clearly labeled with the ECOG-ACRIN protocol number (EA9152), ECOG-ACRIN patient sequence number, patient's initials, date of collection and specimen type.

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10.1 Submissions to the ECOG-ACRIN Leukemia Laboratory at MD Anderson Cancer Center

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10.1.1 Specimen Preparation Guidelines

The following are to be submitted:

1. Heparinized bone marrow aspirate (the laboratory will accept any amount as long as it represents a first pull). Ideally, 2-3mL of aspirate from a separate aspiration site should be submitted.

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   For patients with an inaspirable bone marrow ('dry tap'), or if a bone marrow has been done previously and the patient refuses to have another aspiration done, call the EA Leukemia Laboratory at (713) 745 -7846 or (713) 563-1943 to discuss the case and the possibility for submitting peripheral blood only. Be prepared to report the WBC count and the blast count in the peripheral blood at the time of the call. Patients without bone marrow or circulating disease, especially in the case of lymphoblastic lymphoma, may submit peripheral blood after discussion with the study chair.

   - Submit at baseline and relapse from patients who answer "Yes" to "I agree to have my samples collected and I agree that my samples and related information may be used for laboratory studies."

2. Heparinized or EDTA peripheral blood (four (4) green or purple top tubes, 30-40mL).
   - Submit at baseline and relapse from patients who answer "Yes" to "I agree to have my samples collected and I agree that my samples and related information may be used for laboratory studies."

3. Two (2) red top tubes of peripheral blood (15-20mL).
   - Submit at baseline from patients who answer 'Yes' to "I agree to provide additional samples for research."

4. MANDATORY AT ALL TIME POINTS: A copy of the institutional pathology report on the bone marrow must be submitted via Medidata Rave. The pathology report must include cytogenetic results and any results from fluorescence-in-situ (FISH) hybridization and/or molecular studies done at the submitting institution.

   Please fax to the EA Leukemia Laboratory at (713) 563-6506.

5. Buccal Cell Specimens
   - Preferably, Scope, a commercial brand mouthwash, or normal saline in a small sealed bottle can be given to the patient for a mouthwash.
   - Aseptic techniques must be used to collect buccal cells from patients on site and buccal cells must not be contaminated with cells from any other source. Patients should not brush their teeth or consume food within an hour prior to buccal cell collection.
   - If mouthwash (e.g., Scope) or normal saline is used, the patient should pour approximately 10cc of mouthwash or saline into his/her mouth and vigorously swish it against the cheeks for 10 seconds and deliver the solution into a labeled 50mL sterile polypropylene test tube or a sterile urine cup. Among mouthwashes, the Scope brand fares best in collecting buccal cells for the preparation of high-quality DNA in high yield.
   - It is important that buccal cells do not dry out during shipping. Institutions are advised to seal the container containing the buccal cells tightly. Ship containers on cool packs, together with the patient's peripheral blood and bone marrow specimens.
   - Submit from patients who answer "Yes" to "I agree to provide additional samples for research."

     NOTE: Buccal rinse is strongly encouraged to be collected prior to the start of treatment, but can be collected at any other time during the study, if necessary.

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10.1.2 Shipping Procedures

The EA Leukemia Laboratory must be notified by telephone or email the day of shipment <u>for ALL shipments, including follow up submissions.</u>

The laboratory must be aware that specimens are forthcoming as immediate processing is essential to the integrity of the specimens.

Telephone: (713)745-7846 or (713) 563-1943

For questions regarding the shipment, Dr. Loghavi can be reached via email (sloghavi@mdanderson.org) or by calling her cell phone (310-990-3703).

Heparinized bone marrow and peripheral blood or EDTA specimens, coagulated blood in red top tubes and buccal cells must be sent fresh (on the day of collection) on **cool packs** (do not freeze and do not use ice cubes)Monday –Thursday by overnight courier (preferably Federal Express) to arrive within 24 hours.

Friday shipments are ill advised, similarly shipping before holidays is often problematic, due to closures or courier delivery problems. The laboratory is closed Saturday, Sunday and holidays.

Ship using the CBPF's FedEx account using the FedEx on-line ship manager

Ship to:

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ECOG-ACRIN Leukemia Bank
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Boulevard
Houston, TX 77030
Phone: Toll Free (713)-745-7846 or (713) 563-1943
Fax: (713) 563-6506
Email: UM-EALB@mdanderson.org

An STS shipping manifest form must be generated and shipped with all specimen submissions.

Please enter all information into the STS, including time and date of specimen collection and peripheral blood WBC count and blast count.

10.2 Use of Specimens in Research

Bone marrow and peripheral blood specimens will be distributed to Dr. Adolfo Ferrando at Columbia University. See Section 11 for the description of the laboratory research studies to be performed.

Specimens submitted will be processed to maximize their utility for current and future research projects. DNA, RNA, serum, and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

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Specimens from patients who consented to allow their specimens to be used for future approved research studies will be retained in the ECOG-ACRIN Leukemia Bank (LB). Specimens will be de – identified prior to distribution for any approved research studies.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study.

10.3 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Please note that the STS software creates pop-up windows, you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.4 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Leukemia Correlative Studies

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11.1 PHASE I ONLY: Immunophenotype

Immunophenotyping has become an essential part of the diagnostic work-up of all leukemia patients. In fact, the diagnosis of leukemia without immunophenotypic characterization is no longer acceptable. ECOG-ACRIN has, therefore, developed a model system for antigenic data collection that requests specimens from all patients entered on ECOG-ACRIN leukemia treatment trials be studied by the ECOG-ACRIN Leukemia Laboratory at MD Anderson Cancer Center. In addition to establishing the leukemia subtype, this centralized testing and data collection has allowed that research questions of clinical relevance to be applied to a growing database (e.g., definition of prognostically significant antigen expression levels to eventually yield specific treatment subcategories). Depending on the study protocol and tissue availability, anti-coagulated (heparin, EDTA, ACD) peripheral blood or bone marrow or both are to be submitted to the EA Leukemia Laboratory.

In addition to the study of abnormal hematopoietic cells, the focus of research on circulating serum factors in patients with leukemia or myelodysplasia has increased. Two tubes of coagulated peripheral blood (red top tubes) are requested for future research studies that may aim at identifying pathogenetic, diagnostic, or prognostic factors associated with leukemia or myelodysplasia.

Serum and cells from peripheral blood or bone marrow from patients entered on studies of hematologic malignancies are stored in ECOG-ACRIN's Leukemia Laboratory for EA9152 embedded and future laboratory studies. The bank provides the scientific community a source of leukemia specimens that are collected, processed, and maintained following quality control and quality assurance guidelines. An amendment or proposal for any correlative science studies to be performed on biological specimens will be submitted to CTEP for review according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked specimens will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Specimens will not be released until the appropriate NCI approvals are in place.

11.2 Molecular and Transcriptional Analysis of Adult ALL and Prognosis of Response to Combination Therapy – Adolfo Ferrando, MD, PhD

Gene expression profiling (GEP) and the analysis of driver mutations has helped to sub-classify malignancies, including adult ALL, as well as provide valuable information in regards to prognosis. The Ferrando group has previously identified prognostic expression patterns and mutations of interest in previous studies across various ALL subtypes.[52,53] A transcriptional signature prognostic of response to therapy will be investigated using RNAseq gene expression profiling data from diagnostic specimens. Towards this goal, we will divide the cohort into a test set composed of 2/3 of the specimens and a validation set consisting of the remaining 1/3 of the cases. Genes significantly associated with the strongest response to therapy in the test set will be identified by t-test with correction for multiple comparisons. Top scoring genes will be further selected based on their sensitivity and specificity for the prognosis of clinical response using a leave-one-out cross-validation approach. Finally, the selected panel of genes prognostic of response to therapy identified in the test set will be evaluated in the validation set

of specimens using a K-mean clustering approach. Matched RNAseq data from specimens obtained at diagnosis and at the time of relapse will be analyzed to explore the underlying mechanisms mediating disease progression. Specifically supervised analysis using paired t-test with correction for multiple comparisons will be used to identify differentially expressed genes at diagnosis and relapse. Functional characterization of these signatures will be addressed via functional annotation using DAVID and via GSEA using the MsigDB collection of annotated gene-sets.

11.3 BH3 Profiling of Adult Lymphoblastic Leukemias Relapsed After or Refractory to Therapy

With the intent of BH3 profiling (as described in Section 1.3.1), the study will bank specimens of bone marrow at the time of study entrance and relapse.

As described above, the intrinsic apoptotic pathway is governed by the BCL-2 superfamily of proteins, which can be subdivided based on their function into four groups: activators, sensitizers, repressors and effectors of apoptosis. The repressor class, of which BCL-2, BCL-Xl, and MCL-1 among others, are members, is responsible for preventing cells from undergoing apoptosis in opposition to upstream, pro-apoptotic signaling. Using the unique binding patterns of various activator and sensitizer BH3 peptides, the dependency of a particular cell line on a repressor can be inferred. For example, it is established that the sensitizer protein NOXA-A binds to and inhibits only MCL-1. Therefore, if a cell line undergoes apoptosis in the presence of additional, exogenous NOXA-A, that cell line thought to be MCL-1 dependent for its survival.

BH3 profiling is the term used to describe the investigation of the relative state, also called “priming,” of a particular cell line in regards to its closeness to undergoing apoptosis as well as on which anti-apoptotic protein or proteins a sample is dependent. In this way, a sample’s BH3 profile can also predict response to BCL-2 inhibitors among other chemotherapeutic agents.

One method of BH3 profiling determines the degree of priming by measuring the change in mitochondrial outer membrane polarization in response to variety of conditions that can include synthetic BH3 proteins or chemotherapy. Frozen patient samples before treatment and after relapse are thawed, resuspended, and viability determined. Viable cells are then made permeable with digitonin, which allows for uniform exposure to various exogenous BH3 peptides, and are subsequently treated with JC-1. JC-1 stains mitochondria and fluoresces proportionally to the degree of polarization of mitochondria, which is then analyzed and reported by FACS as a median fluorescence intensity (MFI).

The MFI of positive controls, which uniformly depolarize mitochondria, and negative control peptides, which result in no additional depolarization, are compared to the MFI of the sample after the addition of synthetic BH3 sensitizer proteins. The comparison of these is described by the following formula as % primed:

$$\% \text{ priming} = (1-(MFI_{sample} - MFI_{positive})/(MFI_{negative} - MFI_{positive})) \times 100$$

Percent priming for responders (CR, CRi and PR) versus non-responders, as defined by response criteria in Section 6.1-6.4 will be calculated for samples after exposure to a variety of BH3 proteins, including NOXA-A, HRK, BIM, BID. Univariate comparisons will be made utilizing Mann-Whitney testing. OS and

PFS will be tested for correlation with % priming by log-rank test for trend. In addition, a receiver operation characteristic curve to test whether BH3 profiling can predict CR to the regimen will be performed.

NOTE: An amendment for any BH3 profiling to be performed on biological specimens will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Specimens for testing will not be released until the appropriate NCI approvals have been obtained.

11.4 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the Investigator.

12. Electronic Data Capture

Please refer to the **EA9152** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

12.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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A Phase Ib/II Study of Venetoclax (ABT-199) in Combination with Liposomal Vincristine or Vincristine Sulfate in Patients with Relapsed or Refractory T-cell or B-cell Acute Lymphoblastic Leukemia

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Phase Ib/II Study of Venetoclax (ABT-199) in Combination with Liposomal Vincristine or Vincristine Sulfate in Patients with Relapsed or Refractory T-cell or B-cell Acute Lymphoblastic Leukemia

Appendix II

Patient Pill Diary - Venetoclax

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. Venetoclax tablets should be taken with a meal and water at approximately the same time each day. The tablets should be swallowed whole and not chewed, crushed, or broken.
3. At least 8.5 cups of water (2 L) should be consumed every day starting 2 days before the first dose and throughout the treatment, especially the first day of each dose increase.
4. You should avoid grapefruit products, Seville oranges, and starfruit during treatment.
5. If you miss a dose within 8 hours of the time it is usually taken, you should take the missed dose as soon as possible and resume the normal daily dosing schedule. If you miss a dose by more than 8 hours, you should not take the missed dose and should resume the usual dosing schedule the next day.
6. If you vomit after taking the pill, you should not take another pill be that day. The next prescribed dose should be taken at the usual time
7. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

Rev. Add4

Patient Pill Calendar

Rev. Add11 This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. Note the times and the number of tablets that you take each day. If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

DAY	Date Month	Day	Year	Time capsules taken	Number of capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						

DAY	Date Month	Day	Year	Time capsules taken	Number of capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
28						

Rev. Add4 Patient Signature: _____ Date: _____

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Cycle 2+: Arm _____ - Dose Level _____ (_____ mg)

DAY	Date Month	Day	Year	Time capsules taken	Number of capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1						
2						
3						
4						
5						
6						
7						
8						
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10						
11						
12						
13						
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17						
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19						
20						
21						
22						
23						
24						

DAY	Date Month	Day	Year	Time capsules taken	Number of capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
25						
26						
27						
28						

Rev. Add4 Patient Signature: _____ Date: _____

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Appendix III

ECOG Performance Status

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

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Rev. Add7

Appendix IV

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on venetoclax, or within 28 days of the female patient's last dose of venetoclax must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERs)

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

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERs.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- *It is recommended the female patient be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERs report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Rev. Add3

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

It must be reported via CTEP-AERs as Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A newborn death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational/IND exempt agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERs AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to venetoclax must also be reported via CTEP-AERs.

It must be reported via CTEP-AERs as Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix V

CYP3A Inhibitors and Inducers and P-Glycoprotein (PGP) Medications

The medications or substances that are listed in the table below are **strong or moderate inhibitors/inducers** of CYP3A4.

Strong and moderate inhibitors of CYP3A4 or PGP, and are contraindicated during this protocol.

Excluded
Anticancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives prior to first dose and throughout venetoclax administration **Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent:** Excluded 30 days prior to first dose and throughout venetoclax administration
Excluded during ramp-up phase and Cautionary at the Cohort Designated Dose:
Strong and Moderate CYP3A inhibitors Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and reduce the venetoclax dose by 50% for moderate inhibitors and at least 75% for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the initial maintenance/target dose. **Strong and Moderate CYP3A inducers** Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications at the cohort designated dose, use with caution and contact AbbVie medical monitor for guidance. **Strong CYP3A inducers -** avasimibe,carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort **Moderate CYP3A inducers** - bosentan, efavirenz, etravirine, modafinil, nafcillin **Strong CYP3A inhibitors -** boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, paritaprevir/ritonavir combinations, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole **Moderate CYP3A inhibitors -** amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem[1], erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil
Cautionary
Warfarin** **P-gp substrates** Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor **BCRP inhibitors**

Geftinib*

Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruits.

* These are anticancer agents; consult contact AbbVie medical monitor before use.

** Closely monitor the international normalized ratio (INR).

[1] Moderate CYP3A inhibitor per venetoclax FDA USPI.

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

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

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

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

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

Venetoclax (Venclaxta) must be used very carefully with other medicines that use certain liver enzymes. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A4.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- You should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study because it contains ingredients that could interact with your study drug.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

  _____ and he or she can be contacted at

  _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **venetoclax (Venclaxta)**. This clinical trial is sponsored by the NCI. **Venetoclax** may interact with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Venetoclax interacts with a specific liver enzyme called CYP3A4, and must be used very carefully with other medicines that interact with this enzyme.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***strong inducers/inhibitors or substrates of CYP3A4.***
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

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Rev. Add2

Appendix VI

EA9152 Venetoclax Study Drug Request Form and EA9152 Investigational Product Destruction Record

Downloading the EA9152 Venetoclax Study Drug Request Form and EA9152 Investigational Product Destruction Record: These forms are available for download from the EA9152 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA9152
- Click on Documents tab, select the Pharmacy tab, and download and complete the forms provided.