Azacitidine and Venetoclax (ABT-199) as Induction Therapy with Venetoclax Maintenance in Previously Untreated Elderly Patients with Acute Myeloid Leukemia

Study Sponsor / Principal Investigator	Daniel A. Pollyea, MD, MS University of Colorado Cancer Center 1665 Aurora Court Mail Stop F754 Aurora, CO 80045 Phone: 720-848-8084 Fax: 720-848-1786 Daniel.pollyea@cuanschutz.edu
Study Location	University of Colorado Cancer Center
Protocol / COMIRB#	17-7821
Version Date	September 15, 2025
Indication to be studied	Previously untreated elderly patients with acute myeloid leukemia (AML)
Study Agents:	1. Venetoclax (ABT-199, Abbvie), is not currently FDA approved for AML. 2. Azacitidine (Vidaza™, Celgene) is not currently approved for AML, but it is routinely used as the standard of care treatment.

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Daniel A. Pollyea, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Daniel A. Pollyea, MD
Print/Type Name

Signature

Date

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LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
IIT	Investigator-Initiated Trial
LSC	Leukemia stem cell
AML	Acute myeloid leukemia
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
TLS	Tumor lysis syndrome
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
MLFS	Morphologic leukemia free state
AE	Adverse event
SAE	Serious adverse event
UGT	UDP-glucuronosyltransferases
OATP	Organic anion transporting polypeptide
BCRP	Breast cancer resistance protein
CYP	Cytochrome P
RBC	Red blood cell
AUC	Area under the curve
CLL	Chronic lymphocytic leukemia
NHL	Non-Hodgkin lymphoma
eCRF	Electronic case report form
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
LDH	Lactate dehydrogenase
PT	Prothrombin time
INR	International normalized ratio
PTT	Partial thromboplastin time

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1 PROTOCOL SYNOPSIS

PROTOCOL TITLE: Azacitidine and Venetoclax (ABT-199) as Induction Therapy with Venetoclax Maintenance in Previously Untreated Elderly Patients with Acute Myeloid Leukemia
INDICATION: Previously untreated elderly patients with acute myeloid leukemia (AML)
STUDY PHASE: II
BACKGROUND AND RATIONALE: The majority of patients with AML are elderly, but standard approaches to this disease involve treatment with intensive chemotherapy which is prohibitively toxic with sub-optimal response rates. Less toxic and more effective therapies are needed. Venetoclax is a specific BCL-2 inhibitor that has been highly effective in a large-scale phase 2 study when paired with the hypomethylator azacitidine and given continuously in this population. However, both of these therapies result in cytopenias, and the degree and severity of this complication can be limiting for patients who are otherwise deriving anti-leukemia benefit. Therefore, a clinical trial using this combination that is designed to allow for a deep response followed by a more tolerable maintenance strategy, guided by the presence or absence of minimal residual disease, is proposed.
STUDY OBJECTIVES: **Primary:** To determine the remission duration experienced by elderly previously untreated AML patients with azacitidine plus venetoclax followed by venetoclax alone as a maintenance therapy for patients who achieve a minimal residual disease (MRD) negative remission. **Secondary:** • To determine the rate of MRD negative composite responses (includes complete remission [CR], complete remission with incomplete count recovery [CRi], and morphologic leukemia free state [MLFS]) with azacitidine plus venetoclax • To determine the median time to achieve a MRD negative composite response
STUDY DESIGN: This is an open label, Phase 2 study for elderly, previously untreated patients with AML using azacitidine with venetoclax as “induction” therapy followed by venetoclax maintenance in those patients who achieve a MRD negative response to induction. After consent and screening, patients will be admitted to the hospital for dose escalation of venetoclax. After dose escalation has completed patients may discharge and continue management in the outpatient setting if appropriate. On day 1 of cycle 1, azacitidine 75 mg/m^2 SC or IV will be given, and will continue for 7 days.

Starting on day 1 of cycle 1, venetoclax will be escalated to a target dose of 600 mg. This will involve administration of 100 mg on day 1, 200 mg on day 2, 400 mg on day 3 and 600 mg on day 4. Subsequently, patients will take venetoclax 600 mg daily.

On cycle 1 day 8, a bone marrow biopsy will be performed.

On cycle 1 day 28, a bone marrow biopsy will be performed to determine response status. This will include an assessment of MRD, with an ability to quantify and detect disease to a level of at least 0.1%.[1,2]

Patients who do not achieve a MRD negative composite response after the first cycle will repeat the cycle, with both azacitidine and 600 mg venetoclax given on day 1. A bone marrow biopsy will occur after cycle 2. If there is not a MRD negative composite response, patients will receive a third cycle, identical to the second. A bone marrow biopsy will be performed after the third cycle. If there is not a MRD negative composite response after the third cycle, patients will continue with azacitidine and venetoclax, now given at 400 mg daily, starting on day 1 of each cycle, with bone marrow biopsies after each odd-numbered cycle until they achieve a MRD negative composite response, progress or experience unacceptable toxicity. If patients achieve a CR/CRi/MLFS that remains MRD positive by cycle 9, they will have a bone marrow biopsy after cycle 12 and then every 6 cyclesthereafter.

Once patients achieve a MRD negative composite response, azacitidine will be discontinued and venetoclax decreased to 400 mg daily, defined as “maintenance”. Patients will undergo bone marrow biopsies every three cycles for the first year, and every six cycles thereafter, with MRD assessments performed with every biopsy.

STUDY ENDPOINTS

Primary: Remission duration

Secondary:

- Response rate, with responses defined as CR, CRi and MLFS, and the incidence of MRD-negative responses, with induction therapy
- Median time to achieve MRD negative composite response
-

STUDY DURATION: 3-4 years	**TOTAL SAMPLE SIZE:** 42

2 SCHEDULE OF STUDY ASSESSMENTS[1]

Procedures	Screen[2]	Cycle 1 "Induction"					Induction Cycles 2+		Maintenance Cycles		End of Treatment	Safety Follow Up[3]
		Day 1	Days 2 to 4	Days 5 to 7	Day 8	Day 28	Day 1	Day 28	Day 1	Day 28		
Allowable Window	28 days				+/-1 days	+/-3 days	+/-7 days	+/-3 days	+/-7 days	+/-3 days	+/-14 days	+/-10 days
Informed Consent	X											
History	X											
Physical Exam	X	X			X	X	X		X		X	X
Vital Signs[4]	X	X	X	X	X	X	X		X		X	X
ECOG PS	X	X				X	X		X		X	
Cytogenetics	X					X		X[5]		X[6]	X	
MRD	X					X		X[6]		X[6]	X	
AE&Con Meds	X	X	X	X	X	X	X		X		X	X[6]
12-lead EKG[7]	X											
TLS Labs[8]		X	X									
Hematology/Chemistry	X[9]	X	X	X		X	X		X		X	
Azacitidine		X	X	X			X[10]					
Venetoclax		X	X	X	X	X	X		X			
BM aspirate and biopsy	X				X[11]	X		X[12]		X[13]	X[15]	
Calendar & Diary-Dispense/Collect		X				X	X		X		X	

[1] For detailed description of all elements please see section 5.10
[2] Screening assessments must occur within 28 days of cycle 1 day 1 (unless historical record)
[3] A separate safety visit does not need to be performed for subjects with a final visit ≥30 days after discontinuation of study drug
[4] Includes weight, temperature, blood pressure, pulse, respiratory rate and, if needed, oxygen saturation. All methods of measurement and practices will be per institutional practice
[5] Occurs with each bone marrow biopsy
[6] Only adverse events need to be followed through safety follow up (until 30 days after the patient's last study treatment), con med collection to end at EOT
[7] A single 12-lead resting EKG will be obtained at screening, and as needed
[8] Within 4 hours prior to the venetoclax dose and again 6 and 12 hours after the dose (+/- 2 hours)
[9] Coagulation testing only occurs at screening
[10] Administer azacitidine on days 1-7
[11] Only Aspirate required; can be performed on D7 after final dose of azacitidine
[12] Will occur after cycle 2 and if needed cycle 3. In the absence of a MRD negative response biopsies will occur at the investigator's discretion after cycle 3. Biopsies will be mandated after each odd # cycle until cycle 9. After this, they may be performed after every 3-6 cycles at the investigator's discretion.
[13] Will occur every 3 cycles for the 1st year, then every 6 cycles, or at investigator's discretion
[15] If aspirate & biopsy with cytogenetics and MRD occurred within 14 days of EOT visit, procedure is not required at EOT

3 INTRODUCTION

3.1 Background and Rationale

Acute myeloid leukemia (AML) is the most common acute leukemia in adults,[3] afflicting about 20,000 patients and causing over 10,000 deaths in the United States annually.[4] The standard of care for newly diagnosed patients for over the last 40 years is for them to receive intensive chemotherapy with infusional cytarabine and intermittent dosing of an anthracyline[5]. Depending on their risk profiles, some patients who achieve a remission can be cured with an allogeneic stem cell transplantation and others with more chemotherapy, but the vast majority of patients relapse and die from their disease.[6]

Elderly patients (>60 years) have extremely poor outcomes, with almost no patients in this group experiencing long-term meaningful survival.[7,8] This is due to both biological disease related features that make them more resistant to standard chemotherapy approaches, and to increased comorbidities that increase treatment-related mortality.[9] There are no FDA approved agents specific to this population; however, these patients constitute the majority of those with AML, as the median age at diagnosis is in the seventh to eighth decades of life.[9] More effective and more tolerable therapies are urgently needed for this population.

Azacitidine (Vidaza™, Celgene) is a pyrimidine nucleoside analog of cytidine. It incorporates into DNA and RNA and binds to DNA methyltransferase enzymes, preventing the methylation of cytosine residues at CpG dinucleotides and resultant transcription of genes with heavily methylated promoter regions.[10] In patients with myelodysplastic syndrome (MDS) and AML, treatment with azacitidine decreases the methylation of tumor suppressor gene promoters, which correlates with clinical outcomes.[11] Furthermore, in AML patients who attain a clinical remission, methylation levels correlate with relapse risk and are inversely related to relapse-free survival.[12] In older patients with AML who were thought to be poor risk candidates for induction chemotherapy, the use of single-agent azacitidine had an overall response rate of 60%, a CR rate of 20%, and in patients who responded, a median survival of over 15 months.[13] Based on this data, although not approved for AML, it has become the de facto standard of care treatment for elderly patients with AML.

Venetoclax (ABT-199, Abbvie) is a potent, selective and orally bioavailable small molecule inhibitor of BCL-2 that binds with > 1,000-fold higher affinity to BCL-2 (Ki < 0.010 nM) than other apoptotic pathway proteins BCL-XL (Ki = 48 nm) or MCL-1 (Ki > 444 nM).[14] Leukemia stem cells (LSCs) overexpress BCL-2,[15] and BCL-2 overexpression has been associated with

worse outcomes in AML[16,1716,1716,17.16,17] Pre-clinical studies using cell lines and primary specimens showed sensitivity to venetoclax,[18] and a single-agent study in patients with relapsed and refractory disease displayed efficacy with an acceptable toxicity profile.[19]

When used in combination with a hypomethylator (azacitidine or decitabine) or with low-dose cytarabine in older patients unfit for standard induction chemotherapy who had never before been treated, results were promising. The regimen was well tolerated, and remission rates approached 80% with durable responses.[20] One potential explanation for the improvement in efficacy when comparing these two clinical trials is that the venetoclax synergizes with the backbone therapy. MCL-1 can result in resistance to BCL-2 inhibition, and cytarabine and azacitidine have shown the ability to down-regulate MCL-1[21,22]. In support of this concept, pre-clinical studies using a less selective BCL-2 inhibitor with azacitidine resulted in synergistic cell killing and the prevention of engraftment in an immunocompromised mouse model. An alternative explanation for the improvement in outcomes in the combination study compared to the single agent study may be due more to the setting in which patients were treated. LSCs become significantly more abundant and heterogeneous in the relapsed setting;[23] therefore, one might expect a LSC-directed therapy to have better efficacy in the up-front treatment setting compared to patients with relapsed disease.[24] The improved outcomes in the combination study may have less to do with the combination and more to do with the fact that venetoclax is being given to patients with a relatively homogenous LSC population that can be effectively targeted.

As of March 9, 2016, 45 patients 65 or older with newly diagnosed AML who were not eligible to receive standard induction therapy were enrolled into the escalation stage of the Phase 1b study (M14-358) of venetoclax in combination with a hypomethylator. Three dose levels were administered, 400, 800 and 1200 mg. Venetoclax was administered daily during continuous 28-day cycles in combination with decitabine or azacitidine, and preliminary safety and efficacy data have been reported.[20] The most common adverse events (AEs) for all subjects were nausea (53.3%), diarrhea (44.4%), febrile neutropenia (40.0%), neutropenia (31.1%), thrombocytopenia (28.9%), cough (28.9%), fatigue (28.9%), peripheral edema (26.7%), and hypokalemia (26.7%). The majority of patients (91.1%) had grade 3 or greater events; the most common was febrile neutropenia (40%). Serious adverse events (SAEs) occurred in 60% of patients, including febrile neutropenia (24.4%), atrial fibrillation, abdominal pain, non-cardiac chest pain, pyrexia, pneumonia, sepsis and bone pain (4.4% each, each event occurring in a single patient).

This was widely regarded as an acceptable safety profile in this population. However, as noted above, hematological toxicity was not insignificant. Venetoclax can result in bone marrow suppression; in heavily pre-treated patients with chronic lymphocytic leukemia (CLL), the grade 3/4 incidence of neutropenia was 40-50%, but lower in patients with non-Hodgkin lymphoma who had fewer prior therapies and higher doses of venetoclax.[25] Fewer patients experienced grade 3/4 thrombocytopenia and anemia (12% for both)[26]. With single-agent use of venetoclax in relapsed and refractory AML patients, 31% experienced febrile neutropenia. Azacitidine has overlapping toxicity when it comes to myelosuppression; in a study of elderly AML patients who received azacitidine, 28% had febrile neutropenia, 26.3% had grade 3/4 neutropenia, 23.7% had grade 3/4 thrombocytopenia and 15.7% had grade 3/4 anemia.[27]

Patients enrolled in the hypomethylator plus venetoclax study were noted to have rapid responses, with most remissions occurring within the first two cycles of therapy. In addition, there were many deep remissions noted, either by molecular analysis or the clearance of a cytogenetic abnormality. However, patients receiving this treatment continue therapy indefinitely with sequential cycles even after achieving a remission, in the hopes that continuous therapy will prolong the remission duration of a regimen not thought to be curative. Given the hematological toxicity of continued therapy, and the potential for increased complications, costs and negative impact on quality of life from treatment-induced bone marrow suppression, it would be appealing to adapt the current venetoclax with azacitidine regimen to allow for an “induction” phase in which a remission is rapidly induced, and quickly follow that up with a “maintenance” phase to prolong the remission.

In protocol M14-358, patients receive either 400 or 800 mg of venetoclax daily with the standard dose and schedule of azacitidine (75 mg/m^2 on d1-7) of each cycle. There is some suggestion that the 800 mg cohort experienced faster remissions than the 400 mg cohort; they also had increased hematologic adverse events. Therefore, this protocol will utilize an “induction” phase consisting of azacitidine at the same dose and schedule, with a higher dose (600mg) of venetoclax. When patients achieve a deep response as defined as the absent detection of minimal residual disease (MRD), they will enter “maintenance” phase, in which they are maintained on only single agent venetoclax at the 400 mg dose, with the rationale that a LSC directed therapy as a single agent can continue to target low-level disease and prolong remissions[24,28], and allow for greater tolerability and reduced hematologic toxicity.

Hypothesis: Patients who achieve a MRD-negative response with "induction" phase of venetoclax with azacitidine can be maintained on a reduced dose of venetoclax alone with equivalent response duration and less hematologic toxicity compared with indefinite maintenance therapy with venetoclax and azacitidine.

3.2 Venetoclax

3.2.1 Preclinical Pharmacokinetic Profile

In mouse, rat, monkey, and dogs, the venetoclax pharmacokinetic profile was characterized by low plasma clearance (CLp = 0.02 to 0.27 L/hr•kg) and low volumes of distribution (Vss = 0.3 to 1.1 L/kg). Half-lives ranged from 2.2 hours in monkeys to 12.0 hours in dogs. Formulation-dependent oral bioavailability was noted in all species. Studies in both rat and dog have defined the behavior of the amorphous solid dispersion for both toxicology and first-in-human evaluation. Plasma concentrations obtained from fed dogs were 30% to 50% higher than those obtained from fasted animals.

Venetoclax and its M27 metabolite are predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. Venetoclax is also substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. No active uptake of venetoclax was observed in cells overexpressing organic anion transporting polypeptide 1B1 (OATP1B1) or OATP1B3. Based on in vitro results, venetoclax was a P-gp, BCRP, and OATP1B1 inhibitor. It was not a potent in vitro inhibitor of CYP3A4, CYP1A2, CYP2B6, or CYP2D6 (IC50 > 30 µM), and it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 µM. Venetoclax is also not predicted to cause inhibition of CYP2C19, CYP2C8, CYP2C9, and UGT1A1 at clinically relevant concentrations. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9 and UGT2B7.

3.2.2 Preclinical Toxicology

Toxicology studies completed with venetoclax are general toxicology studies with periods of once-daily oral dosing ranging from 2 weeks to 6 months in mice, from 2 weeks to 13 weeks in rats, and from 1 week to 9 months in dogs. In vitro and in vivo genetic toxicology and dose range-finding studies in mice and rats to support dose selection for possible carcinogenicity assessments, embryo-fetal development in mice and rabbits, fertility and early embryonic development in male and female mice, dose range-finding in juvenile mice, and phototoxicity in mice studies have been performed. Other studies

were in vitro genetic toxicity testing of the M27 major human metabolite and in vitro and in vivo impurity qualification. Reversibility of venetoclax-related changes was assessed in the 4-week study in mice and in the 2- and 4-week studies in dogs. The primary toxicities associated with repeat-dose administration of venetoclax are effects on the hematologic system (decreased lymphocytes and red blood cell mass in mice, rats and dogs), the male reproductive system (testicular germ cell depletion in dogs), and embryo-fetal toxicity in mice. Other noteworthy findings are epithelial single cell necrosis in multiple tissues and hair coat color change, both in dogs. Maximum venetoclax plasma exposures (mean AUC0-24 h, combined male and female values) achieved in the 4-week studies were 92 µg•hr/mL (at 600 mg/kg/day) in mice and 572 µg•hr/mL (at 150 mg/kg/day) in dogs. In the 6-month mouse and 9-month dog chronic toxicity studies, AUCs reached 34.1 µg•h/mL (at 300 mg/kg/day) in mice and 85.6 µg•h/mL (at 20 mg/kg/day) in dogs. In rats, exposures were higher in females than in males; at dosages of 150 and 400 mg/kg/day in the 13-week maximum tolerated dose study, exposures ranged up to 83.1 to 127.8 µg•h/mL in females and up to 26.4 to 44.3 µg•h/mL in males. Venetoclax produced generally dose-related decreases in lymphocytes in the peripheral blood (up to –75% in mice, –64% in rats, and –81% in dogs) and in lymphoid tissues. These findings are consistent with the expected pharmacology of venetoclax (a selective Bcl-2 inhibitor)[29]. Following a 4-week recovery period, lymphocyte counts remained minimally decreased by 21% to 26% in mice, indicating that reversibility was occurring but was not complete. In dogs, the recovery of decreases in peripheral blood total lymphocytes and lymphocyte subsets (CD4+ T-cells and CD8+ T-cells and [CD21+] mature B cells) was prolonged, requiring up to 18 weeks after a single dose or after completion of 2 weeks of dosing. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease (> 90%) and/or the length of time required for recovery. Lymphocyte decreases in lymphoid tissues were reversible in mice and dogs, but as with peripheral blood lymphocytes, required up to 18 weeks in dogs. Decreases in lymphocyte counts can be readily monitored in clinical trial subjects.

In the 4-week mouse and dog studies, dose-related reversible decreases in red blood cell (RBC) mass were observed. Effects on RBC mass were typified by hemoglobin decreases. At the highest dosages administered, decreases in hemoglobin reached 21% in mice at 600 mg/kg/day and 23% in dogs at 150 mg/kg/day, and were considered to be adverse based on a criterion of 20% decrease. In rats, decreases in hemoglobin were more severe than in mice and dogs at comparable exposures and reached 30% to 49% at ≥150

mg/kg/day in female rats. Hematologic parameters are readily monitored in clinical trial subjects.

No effects of venetoclax have been identified on the female reproductive tract of mice, rats, and dogs. However, in dogs venetoclax produced adverse, non-dose-related microscopic findings of testicular germ cell loss at all dosages tested (2 to 150 mg/kg/day). In the 4-week study, testicular spermatogonia were decreased at the end of the dosing period, and their loss was consistent with the observed depletion of all germ cell types at the end of the 4-week recovery period. There were no testicular effects in mice or rats; in these animal species, exposures overlapped those in dogs. Venetoclax-induced testicular changes may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis.[30-32] There are currently no data assessing the effect of venetoclax on human spermatogenesis, and the actual risk to humans for testicular findings similar to those observed in dogs remains unknown. In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with advanced hematologic malignancies. In the mouse embryo fetal development study, increased post-implantation loss and decreased fetal body weights occurred at the highest dosage administered (150 mg/kg/day); the NOAEL was defined at the mid dosage of 50 mg/kg/day. No fetal toxicity was observed in rabbits, but exposures were approximately one-tenth those in mice. Venetoclax was not teratogenic in mice or rabbits, and there were no other effects on development or fertility.

Additional effects of venetoclax were white hair coat discoloration in dogs at ≥ 6 mg/kg/day and single-cell necrosis in multiple epithelial tissues at ≥ 2 mg/kg/day in dogs. Hair coat discoloration (increased amount of hair that was white) was observed in the dog after approximately 3 months of dosing in the 9-month chronic toxicity study. This change was consistent with loss of pigment in the hair and correlated histopathologically with decreased pigment in hair follicle bulbs. A change to gray coat color was also seen in NZBWF1 mice treated daily with 33 or 100 mg/kg venetoclax, but not at lower dosages. Evidence from Bcl-2 knockout mouse (Bcl-2 -/-) studies indicates that hair hypopigmentation occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival.[33] In the dog, pigmentation of the skin and in the eye (particularly in the pigmented iris and fundus) appeared unaffected; this was confirmed by the absence of associated histopathologic findings in skin (other than in hair follicles) and in the eye. The risk of hair graying in clinical trial subjects treated with venetoclax is unknown.

Single cell necrosis occurred in the gallbladder, exocrine pancreas, epididymides, prostate, and stomach of dogs. These changes were minimal except for non-dose dependent minimal to mild single cell necrosis in the pylorus of the stomach at ≥ 2 mg/kg/day in the 9-month study. After 4 weeks of dosing and a 4-week recovery period, reversibility was observed in the gallbladder and exocrine pancreas, but minimal single cell necrosis was still present in the epididymides and prostate (potentially related to the testicular effects) and in the stomach. Single-cell necrosis was considered not to be adverse due to its minimal to mild magnitude and because no loss of mucosal integrity was observed microscopically. Single cell necrosis was not found in the mouse or rat; maximum achieved exposures were comparable to or greater than the lowest exposures at which this finding occurred in dogs.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, nor was there evidence of phototoxicity (tested in vivo in hairless mice). Venetoclax administration in dogs in the 4-week study was associated with dose related, transient post-dose emesis, increased salivation, and fecal alterations (unformed or watery feces) at dosages of ≥ 5 mg/kg/day. These clinical signs were present throughout the dosing phase, but were not dose-limiting and were not observed in the recovery phase. In the 9-month dog study, non-adverse decreases in mean body weight and body weight gain, associated with decreases in food consumption, were present at ≥ 2 mg/kg/day. Dogs at the high dosage of 150 mg/kg/day in the 4-week study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most but not all animals (8 of 10 dogs) were affected, and in three dogs the swelling reaction was observed after the first dose. The clinical signs were limited to the 150 mg/kg/dosage, were transient and sporadic in occurrence, and were absent during the recovery period. A mechanistic basis for the swelling reactions was not established, but the clinical signs were mild to moderate in severity and reversible, and there were no signs of anaphylaxis.

M27 is a major human metabolite observed at steady state in chronic lymphocytic leukemia (CLL) or non-Hodgkin's lymphoma (NHL) patient plasma samples. It is present at significantly lower exposure levels (0.04- and 0.06-fold, respectively) in the mouse and dog, and therefore is a disproportionate metabolite. M27 was negative in Ames and chromosome aberration in vitro assays, has at least 58 fold less in vitro potency than venetoclax, and demonstrates low off-target toxicity potential based on in vitro secondary pharmacology assays. Taken together, these nonclinical results suggest that M27 does not represent a significant safety risk, and does not change the

benefit/risk ratio for clinical trial subjects with advanced hematologic malignancies treated with venetoclax.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the central nervous system /neurobehavioral or respiratory studies in mice at oral doses up to and including the highest oral dose of 600 mg/kg. No effects on QTc were observed up to a maximum plasma concentration of 46 µg/mL in dogs. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (Cmax = 16 µg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (6% to 13%) and cardiac output (11% to 19%) at plasma concentrations of ≥ 16 µg/mL and ≥ 32 µg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in humans (average Cmax = 6.09 µg/mL at the 1200 mg/day dose).

On the basis of nonclinical toxicology and safety pharmacology evaluations of venetoclax, and on the basis of nonclinical and human studies of related anti-apoptotic Bcl-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia, signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Although no effects of venetoclax on female reproductive tissues have been observed in general repeat-dose toxicology studies, embryo-fetal toxicity studies in animals have identified a fetal toxicity risk. Thrombocytopenia has not been a significant finding in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-XL sparing) inhibitor. Consequently, thrombocytopenia is not expected to be dose limiting.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the current Investigator's Brochure.

3.2.3 Clinical Data

As of 28 November 2015, based on the data available in the AbbVie and Genentech/Roche clinical databases, a total of 1509 subjects have been exposed to at least 1 dose of venetoclax in the oncology development program. Of these, data are available for 1498 subjects; 102 had AML, 935 subjects had CLL/SLL, 346 subjects had NHL, and 115 subjects had multiple myeloma. An additional 66 subjects were healthy volunteers who participated in the DDI studies. Based on the available data, a total of 564 oncology subjects

received the drug as monotherapy and 933 subjects received the drug in combination with other therapies.

Based on the mechanism of action and nonclinical and clinical data available to date, the safety profile of venetoclax is well described. The most common adverse drug reactions across all indications are nausea, diarrhea, hematological effects, and serious and/or opportunistic infections. Hematologic effects include neutropenia/febrile neutropenia, thrombocytopenia, anemia, and lymphopenia. Upper respiratory tract infections are among the most common infections. Tumor lysis syndrome (TLS) is an important identified risk and is predominantly seen in the CLL population with high tumor burden. Based on pre-clinical data, decreased spermatogenesis has been identified as a potential risk for venetoclax.

Overview of Phase 2 Study M14-212: Venetoclax Monotherapy in AML

In this completed single agent venetoclax trial (Study M14-212) in subjects with relapsed/refractory (R/R) AML 32 subjects have been dosed. Exposure, safety, and efficacy data are available for this study[19]. The most common adverse events observed in ≥ 10% of the subjects in study M14-212 were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., 1 event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia).

As of 11 March 2015, efficacy data for Study M14-212 are available for 32 subjects, the majority (30, 94%) of the subjects had R/R AML and a few were (2, 6%) deemed unfit for intensive therapy. The ORR was 19% (6 of 32 subjects), with complete remission (CR) in 2 (6%) and complete remission with incomplete marrow recovery (CRi) in 4 (13%) subjects. Anti-leukemic activity was observed in and additional 6 (19%) subjects, with 2 (6%) subjects each showing ≥ 50% reduction with 2 cell line recovery with transfusion independence, 1 cell line recovery, and no hematologic recovery, respectively.

Treatment failure due to progressive disease or less than a partial remission (PR) was observed in 20 (63%) subjects.

Overview of Phase 1b Study (M14-358): Venetoclax in Combination with HMA in Treatment Naïve AML

As of March 9, 2016, a total of 45 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled into the escalation stage at 3 dose levels of venetoclax at 400 mg, 800 mg, and 1200 mg. Venetoclax was administered daily during the 28-day cycles in combination with decitabine (20 mg/m2 intravenously on Days 1 – 5 once every 28 days) or azacitidine (75 mg/m2 intravenously or subcutaneously on Days 1 – 7 once every 28 days). Preliminary safety and efficacy data are available from the ongoing dose escalation stage of this trial.

The most common adverse events for all subjects in Study M14-358 were nausea (53.3%), diarrhea (44.4%), febrile neutropenia (40.0%), neutrophil count decreased (31.1%), platelet count decreased, cough, and fatigue (28.9% each), edema peripheral and hypokalemia (26.7% each). Events grade 3 and above were reported for the majority (91.1%) of subjects; the most common event was febrile neutropenia (40.0%). Serious adverse events were reported for 27 (60.0%) subjects, including febrile neutropenia (11 subjects), malignant neoplasm progression (3 subjects) atrial fibrillation, abdominal pain, non-cardiac chest pain, pyrexia, pneumonia, sepsis, bone pain (2 subjects each). All other events occurred in 1 subject each. The combination of venetoclax with decitabine and azacitidine demonstrates a tolerable safety profile.

As of March 9, 2016, the ORR, as assessed by the investigators for the subjects enrolled into the 3 dose levels, was 62.2% (28 of 45), with CR in 12 (26.7%), CRi in 15 (33.3%), and PR in 1 (2.2%). Four subjects (8.9%) were reported to have morphologic leukemia free state (less than 5% blasts in bone marrow aspirate sample with at least 200 nucleated cells) after completion of Cycle 1. Eight patients (17.8%) had resistant disease. However, all of the patients with resistant disease had evidence of blast reduction at completion of Cycle 1. The patients enrolled into the 1200 mg dose level had a shorter follow-up at the time of this analysis.

The maximum tolerated dose has not been reached in either arm and dose escalation stage has completed enrollment. Enrollment into safety expansion at 400 mg and 800 mg dose of venetoclax in combination with both HMAs is ongoing.

Additional safety and efficacy data are described in more detail in the current version of the Investigator's Brochure.

3.3 Azacitidine

Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, DNA synthesis and metabolism, and causes cytotoxicity. Since the early 1970s, azacitidine has been investigated in the US for the treatment of acute leukemia, with clinical trials focused primarily on patients with refractory disease. These investigations indicated azacitidine has activity in the treatment of AML.

The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. The ability of azacitidine to cause differentiation is attributed to its activity as a hypomethylating agent. Therefore, an inhibitor of DNA methylation such as azacitidine would be a rational approach to revert epigenetic changes in the malignant clone and re-establish the antiproliferative signals extinguished by hypermethylation.

3.3.1 Preclinical Pharmacokinetic Profile

Early PK studies used ^{14}C-radiolabeled azacitidine to evaluate drug disposition. Based on total radioactivity in plasma, azacitidine was absorbed when given subcutaneously (SC), with maximum concentrations found 0.5 to 2 hours after dosing. Azacitidine and/or its metabolites were then cleared by the kidneys. The plasma $t^{1/2}$ (3.4 to 6.2 hours) and amount of radioactivity recovered in urine (50-98% of administered dose) were similar after IV and SC dosing.

Drug-drug interaction studies of azacitidine have not been conducted in clinical trials. Two in vitro metabolism studies and three in vitro drug interaction studies have been completed. Some evidence of hepatic metabolism was observed when azacitidine was incubated in human liver fractions. The metabolism of azacitidine was compared using [^{14}C]5-azacitidine and hepatic S9 fractions from human and mouse origin; the formation of deaminated metabolites (formylamidinoribofuranosylbiuret and ribofuranosylbiure) was independent of nicotinamide adenine dinucleotide phosphate (NADPH), implying that metabolism was catalyzed by cytosolic enzymes. Azacitidine was not an inducer of the isozymes 1A2, 2C19, or 3A4/5. Azacitidine showed no notable inhibition of P450

isoenzymes (Cytochrome P450 [CYP450] 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) in the concentration range of 0.1 to 100 µM. Therefore, clinically relevant inhibitory or inductive effects on the metabolism of CYP450 substrates are unlikely. Azacitidine is neither a substrate nor an inhibitor of P-glycoprotein (P-gp) and therefore unlikely to produce any clinically relevant interactions as a P-gp substrate or an inhibitor. The effect of inducers or inhibitors on the metabolism of azacitidine has not been studied.

3.3.2 Clinical Data

The safety profile of azacitidine has been well characterized and is based on an extensive amount of patient exposure across a wide range of doses and indications. Adverse events (AEs) reported most frequently were hematologic events of thrombocytopenia, neutropenia, anemia, and leukopenia, and were typically assessed as grade 3 or 4 events. Despite the increased percentages of these hematologic events, azacitidine did not appear to increase the risk of events of infection or bleeding when compared with patients treated with best supportive care only. Non-hematological AEs that were reported most often were events related to either the administration of the drug (injection site reactions, nausea, vomiting) or consequences of the antiemetic treatment (constipation). These events were generally graded 1 or 2 in intensity. The reporting frequencies for the common hematologic and non-hematological events were generally highest during cycles 1 and 2, after which time the frequencies decreased over subsequent treatment cycles. Within the cycle, the hematologic events tended to occur across the first 3 to 4 weeks of the cycle, whereas the events associated with the administration of azacitidine tended to occur in the first week. These findings suggested a lack of cumulative toxicity and that adverse effects of azacitidine attenuate over time.

A recent randomized phase 3 study of older newly diagnosed patients with AML who received azacitidine versus conventional care regimens showed a CR+CRi rate of 27.8% and a median OS of 10.4 months.[27]

3.4 Differences Statement

This study will employ MRD testing to adjust the intensity of the regimen for each individual patient, in an attempt to minimize hematological toxicity. There are ongoing clinical trials of the combination of hypomethylators and low dose cytarabine with

venetoclax for elderly unfit AML patients, as well as a combination with cobimetinib or idasunutlin for patients with relapsed or refractory AML. In addition, studies with venetoclax are ongoing for other indications, including multiple myeloma, MDS and CLL/NHL.

4 STUDY OBJECTIVES

4.1 Primary Objective

To determine the response duration of "induction" therapy with azacitidine plus venetoclax followed by maintenance therapy with venetoclax alone for patients who achieve a MRD negative response state.

4.2 Secondary Objectives

- To determine the rate of MRD negative composite responses (includes CR, Cri/CRp and MLFS) with the "induction phase" of azacitidine and venetoclax
- To determine the median amount of time needed to achieve an MRD negative composite response
- To determine the one-year overall survival (OS) of older, newly diagnosed AML patients treated with "induction phase" of azacitidine with venetoclax followed by a maintenance phase of venetoclax alone
- To assess the hematologic toxicity of "induction" venetoclax with azacitidine followed by maintenance venetoclax alone

Commented [BB1]: I think this is general enough that we can keep this as is but I'm just highlighting it for review just in case.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is an open label, phase 2 single institution pilot study for older, untreated AML patients employing an "induction" phase of venetoclax with azacitidine followed by maintenance therapy with venetoclax alone in patients who experience a MRD negative response.

5.1.1 Study Schema

After consent and screening, patients will be admitted to the hospital for the venetoclax dose escalation during cycle 1. Cycles are defined as 28-day periods. After dose escalation has completed patients may

discharge and continue management in the outpatient setting if appropriate.

On day 1 of cycle 1, azacitidine 75 mg/m^2 SC or IV will be given, and will continue for 7 days. Antiemetic premedication will be administered per institutional protocol. Depending on the cycle or the clinical situation, azacitidine may be administered in the inpatient or outpatient setting. The route of administration will be at the discretion of the investigators. Administration will be performed in accordance with institutional protocol.

Starting on day 1 of cycle 1, venetoclax will be escalated to a target dose of 600 mg. This will involve administration of 100 mg on day 1, 200 mg on day 2, 400 mg on day 3 and 600 mg on day 4 (Figure 1). Subsequently, patients will take venetoclax 600 mg daily and may be discharged from the hospital if medically appropriate.

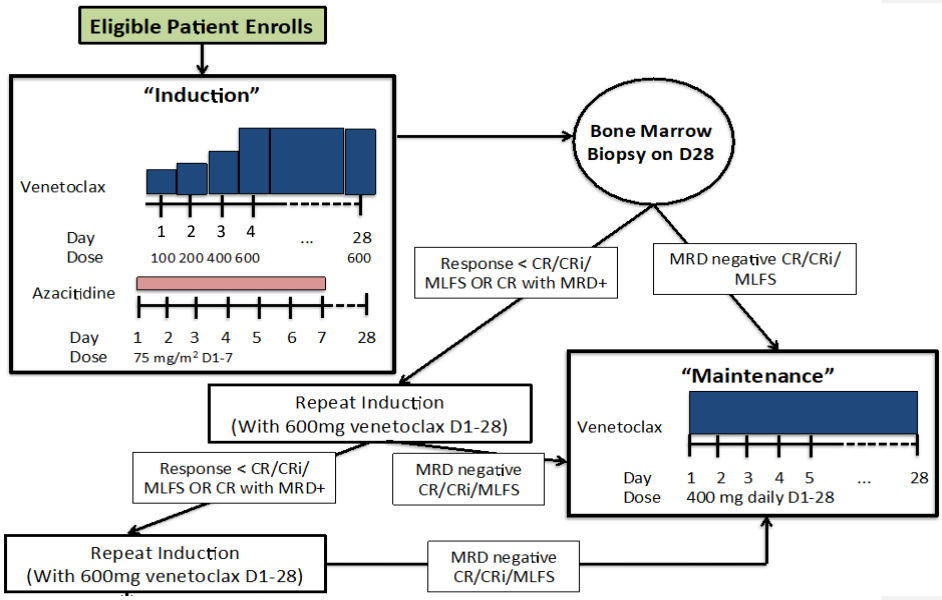
On day 8 of cycle 1 (or day 7 after the last dose of azacitidine is administered), a bone marrow biopsy will be performed.

On day 28 of cycle 1 (with a 3-day grace period), a bone marrow biopsy will be performed to determine response status (see Section 5.1.2). This will include an assessment of MRD by multi-dimensional flow cytometry[1,2] or digital droplet PCR, allowing for quantification of disease to at least 0.1%. Persistence of cytogenetic abnormalities will be defined as MRD positive. Undetectable disease will be defined as MRD negative.

Patients who do not achieve a MRD negative composite response after the first cycle will repeat another 28-day cycle, this time with 600 mg venetoclax given days 1-28, with a bone marrow biopsy to determine response status at the completion of the cycle, again with a 3-day grace period. Patients who do not achieve a MRD negative composite response after the second cycle will repeat another 28-day cycle, identical to cycle 2, with a bone marrow biopsy after the third cycle. If a MRD negative response is not achieved after the third cycle, patients will continue sequential cycles of azacitidine and venetoclax, now dose reduced to 400 mg daily, and given on day 1 of each cycle. Bone marrow biopsies will occur at the conclusion of every odd-numbered cycle until cycle 9. If by cycle 9 a CR/CRi/MLFS with persistent MRD occurs, another bone marrow biopsy will occur after cycle 12 and then every 6 cycles, or at the discretion of the investigator. “Induction phase” will continue until the achievement of a MRD negative composite response, progression, or unacceptable toxicity.

Once a patient achieves a MRD negative composite response, regardless of when it occurs, they will enter the maintenance phase; azacitidine will be discontinued, and the dose of venetoclax will decrease from 600 mg daily to 400 mg daily if it has not already been reduced. Patients will undergo bone marrow biopsies (to determine response status) every 3 cycles for the first year of maintenance therapy, and then every 6 cycles thereafter, or at the discretion of the investigator. MRD assessments will be performed at each bone marrow biopsy.

Figure 5-1



5.1.2 Response Assessments

Response assessments will be made by physical examination and evaluation of peripheral blood findings and bone marrow biopsies at the required time points (see Section 5.1.1), using the 2017 ELN AML response criteria[34] and the definition of disease progression made according to the IWG[35] (see Section 5.11).

5.1.3 Continuation and Interruptions

Patients who achieve a response and are tolerating therapy can continue to receive sequential treatment cycles indefinitely. Patients who experience disease progression or significant treatment-related toxicity, as assessed by the investigator or the patient, will discontinue therapy. Patients who proceed to SCT will discontinue.

After cycle 1, subsequent cycle delays are not required for any grade of hematologic toxicity; however, cycles may be delayed for any grade of hematologic toxicity, and myeloid growth factors may be used according to standard practices and at the discretion of the investigator, in the absence of evidence of ongoing disease. Subjects who require brief interruption of venetoclax for reasons other than progression of disease may continue on azacitidine therapy alone until they resume venetoclax. When the following cycle is resumed, venetoclax and azacitidine will resume on the same day. Azacitidine may be delayed at the discretion of the investigator, typically for febrile neutropenia, active infection or bleeding complications, and be resumed once the condition has improved or been stabilized with adequate treatment. Delays of azacitidine do not require delays of venetoclax.

Dose decreases can be considered, see Section 5.14.

5.2 Study Endpoints

5.2.1 Primary Endpoint

- Duration of overall response (CR+CRi+MLFS), as measured by the first day a response is documented on a bone marrow biopsy to the first day the disease progresses, based on bone marrow biopsy, peripheral blood findings, clinical examination or radiographic study.

5.2.2 Secondary Endpoints

- Incidence of MRD negative responses (CR+CRi+MLFS)
- Median time to achieve a MRD negative response (CR+CRi+MLFS)
- One-year overall survival, stratified by response type and achievement of MRD negative state

Commented [BB2]: Same comment as on p. 7 above.

- Incidence of febrile neutropenia, ≥ grade 2 bleeding complications and number of transfusions received (red blood cells and platelets)

5.3 Selection of Study Population and Enrollment Procedures

All subjects will be screened for eligibility. The investigators will be responsible for keeping a record of all subjects who sign an informed consent form for entry into the study. After the patient has signed and dated the informed consent form, all screening procedures have been completed and clinical eligibility has been confirmed, the patient can be officially enrolled in the study. All patients must meet the qualifications as outlined below.

5.3.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria within 28 days prior to the first day of therapy. Historical records are permitted per Investigator discretion.

1. Subject must have confirmation of non-APL AML by WHO criteria[36] and be ineligible or unwilling to undergo treatment with a standard cytarabine and anthracycline induction regimen due to co-morbidities or other factors

2. Subject must have received no prior treatment for AML; hydroxyurea is not considered a treatment and is allowed

3. Subject must be ≥ 60 years of age

4. Subject must have a projected life expectancy of at least 12 weeks

5. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance status of ≤2

6. Subject must have adequate renal function as demonstrated by a calculated creatinine clearance ≥ 30 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft Gault formula

7. Subject must have adequate liver function as demonstrated by:

   - aspartate aminotransferase (AST) ≤ 3.0 × ULN*
   - alanine aminotransferase (ALT) ≤ 3.0 × ULN*
   - bilirubin ≤ 3.0 × ULN, unless due to Gilbert's syndrome*

* Unless considered due to leukemic organ involvement

8. Non-sterile male subjects must use contraceptive methods with partner(s) prior to beginning study drug administration and continuing up to 90 days after the last dose of study drug. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of study drug.

9. Female subjects must be either:

   - Postmenopausal; defined as Age > 55 years with no menses for 12 or more months without an alternative medical cause;

   OR

   - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy)

10. Subject is informed that consumption of the following fruits is prohibited 3 days prior to the initiation of study treatment and throughout participation: grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit.

11. Subject must voluntarily sign and date an informed consent, approved by an Institutional Review Board (IRB), prior to the initiation of any research directed screening or procedures.

5.3.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has received treatment with a hypomethylating agent and/or other chemotherapeutic agent either conventional or experimental for myelodysplastic syndrome (MDS) or AML

2. Subject has acute promyelocytic leukemia

3. Subject has known active CNS involvement from AML

4. Subject is known to be positive for HIV. HIV testing is not required

5. Subject is known to be positive for hepatitis B or C infection with the exception of those with an undetectable viral load. Hepatitis B or C testing is not required and subjects with serologic evidence of prior vaccination to HBV (i.e., HBs Ag, anti-HBs+ and anti-HBc–) may participate

6. Subject has received anticancer therapies including chemotherapy, radiotherapy or other investigational therapy, including targeted small molecule agents within 5 half-lives prior to first dose of study drug. ATRA given for clinical suspicion of APL will not be exclusionary and no washout will be required in this scenario.

7. Subject has received biologic agents (e.g. monoclonal antibodies) for anti-neoplastic intent within 30 days prior to first dose of study drug

8. Subject has received the following within 7 days prior to the first dose of the study drug:
    - Steroid therapy for anti-neoplastic intent;
    - Strong and Moderate CYP3A inhibitors (see Appendix A for examples)
    - Strong and Moderate CYP3A inducers (see Appendix A for examples)

9. Subject has any history of clinically significant condition(s) that in the opinion of the investigator would adversely affect his/her participating in this study including, but not limited to:

    - New York Heart Association heart failure > class 2
    - Renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or bleeding disorder independent of leukemia

10. Subject has a malabsorption syndrome or other condition that precludes enteral route of administration

11. Subject exhibits evidence of uncontrolled systemic infection requiring therapy (viral, bacterial or fungal)

12. Subject has a history of other malignancies prior to study entry, with the exception of:

- Adequately treated in situ carcinoma of the breast or cervix uteri
- Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin
- Prostate cancer with no plans for therapy of any kind
- Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent

13. Subject has a white blood cell count > 25 × 10^9/L. Note: hydroxyurea is permitted to meet this criteria

14. Any subject who is a candidate for intensive induction therapy and agrees to receive intensive induction therapy

5.4 Duration of Study

After treatment discontinuation, all patients will have a safety follow-up visit approximately 30 days following patient's last study treatment.

5.5 Drug Administration

5.5.1 Venetoclax Administration

Although it has not been clinically observed thus far, tumor lysis syndrome (TLS) may occur upon initiation of dosing with venetoclax with azacitidine. To mitigate the risk of TLS in AML patients the regimen is designed to escalate the dose of venetoclax rapidly and safely with standard doses and schedules of azacitidine to optimize the opportunity for achieving a response and enable close subject monitoring. For additional safety and efficacy data please refer to the current Investigator Brochure.

During cycle 1, venetoclax will be administered orally once daily days 1 through 28. Each dose of venetoclax will be self-administered with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast. The dose should be administered at the same time each day. On days the subject is given azacitidine, venetoclax must be given first.

If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, another dose may be taken and the

second dose noted in the drug log. Otherwise, no replacement dose is to be taken.

Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit within the 3-day period prior to the first study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Subjects will be admitted to the hospital where they will be confined from cycle 1 day 1 until at least 24 hours after receiving the 600 mg target dose. Dose modifications of venetoclax during escalation may be implemented for individuals at risk for TLS or any new adverse events > Grade 2 (see Section 5.14.3). To mitigate the potential risk of TLS[37] subjects will receive TLS prophylaxis which will include hospitalization for observation, administration of a uric acid reducing agent and adequate oral and intravenous hydration.
If a subject develops any laboratory changes suggestive of TLS within the first 24 hours after either the first dose or during dose escalation, venetoclax dose escalation should be withheld or the dose should be reduced. Refer to Section 6.10, Management of Tumor Lysis Syndrome, for details on TLS prophylaxis.

Venetoclax dose decreases may be considered, see Section 5.14.3, and for adverse event management guidelines please refer to Section 6.

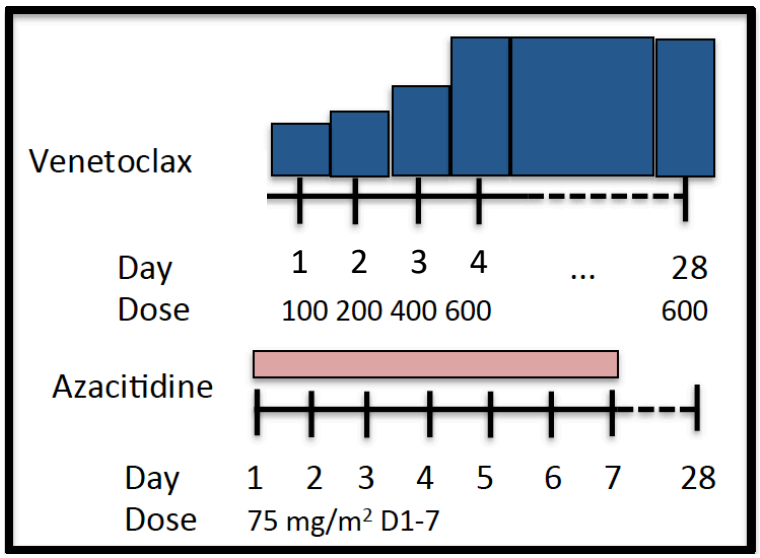
Patients who take more than the prescribed dose of venetoclax should be instructed to seek emergency medical care if needed and contact study staff immediately. If a dose of venetoclax is missed or forgotten, it should be taken as soon as possible, ensuring it is taken within 8 hours of the missed dose with food; otherwise the dose should not be taken. Missed doses should not be made up.

Venetoclax tablets will be packaged in high-density polyethylene plastic bottles or blister cards. Each bottle or blister card will be labeled per institutional requirements. It must be stored at 15° to 25°C (59° to 77°F). Venetoclax is for investigational use only and is to be used only within the context of this study. It must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned. Abbvie will provide venetoclax and it will be kept by the investigational pharmacy.

5.5.2 Azacitidine Administration

Azacitidine 75 mg/m^2 should be prepared and administered per the package insert and institutional guidelines. IV or subcutaneous administration is permitted.

Table 1 Dose escalation of venetoclax with azacitidine



5.6 Assuring Patient Compliance

The investigator and designated and qualified representatives will dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Patients will receive all dosages of azacitidine in the inpatient or outpatient setting.

After the cycle 1 dose escalation, venetoclax will be self-administered at home. Patients will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses. Patient compliance will be assessed on day 28 of a completed cycle or day 1 of a subsequent treatment cycle. Patients

will be required to bring their diary, any remaining capsules, and the bottle, even if empty, to clinic during this visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary. Compliance will be monitored and documented by the study coordinator. Poor compliance will result in counseling of the subject by study site personnel. Any unused venetoclax will be returned to the pharmacy.

5.7 Drug Accountability

The investigator and his representatives will verify that study drug supplies are received intact and in the proper amounts. This will be documented. The investigator or his representatives will administer study drug only to subjects enrolled in the study. A current (running) and accurate inventory of study drug will be kept by the investigator and will include shipping invoices and the date on which study drug is dispensed to the subject. Upon completion or termination of the study, all original containers (containing partially used or unused study drug) will be returned to the sponsor according to their instructions. Empty containers will be destroyed at the site.

5.8 Concomitant Therapy

5.8.1 Permitted Concomitant Therapy

Transfusion of blood and blood products, antibiotics, anti-emetics and other standard supportive care medications are permitted as needed. Hydroxyurea is permitted as needed according to institutional guidelines and to decrease the WBC to $<25 \times 10^9$/L at the time of study entry or during the study, as needed. Filgrastrim may be used according to institutional guidelines. Antibiotics will be used for patients with known infections or neutropenic fevers.

If a subject reports taking any over-the-counter or prescription medications, vitamins, and/or herbal supplements or if administration of any medication becomes necessary, beginning with the screening visit through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate electronic case report form (eCRF).

Strong and moderate CYP3A inducers and inhibitors are excluded during the ramp-up stage of venetoclax, and alternative medications should be considered. (See Appendix A). If subject requires use of a

strong/moderate CYP3A inhibitor after reaching the target dose of venetoclax, use with caution and reduce the venetoclax dose by 50% for moderate inhibitors and at least 75% for strong inhibitors during co-administration (see table below). After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

Venetoclax Dose	Venetoclax Dose Co-Administered with a Moderate CYP3A Inhibitor	Venetoclax Dose Co-Administered with a Strong CYP3A Inhibitor
100 mg (cycle 1 only)	50 mg	25 mg
200 mg (cycle 1 only)	100 mg	50 mg
400 mg	200 mg	100 mg
600 mg	300 mg	100 mg

If a subject requires use of strong/moderate CYP3A inducers after reaching the target dose of venetoclax, use with caution and contact AbbVie for guidance.

5.8.2 Prohibited Concomitant Therapy

Anticancer therapies including chemotherapy, systemic or intrathecal, immunotherapy, radiotherapy, biological agents (monoclonal antibodies) for anti-neoplastic intent, or other investigational therapy, including targeted small molecule agents, and prednisone >20 mg/day.

A sample list of excluded and cautionary medications can be found in Appendix A. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, please refer to the appropriate product label and/or FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Strong and Moderate CYP3A inhibitors

Exclude during ramp-up stage of venetoclax and consider alternative medications. If subject requires use of these medications after reaching the target dose of venetoclax, 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 stage of venetoclax and consider alternative medications. If subject requires use of these medications after reaching the target dose of venetoclax, use with caution and contact AbbVie for guidance.

5.9 Contraception Recommendations

Female subjects must be either postmenopausal defined as:

- No menses for 12 or more months without an alternative medical cause
  OR
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy)

Male subjects must be surgically sterile (vasectomy with medical assessment confirming surgical success) or if the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If the male subject is sexually active with female partner(s) of childbearing potential, he must agree from enrollment through 90 days after the last dose of investigational product to practice contraception with a partner who agrees to at least one of the following contraceptive measures:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to enrollment
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to enrollment
- Bilateral tubal occlusion/ligation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

Additionally, male subject agrees not to donate sperm from randomization through 90 days after the last dose of investigational product.

5.10 Study Procedures

Study procedures listed in section 2 are detailed in this section, with the exception of adverse event information (see Section 6). All study data will be recorded on eCRFs.

Procedures performed at screening will serve as baseline, unless repeated on cycle 1 day 1 prior to dosing, in which case this will serve as baseline. Any abnormal laboratory or vital sign between screening and prior to administration of therapy will be recorded in the subject's medical history and will also serve as the subject's baseline.

Subjects who signed the informed consent will obtain a screening/subject number. Subjects who signed informed consent, have had at least one study procedure conducted, and who are determined to be a screen failure will not proceed to the study. The reason for the screen failure will be documented in the source document and captured in the eCRF. Screening procedures must be performed within 28 days prior to study drug administration. Subjects who complete all screening procedures and meet the inclusion criteria (see section 5.3.1) and none of the exclusion criteria (see Section 5.3.2) will proceed to enrollment.

Informed consent
Signed informed consent will be obtained from the subject or the subject's legally acceptable representative in order to participate in the study. The IRB approved informed consent must be signed and dated by the subject or representative prior to undergoing any research directed procedures or before any prohibited medications are withheld from the subject in order to participate in the study. Laboratory or procedural results obtained standard of care, and prior to consent to research procedures, are considered historical records and may be used in some circumstances at the discretion of the investigator.

History
Involves a complete medical history, with documentation of clinically significant medical conditions, and AML history including the date of diagnosis of AML and any precursor conditions. Also includes review of current medications and allergies.

Physical Exam
Symptom directed, per institutional protocol

Vital Signs
Includes weight, temperature, blood pressure, pulse, respiratory rate and if needed, oxygen saturation. All methods of measurement and practices will be per institutional protocol.

ECOG PS[38]

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

Cytogenetics
By FISH or metaphase cytogenetics, per institutional standards

MRD
Performed by up to 3 procedures, when relevant. 1) Cytogenetic testing, both metaphase cytogenetics and FISH; 2) Multidimensional flow cytometric approach based on differences from normal; 3) Digital droplet PCR. Flow cytometry will always be performed; if a patient has an actionable ddPCR mutation, or cytogenetic abnormality, ddPCR and cytogenetic testing will be performed. MRD will be considered positive if any of the three above modalities is positive. In all cases, protocol-related clinical decision making will only be impacted by MRD testing that is performed in a CLIA-certified laboratory.

AE and Con Meds
On cycle 1 day 1, any serious adverse events observed from the signing of informed consent but prior to administration of azacitidine will be reported, if considered by the investigator to be causally related to study-required procedures. At each visit, including the end of treatment visit, the subject's

medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

All medications, prescription and over the counter, including vitamins and/or herbal supplements, will be recorded beginning with the screening visit and continuing until End of Treatment. Administration of IV fluids does not need to be recorded.

12 Lead EKG
A single 12-lead resting EKG will be obtained at screening or as clinically needed. It will be recorded after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain stationary for the duration of the recording. An investigator will then evaluate it as clinically significant or not clinically significant, which will be entered into the CRFs.

TLS Prophylaxis
See Section 6.10

Clinical Laboratory Tests
All laboratory tests will be performed at the time points listed in the schedule of study assessments, and will be performed at additional time points based on institutional guidelines

Hematology
- Hematocrit
- Hemoglobin
- WBC count
- Differential (if WBC high enough, per institutional standard)
- Platelet count

TLS Chemistry
- Calcium
- Phosphorus
- Potassium
- Uric Acid
- Creatinine

Chemistry
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- Albumin
- Alkaline phosphatase
- Sodium

- Potassium
- Chloride
- Carbon dioxide
- Glucose
- Blood urea nitrogen (BUN)
- Creatinine
- Calcium
- Magnesium
- Phosphorus
- Total Protein
- Uric acid
- Lactate dehydrogenase (LDH)

Coagulation

- Prothrombin time (PT)
- International normalized ratio (INR)
- Partial thromboplastin time (PTT)
- Fibrinogen

Azacitidine
See Section 5.5.2

Venetoclax
See Section 5.5.1

Bone marrow aspirate and biopsy
To be performed at all time points outlined in the schedule of study assessments, in addition to at any time upon concern for relapse. Historical bone marrow aspirates and biopsy at screening may be acceptable; per Investigator discretion.

Attempts to obtain an aspirate and biopsy are required at all listed time points except day 8, when an aspirate alone is sufficient. If a patient is not aspirable after an attempt is made, additional core biopsy specimens should be attempted per institutional protocol. On all time points except for day 8, samples should be sent for morphological assessment, flow cytometry, cytogenetic analysis and molecular testing, as is clinically appropriate. All results will be captured on a CRF. Day 8 aspirates may not involve cytogenetic and molecular assessments, as is clinically appropriate.

Dispensing and Collecting Calendar and Diary
Subject calendars/diaries will be provided at the time of discharge from the hospital. Subjects will bring their calendars/diaries back to be reviewed at each visit.

Subjects will record the date and time of each dose of study drug taken, including whether any doses of the study drug are missed, and whether or not doses were taken within 30 minutes after the completion of a meal (preferably breakfast).

The calendars/diaries will be collected at each visit and will be filed by study staff in the subject source documents.

Safety Follow Up
A safety follow up visit should be performed approximately 30 days following discontinuation of study drug, and should include a history, physical examination and review of systems, and then should be repeated as clinically appropriate until any adverse events have resolved. A separate safety visit does not need to be performed for subjects with a final visit ≥30 days after discontinuation of study drug and did not require additional AE follow up. Patient refusal or inability to attend safety follow up visits will be noted in the source documentation.

5.11 Response Assessments

Assessment of clinical responses will be made according to 2017 ELN AML Recommendations.[34] Definition of disease progression will be made according to IWG criteria.[35] The major criteria for judging responses will include physical examination and examination of blood and bone marrow. In the event that peripheral blood findings improve 14 days after a bone marrow biopsy, whether or not in the setting of a delay in treatment, the response assessment will be adjusted accordingly. Only subjects who complete cycle 1 will be evaluable for response. Patients with un-evaluable bone marrows should be reported as indeterminate and a repeat bone marrow should be completed within 1 week. Response duration is measured from the time all response criteria are first met until relapse is documented.

Complete Remission (CR)

CR requires all of the following:

- Bone marrow blasts <5%
- Absence of circulating blasts and blasts with Auer rods.
- Absence of extramedullary disease

- Absolute neutrophil count >1.0 x 10^9/L
- Platelet count >100 x 10^9/L

Complete Remission with Incomplete Blood Count Recovery (CRi)

CRi meets all CR criteria except for residual neutropenia or thrombocytopenia:

- Absolute neutrophil count <1.0 x 10^9/L
- Platelet count <100 x 10^9/L

Morphologic Leukemia Free State (MLFS)

- No hematologic recovery required
- Marrow should not merely be “aplastic”; at least 200 cells should be enumerated or cellularity should be at least 10%

CR/CRi/MLFS with MRD Negativity

- Any of the above responses with negativity by multi-dimensional flow cytometry with a sensitivity to 0.1%

Partial Remission (PR)

PR meets all hematologic criteria of CR:

- Absolute neutrophil count >1.0 x 10^9/L
- Platelet count >100 x 10^9/L

AND

- Decrease of bone marrow blast percentage to 5% to 25%
- Decrease of pretreatment bone marrow blast percentage by at least 50%

Treatment Failure

Treatment failure will be classified as one of the following:

- Resistant disease (RD): No CR or CRi or MLFS or PR in subjects who survive at least 7 days after completion of cycle 1, with evidence of persistent disease by blood and/or bone marrow biopsy

- Death in aplasia: Deaths occurring ≥7 days following completion of initial treatment while cytopenic, or with an aplastic or hypoplastic bone marrow obtained within 7 days of death that shows no evidence of persistent leukemia
- Death from indeterminate cause: Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available

Relapsed Disease

Relapse for patients with prior CR/CRi/MLFS/PR, independent of MRD status will be defined as:

- Evidence of morphologic relapse with the appearance or reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause. If questionable, a bone marrow biopsy should be repeated within 1 week to distinguish relapse from bone marrow regeneration
- The appearance or reappearance of cytologically proven extramedullary disease

5.12 Reporting of Results

At the conclusion of each bone marrow biopsy performed after C1D8, all patients will be assessed as one of the following responses:

- CR
  - With/Without MRD
- CRi
  - With/Without MRD
- MLFS
  - With/Without MRD
- PR
- RD
- Death in Aplasia

5.13 Stopping Rules

5.13.1 Individual Patient Stopping Rules

All subjects will be included for analysis of safety data. Subjects have the right to withdraw from the study at any time. The investigator will discontinue a subject if this is felt to be necessary for any reason including:

- Non-compliance with the study protocol
- Is it believed to be in the best interests of the subject
- Disease progression
- Toxicity related to study drug that requires more than a 4-week dose interruption of therapy and in the absence of clinical benefit
- Need for other anti-neoplastic agents or radiotherapy for the development of a new primary cancer diagnosis
- Adverse event that precludes further investigational drug administration
- Development of unrelated illness which compromises further participation in the study
- Study endpoints have been achieved

In the event of withdrawal or discontinuation, the reason for discontinuation will be recorded and a final visit, including a physical examination, vital signs, ECOG PS, bone marrow aspirate and biopsy with cytogenetics and MRD, AE assessment with con meds, hematology/chemistry laboratories and collection of the calendar/diary, will be performed as soon as possible after discontinuation. If the subject had a bone marrow aspirate and biopsy with cytogenetics and MRD within 14 days of the end of treatment visit, then a repeated procedure is not required.

5.13.2 Study Stopping Rules

The study will continue until the last patient hasreceiving the last dose of study drug and completed the 30-day safety follow-up period. If the investigator determines that continued exposure to the study drug represents a significant risk to subjects, the study will be stopped. In addition, if at any time an ongoing statistical analysis reveals the median remission duration to fall below 8 months, the study will be stopped (see Section 8.5). All enrolled subjects will be notified of the premature discontinuation and the investigator will administer treatments with other regimens as is appropriate.

5.14 Dosing Delays and Modifications

5.14.1 Missed Doses

If a dose of venetoclax is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients will be encouraged to stay on schedule even if a dose is missed. Dosing will be tracked in the patients' diaries.

5.14.2 Additional Doses

Patients who take more than the prescribed dose of venetoclax should be instructed to seek emergency medical care if needed and contact study staff immediately.

5.14.2.1 Dose Delays

After Induction cycle 1, the start of each subsequent cycle can proceed in the absence of possibly/related > grade 2 toxicity. In the presence of possibly/related > grade 2 toxicity, delay of the subsequent cycle for up to 14 days is allowed. If the possibly/related > grade 2 toxicity resolves to ≤ grade 1 within 14 days, subsequent cycles may resume.

After cycle 1, subsequent cycle delays are not required for any grade of hematologic toxicity; however, cycles may be delayed for any grade of hematologic toxicity, and myeloid growth factors may be used according to standard practices and at the discretion of the investigator, in the absence of evidence of ongoing disease.

Subjects who require brief interruption of venetoclax for reasons other than progression of disease may continue on azacitidine therapy alone until they resume venetoclax.

Azacitidine may be delayed at the discretion of the investigator, typically for febrile neutropenia, active infection or bleeding complications, and be resumed once the condition has improved or been stabilized with adequate treatment. This does not require delay of venetoclax.

Dose decreases can be considered, see Section 5.14.3.

Drug interruption for up to 72 hours following transient (<48 hours) chemical and laboratory TLS are allowed and will not require dose reduction. If the TLS has not resolved within 72 hours, a dose reduction may be considered.

5.14.3 Dose De-Escalation and Re-Escalation

Dose de-escalation of venetoclax can be considered when deemed appropriate by the investigator for toxicity.

During induction and before the completion of cycle 1 or documentation of a CR/CRi/MLFS, the venetoclax dose should remain 600 mg. After a CR/CRi/MLFS has been achieved with ongoing evidence of MRD, every effort should be made to maintain the 600 mg dose of venetoclax until an MRD negative state is achieved or the completion of cycle 3, whichever comes first. However, in the presence of > grade 3 neutropenia/thrombocytopenia that persists >14 days off therapy, the investigator may reduce the dose of venetoclax using the following table:

Clinical Scenario	Venetoclax Dose
First episode of >grade 3 neutropenia/thrombocytopenia >14 days	600 mg daily
Second episode of >grade 3 neutropenia/thrombocytopenia >14 days	400 mg daily
Third episode of >grade 3 neutropenia/thrombocytopenia >14 days	400 mg 21/28 days

If an additional dose reduction is felt to be necessary before the patient achieves a MRD negative state, the patient will discontinue the study. If dose reduction occurs and there is no improvement in the cytopenia, and it is felt to be unrelated to venetoclax, venetoclax may be re-escalated.

If venetoclax dose reduction occurred when a patient achieved MRD negativity and the patient subsequently loses MRD negativity, or if there is concern for this scenario, venetoclax may be re-escalated to 600 mg. Likewise, if venetoclax dose reduction occurred before MRD negativity occurred and it is later felt in the patient's best interests to re-escalate to 600 mg venetoclax, this is permitted.

Azacitidine may be dose adjusted according to the package insert. If three induction cycles do not result in an MRD-negative state, the investigator can opt to discontinue the azacitidine and maintain the venetoclax. If it is deemed in the subject's best interests to re-introduce azacitidine after it has been discontinued, this may occur during day 1 of any subsequent cycle.

During maintenance phase, after MRD negativity has been achieved and the azacitidine has been discontinued, dose de-escalation of venetoclax can be considered using the following table:

Clinical Scenario	Venetoclax Dose
First episode of >grade 3 neutropenia/thrombocytopenia >14 days	300 mg daily
Second episode of >grade 3 neutropenia/thrombocytopenia >14 days	200 mg daily
Third episode of >grade 3 neutropenia/thrombocytopenia >14 days	200 mg 21/28 days
Fourth episode of >grade 3 neutropenia/thrombocytopenia >14 days	200 mg 14/28 days

If an additional dose reduction is felt to be necessary, the patient will discontinue the study.

The "induction" phase may be modified to escalate to 400 mg of venetoclax instead of 600 mg, if the toxicity profile of 600 mg is deemed prohibitive. In this case, the first cycle of "induction" will introduce 100 mg venetoclax on day 1, 200 mg on day 2 and 400 mg on day 3, and no more than 400 mg will be given with each induction cycle.

6 SAFETY PLAN

6.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject on the study. This can include any unfavorable or unintended sign, symptom or disease temporally associated with the use of the therapy, regardless of causality with the therapy. This may include use of the therapy as stipulated in the protocol or as labeled or from accidental or intentional overdose. Worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are AE only if they result in study discontinuation, necessitate medical intervention, meet protocol specific criteria, and/or are considered by the investigator to be clinically significant or AEs. Elective surgeries or procedures scheduled to occur during a study are not AEs if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorated unexpectedly during the study (e.g. the surgery must be performed earlier than planned) then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

A treatment-emergent AE is defined as any AE reported by a subject with onset or worsening from the time that the first dose of study drug is administered until end of treatment.

6.2 Serious Adverse Events

If an AE meets any of the following criteria it is to be considered a serious adverse event (SAE) and must be reported to Abbvie within 24 hours, see Section 6.8.2.

The PI will then review and submit to the University of Colorado regulatory authorities and the FDA, if applicable, in accordance with 21 CFR 312.32.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form. SAE form can be found at:

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Fatal:	AE resulted in death

Life threatening:	The AEs placed the patient at immediate risk of death in the opinion of the investigator. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization or prolongation of hospitalization:	AE that required hospitalization for any length of time or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan are not SAEs by this criterion. Admissions to an outpatient facility, emergency room, palliative unit or hospice care facility are not considered to be hospitalizations and are not SAEs.
Disabling/incapacitating	AE that results in substantial and permanent disruption of the patient's ability to carry out normal life functions. Does not include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. ankle sprain)
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the treatment regimen before conception or during pregnancy.
Important medical event requiring medical or surgical intervention to prevent serious outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death, life-threatening, hospitalization or prolongation of hospitalization, congenital anomaly or persistent or significant disability/incapacity). Any elective or spontaneous abortion or stillbirth is considered a SAE.

For SAEs that result in death, the date and cause of death will be recorded in the case report form.

Deaths due to disease progression will not be recorded as SAEs.

Hospitalization to allow observation and management for the purpose of TLS prophylaxis will not be considered SAEs unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization (e.g., abnormal post-dose TLS laboratories that necessitate therapeutic medical intervention).

Hospitalization of a subject in post-treatment follow up or survival 30 days or more after discontinuation of the therapy will not be recorded as a SAE.

SAEs occurring after informed consent but prior to initiation of therapy will be collected only if felt by the investigator to be causally related to the study required procedures.

For hospitalizations or surgical or diagnostic procedures, the illness leading to the hospitalization or surgical or diagnostic procedure will be recorded as the SAE, not the procedure itself. The procedure will be captured in the narrative as part of the action taken in response to the illness.

6.3 Adverse Events Commonly Associated with AML

Certain AEs are anticipated to occur in this study population at some frequency independent of drug exposure. For example, cytopenias (anemia, neutropenia, thrombocytopenia) are part of the natural history of AML. Therefore, persistent cytopenias at the same CTCAE grade as at baseline are not to be reported as AEs, unless they meet criteria for an SAE, result in permanent discontinuation of a study drug, or the investigator has an identifiable cause other than the underlying disease.

6.4 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.0). If a reported AE increases in severity, the initial AE should be given final outcome date and a new AE must be reported to reflect the change in severity.

For AEs not captured by the CTCAE, the following should be used:

Grade 1	The AE is transient and easily tolerated by the subject (mild).
Grade 2	The AE causes the subject discomfort and interrupts the subject's usual activities (moderate)
Grade 3	The AE causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe)
Grade 4	The AE is life-threatening requiring urgent intervention (severe)
Grade 5	The AE resulted in death of the subject (severe)

6.5 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility of Relationship with Azacitidine	An AE where this is evidence to suggest a causal relationship between azacitidine and the AE
No Reasonable Possibility of Relationship with Azacitidine	An AE where this is no evidence to suggest a causal relationship between azacitidine and the AE
Reasonable Possibility of Relationship with Venetoclax	An AE where this is evidence to suggest a causal relationship between venetoclax and the AE
No Reasonable Possibility of Relationship with Venetoclax	An AE where this is no evidence to suggest a causal relationship between venetoclax and the AE

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." When no reasonable possibility of an association between a study drug and a SAE exists, the investigator must provide another cause.

6.6 Deaths

Death is an outcome of an event. Deaths that occur during the AE reporting period that are attributed by the investigator to AML progression will be recorded as such. For all deaths, the event or condition that caused or contributed to the fatal outcome will be recorded as the single medical concept on the AE CRF. If the cause of death is unknown and cannot be ascertained, “unexplained death” should be recorded. If the cause later becomes available, “unexplained death” should be replaced with the established cause of death.

6.7 Recording Adverse Events

Patient safety will be assessed by reviewing AEs during planned and unplanned visits and physical and laboratory examinations from the time the patient receives the first dose of study drug until 30 days after the patient’s last study treatment. The investigator will assess and record AEs in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to the study drug, and any action taken. For SAEs considered unrelated to study drug, the investigator will provide another cause for the event. AEs may be recorded as the result of a response to a query, an observation by site personnel, or due to a report from a subject. All AEs will be followed to a satisfactory conclusion.

6.8 Investigator Reporting Responsibilities

The conduct of the study will comply with all Food and Drug Administration (FDA) safety reporting requirements. If the FDA determines an IND is necessary, it is a requirement of 21 CFR 312.33 that an annual report be provided to the FDA within 60 days of the IND anniversary date. 21 CFR 312.33 provides the data elements that are to be submitted in the report. The annual report should be filed in the study's regulatory binder, and a copy provided to Abbvie as a supporter of this study.

6.8.1 Adverse Event Reporting

All AE reports will include the patient’s number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to the study (fatal relationship, definitely related, possibly related, unrelated),

date of administration of test medications and the investigators will notify the IRB and DSMC of a SAE according to institutional policy.

6.8.2 Reporting to Abbvie

Serious adverse events (SAE) are defined in Section 6.2.

In addition to compliance with all FDA reporting requirements pursuant to 21 CFR 312, the Principal Investigator shall:

a) Report to Abbvie all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie; and in addition, report all non-serious adverse events of tumor lysis syndrome for studies involving ABT-199.

b) Copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and,

c) Notify AbbVie upon any subjects receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports shall be PPDINDPharmacovigilance@abbvie.com

Product Complaints: In addition to compliance with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, Principal Investigator will report to AbbVie within 24 hours any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labeling, or medical device component (collectively, "Product Complaint"). Principal Investigator will report Product Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the Study or not. AbbVie's contact for reporting Product Complaints shall be RD_PQC_QS@abbvie.com

6.8.3 Reporting From Abbvie

Abbvie will notify the investigators via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity

The investigators will notify the IRB promptly of these new serious and unexpected AEs or significant risks to subjects. The investigators must keep copies of all AE information, including correspondence with Abbvie and the IRB, on file.

6.9 Pregnancy

The likelihood of pregnancy occurring in a subject in this study is very small as all subjects will be aged 60 or older. Subjects who become pregnant during the study must discontinue study drugs immediately. All pre-menopausal subjects will be informed that contraceptive measures should be taken throughout the study and for 30 days after the last dose of venetoclax. Male subjects will be informed that contraceptive measures should be taken by them and by their potentially fertile female partners. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. If the subject's partner should become pregnant during the study, this should be reported. Pregnancy in a study subject is not an AE. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion is considered a SAE and must be reported as such (see Section 6.2).

6.10 Prophylaxis and Management of Tumor Lysis Syndrome

TLS is a potential risk for all patients with AML, particularly those with risk factors such as renal dysfunction and increased WBCs. To mitigate this risk, in addition to intra-patient dose escalation over the course of several days, patients will receive TLS prophylactic measures prior to initial therapy; in some cases, these measures may need to be re-implemented in the setting of a treatment interruption or dose delay prior to resuming therapy. Despite considerations surrounding TLS in CLL patients receiving

venetoclax, safety data from 94 subjects treated with venetoclax in 3 AML studies have shown no evidence of TLS.

Below are the minimum requirements for TLS prophylaxis and monitoring, which will be performed in addition to institutional standards:

- All subjects will be hospitalized on or before cycle 1 day 1 prior to the administration of the initial dose of study treatment, and remain in the hospital for at least 24 hours after reaching the final escalated dose of venetoclax.
- Administration of uric acid reducing agent, adequate oral and intravenous hydration while monitoring the fluid status of the subject prior to and during the venetoclax dose escalation will be performed per institutional standards.
- TLS chemistry tests (calcium, phosphorus, potassium, uric acid and creatinine) will be drawn: A) On the first day of venetoclax dosing, within 4 hours prior to the dose and again 6 and 12 hours (+/- 2 hours) after the first dose, and B) On each day of dose escalation, within 4 hours prior to the dose and again 6 and 12 hours (+/- 2 hours) after the dose. Additional laboratory assessment may be performed at the investigator's discretion post-dose during the escalation and up to 48 hours after reaching the final dose.
- After dose escalation, TLS will be monitored with serial chemistry measurements (see Section 5.10) and more intensive measures may be considered for patients felt to be at higher risk.
- Abnormal chemistry tests should be corrected promptly
- If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax dose should be administered until resolution
- Prophylactic reductions of potassium, phosphorus and/or uric acid above normal ranges are recommended prior to beginning study treatment and should continue based on the ongoing risk of TLS.
- In the setting of rasbirucase, follow institutional sample handling procedures to ensure the proper measurement of TLS laboratory values

6.11 Decreased Spermatogenesis

Based on preclinical data, venetoclax has the potential to decrease spermatogenesis. Male subjects considering preservation of fertility should consider sperm banking before treatment with venetoclax.

6.12 Management of Infection

Anti-infective prophylaxis will be implemented per institutional guidelines with consideration for possible drug interactions. Please see Appendix A for excluded and cautionary medications.

6.13 Management of Other Toxicities

If other events occur that are related to the study drugs, the investigator may interrupt or dose reduce the therapies has appropriate. Grade 3 or greater non-hematologic toxicity that is related to the study drugs will require interruption and possible discontinuation. Therapy may be re-introduced, potentially at a reduced dose, if the toxicity returns to baseline if grade 2 at study entry or ≤ grade 1.

7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, good clinical practice or standard operating procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

Intentional deviations are not allowed unless necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirement and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the study team will keep record of deviations and is responsible for reporting to the IRB as required.

8 STATISTICAL METHODS

Patients who receive at least one dose of venetoclax or azacitidine will be evaluable for safety and efficacy. Patients who do not complete at least one cycle of therapy may be replaced.

8.1 Demographics

Descriptive statistics will be provided for demographic variables.

8.2 Efficacy Analysis

Efficacy will include analyses of ORR as defined as PR+CR+CRi+MLFS, MRD positive responses, and MRD negative CR+CRi+MLFS (MRD-negative composite responses), median time to achieve a MRD negative response, duration of overall response, event free survival and overall survival.

8.3 Safety Analysis

Safety will be assessed by analysis of AEs, SAEs, all deaths, changes in laboratory values and vital sign parameters. Analysis of AEs will include only treatment-emergent events (events that had onset on or after the first dose of study drug). Analysis of AEs and SAEs will not include those that have an onset >30 days after the last dose of study drug. Toxicity grades using NCI CTCAE V4.0 and relationships to study drugs will be assessed. In addition, incidence of febrile neutropenia, ≥ grade 2 bleeding complications (red blood cells and platelets) will be assessed.

8.4 Deaths

The number of subject deaths will be analyzed by those that occurred within 30 days of the last dose of study drug, those that occurred more than 30 days after the last dose of study drug, those that occurred within the first 30 days of the study, those that occurred within the first 60 days of the study, those that were related to study drug and those that were unrelated to study drug.

8.5 Sample Size Determination

In the M14-358 study combining azacitidine and venetoclax (NCT02203773), the median remission duration is 8 months. For the

proposed study, we define success as an observed median remission duration of 12 months and formally define the research hypotheses as follows: H_0: The median remission duration is 8 months and H_1: The median remission duration is 12 months. Under the assumptions of uniform accrual over time, no loss to follow-up, and exponentially distributed remission times[39], we will require 42 patients to allow for 80% power to detect this difference with a significance level of 0.10 given 30 months accrual time and 12 months of follow-up, and a single sample one-sided log-rank test used in the analysis. To allow for a 20% withdrawal or loss to follow up rate, we will enroll 42 patients. A "survival" curve and its 90% confidence interval as well as the median remission duration will be computed for the data.

8.6 Statistical Analysis Plan

For every relapse that occurs before 8 months in patients accrued to the study, the Kaplan-Meier product-limit method will be used to estimate the survival function at the time of relapse ti. For each time ti ≤ 8 months that a relapse is observed, the median survival time will be estimated using linear interpolation and the estimated survival function. If at any time ti ≤ 8 months the median remission duration falls below 8 months, then the study will be stopped. In some instances, too many censored observations (i.e. patients who are still in remission) will result in an inability to estimate the median remission duration. However, this will only occur when more than half of the enrolled patients have not relapsed and there is therefore no statistical evidence to indicate that the observed median remission duration is less than ti. This evaluation will be made on a continuous basis.

9 ETHICS

9.1 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Colorado Multiple Institutional Review Board (COMIRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by COMIRB before the changes are implemented to the study. All changes to the consent form will COMIRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.2 Ethical Standards

Good clinical practice (GCP) requires that the protocol, amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study and any other necessary documents be reviewed by the IRB. The IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB approval of the protocol, informed consent and subject information will be obtained prior to the authorization of drug shipment to the study site.

Amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive essential documents.

During the conduct of the study the investigator will promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects.

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki.

9.3 Informed Consent Process

Prior to the initiation of any screening or study-specific procedures, the IRB approved consent form(s) describing in detail the study agent, study procedures, and risks will be given to the subject and the investigator or her representative will explain the nature of the study to the subject and answer all questions regarding the study. Each informed consent will be reviewed, signed and dated by the subject and the person who administered the informed consent as well as the investigator. Written documentation of informed consent will be required prior to starting intervention/ administering study procedures and a copy of the informed consent will be given to the subject with the original placed in the subject's file. An entry will be made in the source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects

will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10 SOURCE DOCUMENTS AND CASE REPORT FORMS

Accurate, complete, legible and timely records and data will be kept in the source documents of all drug administration, including prescribing and dosing. Source documents are defined as original documents, data and records that pertain to the conduct of the study and distribution of the protocol therapy. These may include but are not limited to, copies of CRFs, hospital records, clinical and office charts, laboratory data/information, subject diaries or evaluation checklists, SAE reports, pharmacy dispending and other records, recorded data from automated instruments, and/or imaging studies. Data collected must be recorded on the appropriate source document.

Study documents will be retained for as long as necessary to comply with all applicable regulations and institutional requirements. By signing the protocol, the investigators agree to adhere to the document/records retention procedures.

The investigator and institution will permit study-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data documents.

Case report forms (CRFs) must be completed for each subject screened/enrolled in the study.

11 STUDY OVERSIGHT – Quality Assurance and Quality Control

11.1 Data Safety and Study Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical

studies at the CU Cancer Center, which is the coordinating institution of this trial.

A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.
Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote); this will also be shared with Abbvie at their request. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

11.2 Clinical Monitoring

Clinical site monitoring visits will be performed by the CU Cancer Center Clinical Monitor on a regular basis, pursuant to the Clinical Monitoring Plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency

monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s). During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI.

11.3 Study Auditing

Independent audits will be conducted by the CU Cancer Center DSMC to ensure monitoring practices are performed consistently across all participating sites, if applicable, and that monitors are following good clinical practices. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

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Appendix A: Excluded and Cautionary Medications and Sample List

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 Or Reduced at the Designated Venetoclax 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 for guidance.
Cautionary
Warfarin **P-gp substrates** **BCRP substrates** **OATP1B1/1B3 substrates** **P-gp inhibitors** **BCRP inhibitors**

Sample List of Excluded and Cautionary Medications

Excluded during ramp-up phase and Cautionary at the Cohort Designated Dose:
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.