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1. OBJECTIVES

1.1 Primary Objectives

Phase 1b: To determine the safety and tolerability and recommended phase 2 dose (RP2D) of omacetaxine in combination with venetoclax for patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome harboring a *RUNX1* mutation

Phase 2: To determine the efficacy of omacetaxine in combination with venetoclax for patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome harboring a *RUNX1* mutation

1.2 Secondary Objectives

The secondary objectives of the study are:

1.2.1. To determine duration of response (DOR), event-free survival (EFS), and overall survival (OS)

1.2.2. To evaluate occurrence of minimal residual disease (MRD) negative status by multiparameter flow cytometry and molecular evaluation

1.3 Exploratory Objectives

1.3.1. To investigate global gene expression profiles, DNA methylation profiles, BH3 profiling and other potential prognostic markers to explore predictors of antitumor activity and/or resistance to treatment

2. BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

2.1.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells, characterized by differentiation arrest and rapid proliferation of abnormal myeloid precursors. These abnormal cells accumulate in the bone marrow and interfere with the production of normal blood cells. More than 20,000 people are diagnosed with AML per year in the United States (US) (SEER, 2015). The median age at diagnosis is 67 years old.

Outcomes for patients with AML remain poor.(Dohner et al., 2017) With modern treatment regimens, expected complete remission (CR) rates for newly diagnosed AML patients are 60-70% yet long term cure rates are only 15-25%. Younger patients (i.e. those 50 years of age or younger) with diploid karyotypes have a CR rate of 70-80% and cure rates of 20-25%, while older patients and/or those with adverse cytogenetics have CR rates of 35-50% and cure rates of $\leq$ 10%. Efforts to improve both the remission rate and the durability of remission in AML patients of all ages are paramount.

2.1.2. Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are malignant clonal disorders characterized by ineffective hematopoiesis, bone marrow dysplasia, peripheral cytopenias including thrombocytopenia, and a propensity to transform into acute myeloid leukemia (AML).(Albitar et al., 2002) Classically, MDS is associated with apoptosis and excessive proliferation, resulting in a paradoxical combination of a hyper-cellular marrow and peripheral cytopenias.(Dansey, 2000) The incidence of MDS in the United States is rising, with approximately 20,000 to 30,000 new cases of MDS diagnosed annually, and a median age at diagnosis of 70 years.(Ma, Does, Raza, & Mayne, 2007)

Over the past decade, clinical use of the hypomethylating agent azacitidine has been shown to improve patient quality of life, decrease transfusion requirements, and improve outcome parameters in MDS patients, and is now a standard of care for MDS patients requiring therapy. With current HMA regimens, achievement of an ORR is estimated at 28-70%, with a CR rate of only 6-34% in patients with MDS treated with front-line HMA therapy, and with a median length of response in the HMA-responders of only 8 to 10 months.(Jabbour et al., 2010; Prebet et al., 2011)

MDS patients requiring therapy include those with intermediate-2 or High-risk disease by IPSS, or high or very-high risk by R-IPSS. In addition, patients with otherwise intermediate MDS with high-risk molecular features including *TP53*, *ASXL1*, *EZH2*, and/or *RUNX1* mutations have

been identified as a subgroup that may benefit from early therapeutic intervention.(Bejar et al., 2012)

Prognosis in HMA-failure patients is extremely poor. Jabbour et al report a median survival of merely 4 months in MDS patients with progressive disease after decitabine, and Prebet et al identified a median survival of 5.6 months in MDS patients with progressive disease after azacitidine. There are no currently approved agents in the setting of HMA-failure MDS patients, and there are limited therapeutic options, particularly given the increased age and frequent comorbidities of this population.

2.1.3. RUNX1 Biology and RUNX1 Mutations in Myeloid Malignancies

Runt-related transcription factor 1 (*RUNX1*) is a key hematopoietic transcription factor that regulates genes involved in myeloid differentiation, and is generally considered to be a classical tumor suppressor (class II) mutation.(Mangan & Speck, 2011) Mutations of *RUNX1* are reported in approximately 10–16% of AML patients and 12–24% of myelodysplastic syndrome (MDS) patients.(Gaidzik et al., 2016) The majority of mutant (mt) RUNX1 are missense, large deletions or truncation-mutations, behaving mostly as loss of function (LOF) mutations.(Mangan & Speck, 2011; Mill et al., 2019)

RUNX1 alterations predominate in the morphologically undifferentiated French-American-British (FAB) M0 subtype. Clinical features associated with this mutation include older age, male sex, and absence of cytogenetic abnormalities.(Gaidzik et al., 2016; Khan et al., 2017)

RUNX1 mutations are correlated with poor clinical outcomes, resistance to chemotherapy and higher rates of refractory disease. Gaidzik et al. compared 53 mutant *RUNX1* and 831 wild-type *RUNX1* newly-diagnosed AML patients, and found inferior rates of event-free survival (EFS), relapse-free survival (RFS), and overall survival (OS) in *RUNX1*-mutated patients in patients 60 years of age or younger and treated with intensive chemotherapy (EFS, 8% vs. 30%; RFS, 26% vs. 44%; OS, 32% vs. 45%). In an analysis of AML patients treated with intensive chemotherapy by Tang et al, the complete remission rate was lower in 62 newly-diagnosed patients with *RUNX1*-mutated AML compared with 408 without the mutation (56.8% vs. 77.5%). A statistically higher incidence of induction-related death in patients with mutant-*RUNX1* AML (10.8% vs. 6.5%) was also identified.(Tang et al., 2009)

We previously reported that knockdown (KD) of RUNX1 (wild type and mtRUNX1) is significantly more lethal toward AML blasts progenitor cells (BPCs) expressing mutant (mt) versus wild type (wt) RUNX1 or normal hematopoietic progenitor cells (HPCs), indicating greater dependency on the residual wtRUNX1.(Mill et al., 2019) Based on higher occupancy of the BET protein BRD4 at the RUNX1 super-enhancer/enhancer (SE/E) and other SE-driven AML-relevant oncogenes, BET inhibitor treatment evicts BRD4 from the chromatin and represses RUNX1 and SE-driven oncogenes, mediating efficacy against AML BPCs expressing mtRUNX1.(Bradner, Hnisz, & Young, 2017; Roe, Mercan, Rivera, Pappin, & Vakoc, 2015; Shi &

Vakoc, 2014) Utilizing the RNA-Seq signature of RUNX1-depleted (by shRNA) AML cells and conducting LINCS (Library of Integrated Network-based Cellular Signatures) 1000-CMap (Connectivity Mapping) analysis (B8), we discovered several expression mimickers (EMs), including the top-ranking protein-translation inhibitor homoharringtonine (HHT), or its semisynthetic analogue omacetaxine mepesuccinate (OM).(Lu & Wang, 2014; Mill et al., 2019) We tested the pre-clinical efficacy of HHT or OM against AML cell lines (OCI-AML5 and Mono-Mac-1) and patient-derived primary AML BPCs expressing somatic mtRUNX1 or wtRUNX1. Treatment with HHT or OM induced more lethality in AML cells, including primary AML BPCs, expressing mtRUNX1 compared to wtRUNX1, or in normal bone marrow progenitor cells ($p < 0.05$).(Mill et al, submitted) Notably, first-time ever, CRISPR-Cas9-mediated knock-in of mtRUNX1 (R174*) into wtRUNX1-expressing the AML HL-60 and OCI-AML2 cells showed that, in this isogenic setting also, HHT or OM, or OTX015 (100 to 1000 nM) treatment induced significantly more lethality in mtRUNX1 versus wtRUNX1-expressing cells ($p < 0.01$). The differential lethal activity of HHT in the AML cells was associated with marked HHT-mediated depletion of c-Myc, c-Myb, PU.1, mt/wtRUNX1 and MCL1 in mtRUNX1 expressing AML HL60-R174* and OCI-AML2-R174* cells.(Mill et al., 2019) Possibly due to HHT mediated MCL1 repression, co-treatment with HHT and venetoclax (10 to 100 nM), synergistically induced in vitro apoptosis of OCI-AML5, HL60-R174* and OCI-AML2-R174* cells (Combination Indices < 1.0) (B11,B12). Compared to vehicle control, whereas daily treatment with OM (1.0 mg/kg, SQ) alone for 3 weeks significantly reduced leukemia burden, co-treatment with OM and venetoclax (20 mg/kg orally) exerted significantly greater reduction in AML burden due to luciferized OCI-AML2-R174* cells engrafted into NSG mice. (Mill et al, submitted) Combined therapy with OM and venetoclax also improved survival of the mice engrafted with OCI-AML2-R174* cells, without inducing weight loss or any other toxicity (Mill et al, submitted).

Additionally, **inherited** mutations in RUNX1 lead to an autosomal dominant cancer predisposition syndrome (OMIM #601399) termed FPD/MM, or *familial platelet disorder with a propensity to myeloid malignancies* (also referred to in medical literature as FPD/AML). In 2016, the World Health Organization (WHO) incorporated germline RUNX1 within a new sub-category of myeloid neoplasms and acute leukemia, defined as “myeloid neoplasms with germline predisposition and preexisting platelet disorder” increasing public awareness of this predisposition.(Arber et al., 2016)

Germline RUNX1 mutations are associated with lifetime mild to moderate thrombocytopenia associated with aspirin-like functional platelet defects, along with a ~44% lifetime risk of developing MDS or AML. Median age at diagnosis of hematologic malignancy is 33 years, though the reported range of 5 to 76 years at the time of MDS or leukemia diagnosis is broad and the cumulative risk of developing hematologic malignancy may be as high as 79% by age 70 years.(Brown, Arts, et al., 2020; Brown, Hahn, & Scott, 2020; Feurstein, Drazer, & Godley, 2016) Among the common somatic co-mutations observed in FPD/MM are mutations in the second RUNX1 allele, GATA2, FLT3, KRAS, BCOR, PHF6, WT1, DNMT3A, TET2 and UTAF. Patients with biallelic RUNX1 mutations are associated with even poorer outcome, indicating a dosage effect.(Brown, Arts, et al., 2020)

We recently also established in culture, first time ever, a germ-line mtRUNX1 (K194N)-expressing FPD/MM cell line (GMR-AML1) form the bone marrow aspirate (BMA) cells of a patient with FPD-MM that also expressed mutations in BCOR, PHF6, SRFS2 and SF3B1. (Mill et al, submitted). Exposure to HHT (10 to 100 nM) dose-dependently inhibited colony growth and induced lethality in GMR-AML1 cells. Treatment with HHT also exerted differentially greater in vitro lethality against HPCs derived from BMA from FPD-MM expressing germline mtRUNX1, along with other MDS/AML-associated co-mutations, compared to RUNX1-FPD HPCs. These studies highlight that treatment with OM could potentially have greater efficacy against AML expressing mtRUNX1. Additionally, in the AML with germline mtRUNX1, OM treatment could potentially revert FPD-MM hematopoiesis back to the RUNX1-FPD status. Collectively, our preliminary findings strongly support the merit of testing co-treatment with OM and venetoclax in patients with AML expressing somatic mtRUNX1, as well as in FPD-MM prior to or instead of allogeneic SCT from an unrelated donor.

2.2. Overview of Treatment

2.2.1. Omacetaxine

OM is a semisynthetic version of a plant alkaloid extracted from Cephalotaxus fortunei, a species of evergreen tree that is indigenous to China. It is available in China for the treatment of hematological malignancies. OM mechanisms of action include protein synthesis inhibition and induction of differentiation and apoptosis.(Boyd & Sullivan, 1984; Huang, 1975) Recent studies indicate OM is affecting histone deacetylase and is also a potent angiogenesis inhibitor. OM has shown activity in AML and other hematologic cancers, including acute promyelocytic leukemia (APL), chronic myeloid leukemia (CML), and MDS. Studies from China reported high response rates in patients with leukemia, trials in the U.S. have shown significant activity as well.(H. Kantarjian et al., 2015; H. M. Kantarjian et al., 2001) In a Phase I-II trial, Warrell et al. treated 49 patients with refractory AML with OM, 5 or 7 mg/m^2 daily for 7 days and 5 mg/m^2 daily for 9 days (25-49 mg/m^2 per course), in a continuous infusion schedule(Warrell, Coonley, & Gee, 1985). Dose escalation beyond 5 mg/m^2 daily resulted in frequent interruption of OM infusion because of hypotension. Hypotensive episodes occurred in approximately 30% of patients; myalgias occurred in 20% of patients and hyperglycemia in 57% of patients (it was severe in 23%). A schedule of 5 mg/m^2 daily for 9 days was judged reasonable. Of 28 evaluable patients with AML who were treated with cumulative doses of 45-49 mg/m^2, 7 (25%) achieved a CR. The recommended dose schedule of OM was 5 mg/m^2 daily for 9 days.

In another study, Kantarjian et al. investigated OM in a lower dose, longer infusion schedule of 2.5-3 mg/m^2 by continuous infusion daily for 14-21 days in patients with refractory-recurrent acute leukemia in an attempt to demonstrate efficacy without hypotensive events. While the response rate was low in this AML refractory group of patients, the longer infusion lower daily dose schedule averted cardiovascular toxicity.(H. M. Kantarjian et al., 1989) The summary Phase I-II trials of OM conducted at the Memorial Sloan-Kettering Cancer Center, New York Medical College, and the Eastern Cooperative Oncology Group included 117 patients with

refractory AML treated at doses of 5-7 mg/m^2 daily by continuous infusion. Among 91 evaluable patients, 14 achieved a CR (15%) and 1 achieved a partial response.

In the New York Medical College studies, Feldman et al. used OM, 5 mg/m^2, by continuous infusion daily for 9 days in patients with refractory-recurrent acute leukemia or blastic phase CML.(Feldman et al., 1992) Sixty-six patients were treated; their median age was 41 years. CRs were achieved in 7 of 43 patients (16%) with recurrent AML, in none of 11 patients with AML that primarily was resistant to anthracycline-cytarabine combinations, and in 2 of 3 patients whose disease was resistant to low-dose cytarabine. Side effects included significant hypotensive events, fluid retention, weight gain (29%), and hyperglycemia (63%). Other studies have also demonstrated the activity of OM in AML.

Given the excellent bioavailability of subcutaneous OM and its ability to be administered in the outpatient setting, OM was subsequently developed as a treatment for CML. Based on promising clinical activity in several phase II studies, OM was granted U.S. Food and Drug Administration approval in October 2012 for treatment of adults with chronic- or accelerated-phase CML who are resistant and/or intolerant to two or more tyrosine kinase inhibitors.

Recently, a trial of low-dose omacetaxine for patients with relapsed MDS was performed at our institution at a dose of 1.25 mg/m2 subcutaneously twice daily on a 3 day schedule.(Short et al., 2019) Forty two patients were enrolled, with a median age of 76 years. The ORR was 33%, with a median OS of 7.5 months. The most common grade $\geq$ 3 adverse events were infections (26%), febrile neutropenia (10%), and hemorrhage (7%) Of importance, two patients had ongoing response to OM lasting 2 years or longer, and both patients were noted to have RUNX1 mutations.

We have recently also reported our experience using OM for 3 days in combination with low-dose cytarabine. This combination was found to be safe and effective in inducting an objective response rate of 50% (CR rate of 30%) with a median survival of 9.3 months.

2.2.2. Venetoclax

See the Prescribing Information for full details on non-clinical and clinical studies.

Hematologic malignancies are highly dependent upon the anti-apoptotic protein BCL-2 for survival. Over-expression of BCL-2 is associated with tumor initiation, disease progression, and drug resistance, and is a compelling target for anti-tumor therapy.(Pan et al., 2014) Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of BCL-2 that binds with > 1,000-fold higher affinity for BCL-2 (K_i < 0.010 nM) than for BCL-X_L (Ki = 48 nm) or MCL-1 (K_i > 444 nM). In vitro, venetoclax has demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines, including acute myelogenous leukemia (AML).(Souers et al., 2013)

In mouse, rat, monkey, and dog, the venetoclax pharmacokinetic profile was characterized by low plasma clearance (CLp = 0.02 to 0.27 L/hr•kg) and low volumes of distribution (V_{ss} = 0.3 to 1.1 L/kg). Half-lives ranged from 2.2 hours in monkey to 12.0 hours in dog. Formulation-dependent oral bioavailability was noted in all species. Studies in both rat and dog have defined the behavior of the amorphous solid dispersion (ASD) 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.

Preliminary efficacy and safety results of venetoclax monotherapy and combination therapy in AML are favorable and support further evaluation of venetoclax in combination approaches.

3.0 STUDY ELIGIBILITY:

3.1. Inclusion Criteria:

1. Patients with a diagnosis of relapsed or refractory AML (or biphenotypic or bilineage leukemia including a myeloid component) or myelodysplastic syndrome
2. For relapsed/refractory AML, patients should not be eligible for approved therapies known to be effective for their AML subtype
3. For MDS patients, patients must have no response, progression, or relapse following at least 4 cycles of azacytidine or decitabine; and/or intolerance defined as grade $\geq$ 3 drug-related toxicity precluding continued therapy.
4. Age >/=18 years
5. Subjects must have documented *RUNX1* gene mutation
6. Eastern Cooperative Oncology Group (ECOG) Performance Status </=2
7. Adequate renal function (creatinine clearance $\geq$30 ml/min)
8. Adequate hepatic function (direct bilirubin < 2x upper limit of normal (ULN) unless increase is due to Gilbert's disease or leukemic involvement, and AST and/or ALT < 3x ULN unless considered due to leukemic involvement)
9. In the absence of rapidly proliferative disease, the interval from prior treatment to time of initiation will be at least 7 days for cytotoxic or non-cytotoxic (i.e. immunotherapy) agents. Oral hydroxyurea, leukapheresis, and/or low doses of cytarabine (i.e. 20 mg/m^2) for patients with rapidly proliferative disease is allowed before the start of study therapy, as needed, for clinical benefit and after discussion with the PI.
10. Male subjects must agree to refrain from unprotected sex and sperm donation from initial study drug administration until 90 days after the last dose of study drug.
11. Willing and able to provide informed consent.

3.2. Exclusion Criteria:

1. Patients with t(15;17) karyotypic abnormality or acute promyelocytic leukemia (French-American-British [FAB] class M3-AML).

2. Patients with any concurrent uncontrolled clinically significant medical condition including active infection or psychiatric illness, which could place the patient at unacceptable risk of study treatment.
3. Patients with active graft-versus-host-disease (GVHD) status post stem cell transplant (patients without active GVHD on chronic suppressive immunosuppression and/or phototherapy for chronic skin GVHD are permitted after discussion with the PI).
4. Patients with any severe gastrointestinal or metabolic condition which could interfere with the absorption of oral study medications.
5. Known active hepatitis B (HBV) or Hepatitis C (HCV) infection, or active/uncontrolled HIV infection, AIDS, or currently taking contraindicated medications for HIV control.
6. Subject has a white blood cell count > 25 x 10^9/L. (Note: Hydroxyurea is permitted to meet this criterion.)
7. Nursing women, women of childbearing potential (WOCBP) with positive urine pregnancy test, or women of childbearing potential who are not willing to maintain adequate contraception for the duration of study extending to 6 months after cessation of study drug
   A. Appropriate highly effective method(s) of contraception include oral or injectable hormonal birth control, IUD, and double barrier methods (for example a condom in combination with a spermicide).

4.0 TREATMENT PLAN:

4.1 Study Design and Description of Study Treatments:

This study will be a Phase 1b/II single center, open-label, non-randomized clinical trial with the dual primary objectives of assessing the safety and efficacy of omacetaxine in combination with the BCL2 inhibitor venetoclax for patients with RUNX1-mutated relapsed or refractory AML or MDS. Up to 12 cycles will be administered.

Patients will be instructed to self-administer OM at home and return unused intact drug syringes to be disposed of by the study staff. Patients will be given a Research Medication Diary to record the medication taken each day. Patients will be instructed to bring the diary and any unused intact medication syringes with them to all study visits. Any unused drug will be disposed of per institutional standard practice.

4.2 Phase 1b Portion:

A maximum of 12 patients will be treated in Arm A (AML) and Arm B (MDS), respectively. Patients will be enrolled in cohorts of 3 within each arm. The starting dose in both arms will evaluate omacetaxine via subcutaneous injection at a dose of 1.25 mg/m^2 twice daily for 3 consecutive days on days 2-4, in combination with venetoclax 400mg orally daily on days 1-10 per treatment cycle.

The RP2D will be selected at the end of the Phase 1b portion based on safety data , in Arms A and B independently. Preliminary efficacy and PK data for each dose level may also be considered as appropriate. Once the RP2D has been identified, that Arm will transition to the respective Phase 2 portion.

Table 1 below shows the planned dose levels, with the starting dose being dose level 0. Patients treated in the Phase 1b portion that are removed from study before day 28 for any reason other than toxicity, and have not experienced DLT, will be replaced.

Table 1: Dose de-escalation for omacetaxine and venetoclax

Dose Level	omacetaxine	venetoclax
+1	1.25 mg/m2 BID days 2-4	400mg QDAY days 1-14
0 (starting dose)	1.25 mg/m2 BID days 2-4	400mg QDAY days 1-10
-1	1.25 mg/m2 BID days 2-3	400mg QDAY days 1-10
-2	1.25 mg/m2 BID days 2-3	400mg QDAY days 1-7

Dose levels outside of this table may be considered based on review of patient safety and efficacy and PK data and will be detailed in a subsequent amendment, if applicable.

4.3 Phase 2:

Up to 60 patients will be treated; up to 30 patients with AML (Arm A) and up to 30 patients with MDS (Arm B) at the recommended Phase 2 dose level. Note that based on the Phase 1b portion, the dose level for the Phase 2 portion of Arm A and Arm B may not be the same.

Treatment cycles will begin on day 1 of each new venetoclax cycle. Patients will receive one cycle every 4-6 weeks; delays of more than 6 weeks may be allowed if determined by the investigator to be in the best interest of the patient, after discussion with the PI and documentation in the patient's medical record.

4.4 Study Duration:

4.4.1. Treatment will continue for 12 total cycles unless discontinuation occurs earlier due to relapse, unacceptable toxicity, or disease progression. Reasons for study treatment discontinuation include:

- clinically significant progressive disease at any time, or
- Possibility of undergoing allogeneic stem cell transplantation
- intercurrent illness that prevents further administration of treatment, or
- unacceptable adverse event(s), or
- patient decision for study withdrawal, or
- general or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- lack of clinical response by 6 cycles of treatment (clinical response as per Section 6.1.1 or 6.1.3 including ORR or hematologic improvement)

Patients may remain on study for the planned 12 cycles of treatment, as long as the patient continues to demonstrate clinical benefit and no excessive toxicity (i.e. no clinically significant study-drug related grade $\geq$ 3 toxicity).

4.4.2. Dose modifications and interruptions are permitted as necessary for the clinical benefit of the patient. If side effects or toxicity are related to one study drug only; patients may proceed with dose modification and/or discontinuation of that agent and continue treatment with the remaining study agent, if in the investigator's assessment the patient continues to demonstrate clinical benefit and all protocol-specified criteria for continuation of study treatment are met. All dose modifications should be discussed with the PI and clearly documented in the medical record. Treatment may be held as long as clinically necessary for resolution, after discussion with the PI.

For patients with study-drug related clinically significant toxicities, the following dose adjustment rules apply:

- **For Grade 0-2 non-hematological toxicities, no dose reduction is required. For grade 2 toxicities that are persistent and/or intolerable (e.g. stomatitis), patients may have a treatment interruption or dose reduction to the next lower dose level.**
- **For Grade 3-4 clinically significant non-hematological toxicity, hold until recovery to Grade 0-1, or to baseline if Grade 2 at study entry. Dose should be reduced to -1 dose level, if applicable.**

- Dose reductions beyond those mentioned in Table 1 or different to the doses specified should be discussed with the PI and documentation of the justification recorded in the medical record.

For specific recommendations regarding management of myelosuppression at any time on study, please see guidance in Section 5.6 and 5.7 of protocol.

4.4.3. All patients discontinued from study treatment for any reason other than withdrawal of consent for treatment and follow-up will continue to be assessed for survival. **Survival information (i.e. the date and cause of death) will be collected via telephone calls and/or clinical visits every 3 months (+/- 1 month) for a period of 2 years on any remaining subject that has enrolled on the study.**

5.0 STUDY PROCEDURES

5.1 Screening

The following procedures will be performed during screening, staging and workup. These procedures are to be performed within 14 days prior to study drug administration, except as indicated below. The same screening procedures will be performed for both the Phase 1b and Phase 2 study portions.

A signed and dated IRB approved informed consent form must be obtained before any study specific procedures are performed. Procedures that are part of routine care are not considered study specific procedures. All subjects will be screened for eligibility before enrollment. Once the subject has met all inclusion criteria, without meeting any exclusion criteria, they may be enrolled onto the study.

5.2.1. Table of Events

	Screening		Cycle 1				Cycle 2				Add'l Cycles	End of Study (EOS)
Cycle Day		**-1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	
Study Day	**-14 to 0**		**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**-**	
Complete history	X		X				X				X	
Physical examination[a]	X		X		X		X				X	X
TLS prophylaxis initiation		X										
Document all measurable disease (if present)	X											
CBC with differential[b]	X		X	X	X	X	X	X	X	X	X	X
Creatinine, total bilirubin, ALT and/or AST[b]	X		X	X	X	X	X	X	X	X	X	X
TLS Labs (Creatinine, potassium, Calcium, Uric acid, Phosphorus			X[i]									
Pregnancy test[c]	X											
Bone marrow biopsy and aspirate[d]	X					Day 21-28					X[h]	X
correlatives on blood[e]			X	X	X	Day 21-28						X
correlatives on bone marrow[f]	X					Day 21-28					X[f]	X

a) A complete physical examination will be done on day 1 of each cycle (+/- 7 days).
b) CBC with differential, creatinine, total bilirubin, ALT or AST will be done at least once weekly (+/- 4 days) for the first 2 cycles, then every 2-4 weeks on subsequent cycles.
c) Pregnancy test either urine or plasma should be done in women of childbearing potential within 72 hours before initiation of protocol therapy.
d) Bone marrow biopsy and aspiration must be done within 28-days of initiation of therapy; then after cycle 3, cycle 5, every 3 cycles thereafter, and end of study. Cytogenetics and molecular annotation may be used from prior bone marrow analysis (+/- 28 days) if these were not reported on the screening bone marrow.
e) Correlative studies will be collected on peripheral blood at Day 0 or Day 1 (prior to dosing), day 2, day 5, day 15, and between days 21 to 28 on cycle 1. Subsequently, peripheral blood will be obtained at progression if possible. Window of +/- 1 day during cycle 1, afterwards window will be +/- 7 days.

f) Correlative studies will be collected on bone marrow at baseline (prior to dosing), on day 28 (+/-7 days), and at progression.
g) EOS visits include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, AST or ALT). A bone marrow aspiration may be done if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood.
h) At subsequent cycles, bone marrow (aspiration and/or biopsy) will be performed every 3 cycles at the discretion of the treating physician
i) During cycle 1 venetoclax dosing ramp up, TLS lab monitoring (K+, uric acid, Phosphorus, Calcium and Creatinine) should occur at pre-dose, 6-8 hours post dose, and 24 hours post dose (inpatient AM labs may substitute for the 24 hour post-dose labs if applicable).

Correlative Sample Collection and Specifics:

Samples and Studies	Day 0 (prior to starting Ven and OM)	Day 2 (day after starting daily PO Ven but before OM)	Day 5 (At the end of OM treatment)	Day 15 or 22 (after starting therapy and only if AML is without response or progressing)	Day 28 (End of the first cycle of therapy)
Bone marrow aspirate (BMA) sample for NGS, FCM analysis, and Epigenome/transcriptome/proteome analyses	X			X only if AML is without response or progressing	X
Peripheral blood (PB) and/or BMA (if available) (two 8 ml heparinized green-top tubes) samples for harvesting fresh CD34+ mononuclear cells	X	X		X	X
ATAC-Seq and ChIP-Seq analyses on nuclei to determine accessible chromatin SE/E profile	X		X	X	X
RNA-Seq and QPCR analyses on total RNA to determine mRNA expression for gene-sets and signature profile	X		X	X	X
RPPA/Western on cell lysates to determine protein expression profile	X	X	X	X	X
Flow Cytometry on paraformaldehyde fixed cells	X	X	X	X	X
Confocal microscopy on cytospun paraformaldehyde-fixed cells	X		X	X	X

5.2.2. Cycle 1 day -1

To mitigate the risk for TLS, subjects must be receiving tumor lysis prophylaxis, including hydration (oral, intravenous) and treatment with a uric acid reducing agent (allopurinol, rasburicase) per institutional guidelines prior to and during the venetoclax ramp-up period of Cycle 1.

5.2.3. Cycle 1 Venetoclax Ramp Up:

Venetoclax will be administered at a dose of 100 mg (or equivalent) on day 1, 200 mg (or equivalent) on day 2, and 400 mg (or equivalent) on day 3-10 of the first cycle or at the RP2D duration.

During cycle 1 venetoclax dosing ramp up, TLS lab monitoring (K+, uric acid, Phosphorus, Calcium and Creatinine) should occur at pre-dose, 6-8 hours post dose, and 24 hours post dose (inpatient AM labs may substitute for the 24 hour post-dose labs if applicable).

No ramp up is required in subsequent cycles.

5.2.4. Treatment Schedule:

All subjects must complete a screening visit, cycle 1 day 1, cycle 1 day 15 visit, day 1 visits for each new cycle, and an end-of-treatment visit.

Patients may remain on study for up to 12 cycles if the patient demonstrates clinical benefit and no excessive toxicity (i.e. no clinically significant non-hematologic study-drug related grade $\geq$ 3 toxicity). Patients who are experiencing clinical benefit and have not experienced excessive toxicity may be eligible to continue therapy after discussion with the PI and the discussion documented in the patient's medical record.

Bone marrow biopsy and/or aspiration on day 28 (+/- 7 days); if no morphologic evidence of leukemia, venetoclax should be held and bone marrow should be repeated 2 weeks (+/- 7 days) in the absence of count recovery. Bone marrow biopsy and aspiration after cycle 3 and cycle 5; subsequently bone marrow aspirate and/or biopsy, every 3 cycles or as clinically indicated. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests.

Cytogenetics should be performed if abnormal pre-therapy, any time a bone marrow exam is performed. Molecular testing depending on the positive tests pre-study (specific mutations, whole genome sequencing) and should be followed any time a bone marrow exam is performed. Omissions will not be considered as deviations.

Multi-parameter flow cytometry for the presence of leukemia associated immunophenotype (minimal residual disease) any time a bone marrow exam is performed. Omissions will not be considered as deviations.

5.2.5. Outside Physician Participation During Treatment:

Both omacetaxine and venetoclax are self-administered medications. In the event the patient cannot travel to MDACC for a new cycle visit (due to pandemic precautions), a telemedicine visit

including laboratory review is acceptable and medications will be shipped directly to the patient. Local care for the patient includes routine blood work monitoring in between treatment cycles.

1. Communication between the treating physician and/or PI with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.

2. A letter to the local physician outlining the patient's participation in a clinical trial (Dear Doctor Letter) will request local physician agreement to supervise the patient's care.

3. Any protocol required evaluations performed by local physician will be documented by telephone, fax or e-mail.

4. Changes in drug dose and/or schedule must be discussed with and approved by the PI or their representative prior to initiation and will be documented in the patient record.

5. A copy of the informed consent, treatment schema and evaluation during treatment will be provided to the local physician.

6. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

7. The home physician will be requested to report to the physician investigator all life threatening events within 24 hours of documented occurrence.

5.3. Meals and Dietary Requirements:

Venetoclax should be taken together with approximately 240 mL of water and within 30 minutes after the completion of a meal, preferably a low or moderate-fat breakfast.

Subjects should not consume grapefruit or grapefruit products, Seville oranges, or Star fruit within the 3-day period prior to the first venetoclax administration and until the last day of venetoclax is completed due to possible CYP3A mediated metabolic interaction.

A dose missed earlier in a day can be made up later that day as long as it is taken within 6 hours of the missed dose. If more than 6 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose.

Any missed doses should be documented in the subject diary and returned for drug accountability.

If vomiting occurs shortly after a dose of VEN, that dose should not be made up later that day. The subject should continue with the dosing schedule on the next day and inform the investigator and document this in the subject diary.

5.4. CYP3 Inducers and Inhibitors

CYP3A inhibitors are discouraged, but allowed with appropriate VEN dose reduction at all study timepoints as per the U.S. Prescribing Information for venetoclax including an 82.5% dose reduction for posaconazole (i.e. venetoclax 70mg qday instead of 400mg) and 75% dose reduction for other strong CYP3A inhibitors (i.e. venetoclax 100mg qday instead of 400mg in combination with voriconazole).

If a moderate CYP3A inhibitor is prescribed on study, a 50% dose reduction of VEN will be required (i.e. 200 mg instead of 400 mg).

5.5 Supportive Care:

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and Leukemia Department guidelines.

Concomitant intrathecal chemotherapy is permitted for treatment or prophylaxis of extramedullary disease and will be captured in the eCRF.

5.6 Management of Myelosuppression:

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, febrile neutropenia) are common in both treated and untreated patients with AML and MDS. In addition, patients treated with VEN and OM may experience myelosuppression.

If a patient achieves a clinical response including CR, CRi, MLFS (AML) or mCR (MDS), and they have not recovered ANC $\geq$ 500/uL within 14 days of VEN drug interruption unless it is thought to be due to the underlying disease, VEN dosing may be further interrupted until ANC recovery to $\geq$ 500/uL. GCSF may be administered if in the best interest of the patient.

5.7 Recommended Dose Reductions:

Patients with a response (i.e. no marrow evidence of leukemia) who have prolonged (>42 days) count recovery, may have treatment with omacetaxine and venetoclax interrupted until neutrophils recover to ANC ≥ 500/μL and platelets to >50 $x10^9$/L. After interruption, dose adjustment for venetoclax can be made as follows:

Table 2. Suggested dose modifications for venetoclax-related AEs

Dose Level	Venetoclax dose mg	Venetoclax duration
0 **(starting dose)**	400	10 days
-1	400	7 days
-2	400	5 days

- A reduction of 2 dose levels may be considered if the toxicity was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.
- Additional or alternative dose modifications are acceptable when deemed to be in the patient's best interest, after a discussion by the investigator and the PI and with appropriate documentation.

Table 3. Suggested dose modifications for omacetaxine-related AEs

Dose Level	omacetaxine
0	1.25 mg/m2 BID days 2-4
-1	1.25 mg/m2 BID days 2-3
-2	1.25 mg/m2 QDAY days 2-3

- A reduction of 2 dose levels may be considered if the toxicity was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.
- Additional or alternative dose modifications are acceptable when deemed to be in the patient's best interest, after a discussion by the investigator and the PI and with appropriate documentation.

A patient who has had a dose reduction may have their dose re-escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month.

Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale. Dose adjustment/delay of only one of the agents is permissible if the toxicity is most likely judged to be related to one of the agents by the investigator.

6.0 RESPONSE DEFINITIONS:

6.1.1 Primary Efficacy Analysis: Clinical activity assessed based on revised IWG response criteria for AML (Cheson et al., 2003)

The primary endpoint is the overall response rate (ORR), defined as the proportion of patients who had CR (complete remission), CRh (complete remission with incomplete hematologic recovery), CRi (complete remission with incomplete count recovery), PR (partial response) or MLFS (marrow clearance of blasts) within 3 months of treatment initiation among adult patients with AML.

CR: Absolute neutrophil count > 10^3/μL, platelets ≥ 10^5/μL, red cell transfusion independence, absence of extramedullary disease, and bone marrow with < 5% blasts.

CRi: Bone marrow with < 5% blasts, with peripheral neutrophils of < 1000/μL or platelets ≤ 100,000/μL.

CRh: Bone marrow with <5% blasts, with peripheral neutrophils of $\geq$ 500/uL AND platelets $\geq$ 50,000/ul

PR: All of the hematologic values for a CR, but with a decrease of at least 50% in the percentage of blasts, to 5% to 25%, in the bone marrow aspirate.

MLFS Bone marrow with < 5% blasts, absence of extramedullary disease, no hematologic recovery required

Analyses of overall response rate (ORR) as defined by CR + CRi + PR + MLFS, CR rate, CR/CRi rate, CR/CRh rate will be performed for enrolled subjects, with laboratory response assessment occurring +/- 7 days from bone marrow evaluations. The depth of remission such as with exploratory analyses of MRD negativity by flow cytometry and/or concomitant molecular analysis will also be performed.

6.1.2 Primary Efficacy Analysis: Clinical activity assessed based on revised IWG Response Criteria for MDS (Cheson et al., 2006)

The primary endpoint is the overall response rate (ORR), defined as the proportion of patients who had CR (complete remission), PR (partial response), Hematologic Improvement, or mCR (marrow clearance of blasts) within 3 months of treatment initiation among adult patients with MDS.

CR: Absolute neutrophil count > 10^3/µL, platelets ≥ 10^5/µL, hemoglobin ≥11 g/dl, and bone marrow with < 5% blasts. Peripheral dysplasia will be noted.

PR: All of the hematologic values for a CR, but with a decrease of at least 50% in the percentage of blasts, to 5% to 25%, in the bone marrow aspirate.

mCR Bone marrow with < 5% blasts and decrease by ≥ 50% over pretreatment, no hematologic recovery required.

HI Improvement in neutrophil count, platelets, or red cells (see below)

SD Failure to achieve at least PR, but no evidence of progression for > 8 weeks

Analyses of overall response rate (ORR) as defined by CR + PR + mCR + HI, CR rate, will be performed for enrolled subjects, with laboratory response assessment occurring +/- 7 days from bone marrow evaluations. The depth of remission such as with exploratory analyses of MRD negativity by flow cytometry and/or concomitant molecular analysis will also be performed.

6.1.3. Hematologic Improvement Response Criteria:

*Responses must last at least 8 weeks

Proposed Modified International Working Group Response Criteria for Hematologic improvement*	**Response criteria (Responses must last at least 8 weeks)†**
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100 × 10^9/L)	Absolute increase of ≥30 × 10^9/L for patients starting with >20 × 10^9/L platelets Increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 × 10^9/L)	At least 100% increase and an absolute increase >0.5 × 10^9/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by > 1.5 g/dL Transfusion dependence

Source: (Cheson, et al. 2006) Abbreviations: Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement. Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart (modification).
†Modification to IWG response criteria (Cheson, et al. 2003) ‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth.

6.2 Primary Safety Analysis:

The overall incidence and severity of all adverse events using Common Toxicity Criteria v 5.0

An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

6.2.1. Definition of Dose-Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as any grade 3 or higher non-hematologic adverse event or abnormal laboratory value occurring during the first cycle on study that cannot be attributed by the investigator to a clearly identifiable cause such as disease progression, underlying illness, concurrent illness, or concomitant medication, with the following **exceptions**:

- Grade 3 nausea, vomiting or diarrhea that can be managed to < Grade 3 within 7 days with standard antiemetic or antidiarrheal medications
- Grade 3 or 4 electrolyte abnormalities will only be considered DLT if possibly related to study drug, extend beyond 72 hours, and are not corrected by optimal replacement therapy. Venetoclax interruption for up to 72 hours following transient (< 48 hours) chemical changes and laboratory TLS may be allowed and may not be considered a DLT.

Confirmed Hy's law cases will be considered as DLT. A positive Hy's law case is defined as AST or ALT >= 3 x ULN in the setting of total bilirubin >= 2 x ULN, without findings of cholestasis, and no other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

Hematologic DLT is defined as Grade $\geq$ 4 neutropenia and/or thrombocytopenia and no greater than 5% marrow blasts lasting for 6 weeks or more after the start of a course in the absence of underlying MDS. Anemia will not be considered for the definition of DLT.

Patients with neutropenia or thrombocytopenia as a consequence of the disease prior to the start of therapy do not require treatment interruptions for myelosuppression. Dose reductions of the study treatment in these patients may be considered on an individual case basis and discussed with the PI.

6.2.2 Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsored protocol

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug or protocol specific timeline, unless the participant withdraws consent.
- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution**.**
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**
- Additionally, any serious adverse events that occur after the 30 day time period or protocol specific timeline that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.
  It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

The Investigator will communicate the occurrence of any serious adverse events which they believe to be definitely, likely, possibly or probably related to the investigated study product(s), and any exposure of a pregnant study participant to the investigated study product(s), within 24 hours of becoming aware of the event to the supporting drug company, TEVA Pharmaceuticals either via email: Us.clinops.sae@tevapharm.com or Facsimile (215)795-4242.

6.3 Exploratory Biomarker Analysis:

Peripheral blood and bone marrow aspirate samples will be obtained at study specified time points. Biomarker assays include the following:

6.3.1 Leukemia mutation panel

As a standard of care all AML patients at MDACC are evaluated for karyotype and molecular mutation profile using a CLIA-certified next-generation gene sequencing platform. The effects of the combination will be compared not only to historical outcomes in matched groups of patients,

but also at the molecular and cellular level by correlating with karyotype and molecular mutation profile. The Leukemia mutation panel will be performed on the screening BM aspirate and the progression/relapse BM aspirate. An aliquot of DNA will be stored for additional analysis of DNA mutations in responding patients, if these are not identified by the Leukemia mutation panel.

6.3.2 Minimal Residual Disease assessment by flow-cytometry

As a standard of care all BM aspirates will be evaluated for MRD by validated 17-color multiparameter multicolor flow-cytometry.

6.3.3 Gene expression pertubations by RNA sequencing and targeted QPCR analyses

ATAC-Seq, RNA-Seq and targeted QPCR analyses will be performed on the pre-treatment and on study bone marrow and peripheral blood at study defined timepoints to evaluate the hypothesis that concurrent therapy with venetoclax and OM will be synergistically lethal against AML stem progenitor cells.

RNA-Seq analyses will be conducted utilizing Illumina HiSeq4000 platform in the Sequencing and Microarray Facility of MDACC. Additionally, gene set enrichment analyses (GSEA) will be conducted to determine specific pathways affected by the treatments. We will infer specific enriched pathways using the Gene-Set Enrichment (GSEA) method and the gene-set collection from the Molecular Signature Database (MSigDB). (Liberzon et al., 2015; Subramanian et al., 2005) The transcriptional perturbations will be confirmed by QPCR analyses.

6.3.4. Protein Expression Analyses by RPPA, CyTOF, Flow cytometry and Confocal Microscopy.

RPPA will be performed utilizing curated and highly validated antibodies against approximately 300 proteins in the Functional Proteomics RPPA core facility at the MD Anderson Cancer Center, as previously reported.(Saenz et al., 2017) Mass cytometry ‘CyTOF’ analysis of pre- and post-treatment, paraformaldehyde-fixed and permeabilized cells, stained with a cocktail of antibodies conjugated to transition element isotopes used as tags, will be conducted at the Flow Cytometry and Cellular Imaging (FCCI) Core Facility at MDACC. Time-of-flight mass spectrometry measures the different cellular parameters, simultaneously in each cell, and the changes in the normalized mass cytometry data between untreated and treated cells are organized in an unsupervised manner using SPADE (spanning-tree progression analysis of density-normalized events) and displayed as heatmaps relative to the untreated control cells as previously reported.(Behbehani et al., 2015; Saenz et al., 2017) Pre- and post-treatment (Day 0, Day 2 and Day 5) AML cells will also be fixed with paraformaldehyde and permeabilized with

methanol for subsequent Flow Cytometric analyses, to determine the surface and intracellular expressions of proteins.

Additional material will be stored in Dr. Bhalla's laboratory for potential studies of interest.

7.0 REGULATORY AND REPORTING REQUIREMENTS

7.1 Informed Consent:

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative. All consented participants will be registered in the Clinical Oncology Research System (CORe)

7.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC/IRB for written approval.

The investigator must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent form. The investigator should notify the IEC/IRB of deviations from the protocol or serious adverse events occurring at the site.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study.

7.3 Subject Confidentiality

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and

obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

7.4 Study Documentation and Archival

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, and subject identification list

- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB

7.5. Adverse Events:

7.5.1 Monitoring, recording and reporting adverse events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. A diagnosis or syndrome should be recorded rather than the individual signs or symptoms of the diagnosis or syndrome.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

AEs will be recorded by the Investigator from the time the subject signs informed consent until 30 days after the last dose of IP and those SAEs made known to the investigator at any time

thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded in the subject's source documents. The Leukemia-specific Adverse Event Recording and Reporting Guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form (Prometheus) and will include the terminology event name, grade, and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    b. All serious adverse events regardless of attribution to the study drug(s).
    c. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

7.5.1.1 Severity

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

7.5.1.2 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

7.5.1.3 Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

7.5.1.4 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

7.5.1.5 Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Expected or Expected as defined below:

- Not Expected: A causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Expected: There is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality may be reassessed and provided as additional information becomes available.

The Investigator is responsible for assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution.

Attribution - the determination of whether an adverse event is related to a medical treatment or procedure.

- Definite - the adverse event is clearly related to the investigational agent(s).
- Probable - the adverse event is likely related to the investigational agent(s).
- Possible - the adverse event may be related to the investigational agent(s).
- Unlikely - The adverse event is doubtfully related to the investigational agent(s).
- Unrelated - The adverse event is clearly NOT related to the investigational agent(s).

8.0 STATISTICAL CONSIDERATIONS

This is an open label, Phase 1b/2 trial to determine the safety/tolerability (phase 1b) and preliminary efficacy (phase 2) of omacetaxine in combination with venetoclax for patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome harboring a *RUNX1* mutation.

Phase 1b: A maximum of 24 patients will be enrolled into this part of the study, with up to 12 patients in each arm (AML or MDS). The dose levels are show in Table 1 and the starting dose is dose level 0.

Dose limiting toxicity (DLT) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE v5) by organ system. DLTs (see 6.2.1 of the protocol) that occurred within the first 1 cycle after treatment will be used for dose escalation/de-escalation decisions. The Bayesian Optimal Interval (BOIN) design (Liu and Yuan, 2015) will be used to determine the MTD of the combination for each arm. The BOIN design identifies the MTD through minimizing the incorrect decisions of dose escalation and de-escalation (i.e., erroneously escalating/deescalating the dose when the current dose is actually higher/lower than the MTD), thereby optimizing the dose assignment for each enrolled patient. The BOIN design is simple to implement and has been shown to have superior performance through simulations. The BOIN design is algorithm-based, which is similar to the traditional “3+3”; however its overall performance is substantially better.

The following design detail applies to each arm separately. The target toxicity rate for the MTD is $\phi = 0.3$. For each arm, we will enroll and treat patients in cohorts of size 3. To guide dose-escalation decisions, if the observed DLT rate at the current dose is ≤ 0.236, the next cohort of patients will be treated at the next higher dose level; if it is ≥ 0.359, the next cohort of patients will be treated at the next lower dose level. These boundaries were created when minimizing decision errors such that $\varphi_1 = 0.18$ is the highest toxicity probability that is considered sub-therapeutic (underdosing) and $\varphi_2 = 0.42$ is the lowest toxicity probability that is deemed overly toxic (overdosing). For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.3 \mid \text{data}) > 0.95$, where p_j is the true DLT rate of dose level $j, j =$ -2, -1, 0, 1. When the lowest dose is eliminated, stop the trial for safety.

For each arm, the trial design is described through the following three steps:

1. Patients in the first cohort are treated at Dose Level 0.
2. To assign a dose to the next cohort of 3 patients, conduct dose escalation/de-escalation according to the rule displayed in Table 4. When using Table 4, please note the following:
    a. “Eliminate” means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new patients at the current dose.

d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

3. Repeat step 2 until the maximum sample size of 12 is reached for a given arm, or stop the arm if the number of patients treated at the current dose reaches 9.

Table 4. Dose escalation/de-escalation rule for the BOIN design

	1	2	3	4	5	6	7	8	9
Number of patients treated at current dose	1	2	3	4	5	6	7	8	9
Escalate if # of DLT <=	0	0	0	0	1	1	1	1	2
Deescalate if # of DLT >=	1	1	2	2	2	3	3	3	4
Eliminate if # of DLT >=	NA	NA	3	3	4	4	5	5	5

Note. # of DLT is the number of patients with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. "NA" means that a dose cannot be eliminated before treating 3 patients.

After Phase 1b part of the trial is completed, select the MTD for each arm based on isotonic regression as specified in Liu and Yuan (2015). This computation is implemented by the shiny app “BOIN” available at http://www.trialdesign.org. Specifically for each arm, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate. Furthermore, the RP2D will be selected based on safety and efficacy, in Arms A and B independently.

Operation Characteristics

Table 3 shows the operating characteristics of the BOIN design based on 1000 simulations using shiny app “BOIN” available at http://www.trialdesign.org. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3.

Table 3. Operating characteristics of the BOIN design (Dose 0 is the starting dose)

	Dose Level -2	Dose Level -1	Dose Level 0 (starting dose)	Dose Level 1	Number of Patients	% Early Stopping
Scenario 1						
True DLT Rate	0.47	0.55	0.64	0.75		
Selection %	44.2	27.6	8.2	0.1		19.9
% Pts Treated	24.4	36	37.7	1.9	11.8	
Scenario 2						
True DLT Rate	0.11	0.3	0.47	0.67		
Selection %	9.1	52.5	34.3	3.2		0.9
% Pts Treated	5.8	33.8	52	8.4	11.8	
Scenario 3						
True DLT Rate	0.02	0.13	0.3	0.47		
Selection %	0.3	19.3	54.5	25.6		0.3
% Pts Treated	0.4	15.7	58.1	25.9	11.7	
Scenario 4						
True DLT Rate	0.05	0.1	0.15	0.3		
Selection %	0	2.4	26.6	71		0
% Pts Treated	0	3.1	43.8	53.2	11.9	

Phase II:

In phase II portion of the study, patients will be treated at the RP2D level chosen during phase 1b for each arm separately. A maximum of 30 patients will be treated in each arm. For AML patients, the primary efficacy endpoint is overall response, defined as CR, CRh, CRi, PR or marrow clearance of blasts within 3 cycles of treatment. For MDS patients, the primary efficacy endpoint is overall response, defined as CR, PR, HI (Hematologic Improvement), or mCR (marrow clearance of blasts) within 3 cycles of treatment. In addition, we will continue to monitor the DLTs that occurred during the first 3 cycles of treatment.

For each arm, the efficacy and toxicity will be monitored simultaneously using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size and N denote the maximum sample size. Let Y_{eff} and Y_{tox} denote the binary efficacy and toxicity endpoints, with $Y_{eff} = 1$ and $Y_{tox} = 1$ indicating that patients experience efficacy and toxicity, respectively. We assume that the joint distribution of (Y_{eff}, Y_{tox}) follows a multinomial distribution with four elementary outcomes: (Y_{eff}, Y_{tox}) = (1, 1), (1, 0), (0, 1) and (0, 0). Let $\mathbf{p} = (P_{11}, P_{10}, P_{01}, P_{00})$ denote the probabilities of observing the four outcomes, and let $p_{eff} = Pr(Y_{eff} = 1)$, $p_{tox} = Pr(Y_{tox} = 1)$ and $p_{efftox} = Pr(Y_{eff} = 1, Y_{tox} = 1)$.

AML Arm:

The treatment is deemed unacceptable if $p_{eff} \leq 0.2$ or $p_{tox} > 0.2$. Thus, we will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.2|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

or

$$Pr(p_{tox} \leq 0.2|data) < \lambda\left(\frac{n}{N}\right)^{\alpha/3},$$

where λ=0.5 and α=0.51 are design parameters optimized to maximize the study power, i.e., probability of correctly concluding an efficacious and safe treatment as acceptable when $p_{eff} = 0.4$, $p_{tox} = 0.1$ and $p_{efftox} = 0.04$, while controlling that the probability of incorrectly claiming an inefficacious and toxic treatment, i.e., type I error, with $p_{eff} = 0.2$, $p_{tox} = 0.2$ and $p_{efftox} = 0.04$, to 10.4%. Note that in the safety stopping rule, the original publication of the design used the probability cutoff $\lambda(n/N)^{\alpha}$, here the attenuation factor 3 is added (i.e., α/3) to obtain stricter interim stopping boundaries to enhance safety.

This optimization is performed assuming a vague Dirichlet prior $Dir(0.04,0.16,0.16,0.64)$ for $\mathbf{p}$. The prior is chosen such that it corresponds to a prior effective sample size of 1 patient, and the prior estimates of p_{eff} and p_{tox} match the values specified when the treatment is unacceptable. The above decision rule leads to the following optimal stopping boundaries, in cohort size of 6.

Table 4: Optimized stopping boundaries for AML Arm

# patients treated	Stop if # response <=	OR # toxicity >=
6	0	2
12	1	3
18	3	4
24	4	6
30	6	7

When the total number of AML patients reaches the maximum sample size of 30, we conclude that the treatment is acceptable if the number of responses are greater than 6, and the number of toxicities are less than 7; otherwise we conclude that the treatment is unacceptable. The go/no-go criteria in Table 4 are non-binding.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application (BOP2 V1.4.7.0), which is available at http://www.trialdesign.org.

Table 5: Operating characteristics for the interim futility and toxicity monitoring in AML Arm

Scenario	Pr(Eff)	Pr(Tox)	Pr(Eff & Tox)	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.20	0.20	0.040	85.03	10.44	12.8
2	0.40	0.10	0.040	25.31	73.93	24.8
3	0.40	0.25	0.120	80.66	15.88	13.4
4	0.15	0.30	0.045	98.07	0.77	8.5

MDS Arm:

The treatment is deemed unacceptable if $p_{eff} \leq 0.15$ or $p_{tox} > 0.2$. Thus, we will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.15|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

or

$$Pr(p_{tox} \leq 0.2|data) < \lambda\left(\frac{n}{N}\right)^{\alpha/3},$$

where λ=0.52 and α=0.15 are design parameters optimized to maximize the study power, i.e., probability of correctly concluding an efficacious and safe treatment as acceptable when $p_{eff} = 0.3$, $p_{tox} = 0.1$ and $p_{efftox} = 0.03$, while controlling that the probability of incorrectly claiming an inefficacious and toxic treatment, i.e., type I error, with $p_{eff} = 0.15$, $p_{tox} = 0.2$ and $p_{efftox} = 0.03$, to 9.8%. Note that in the safety stopping rule, the original publication of the design used the probability cutoff $\lambda(n/N)^{\alpha}$, here the attenuation factor 3 is added (i.e., α/3) to obtain stricter interim stopping boundaries to enhance safety.

This optimization is performed assuming a vague Dirichlet prior $Dir(0.03,0.12,0.17,0.68)$ for $\mathbf{p}$. The prior is chosen such that it corresponds to a prior effective sample size of 1 patient, and the prior estimates of p_{eff} and p_{tox} match the values specified when the treatment is unacceptable. The above decision rule leads to the following optimal stopping boundaries, in cohort size of 6.

Table 6: Optimized stopping boundaries for MDS Arm

# patients treated	Stop if # response <=	OR # toxicity >=
6	0	2
12	1	3
18	2	4
24	3	5
30	4	7

When the total number of MDS patients reaches the maximum sample size of 30, we conclude that the treatment is acceptable if the number of responses are greater than 4, and the number

of toxicities are less than 7; otherwise we conclude that the treatment is unacceptable. The go/no-go criteria in Table 6 are non-binding.

Below are the operating characteristics of the design based on 10000 simulations using the BOP2 web application (BOP2 V1.4.7.0), which is available at http://www.trialdesign.org.

Table 7: Operating characteristics for the interim futility and toxicity monitoring in MDS Arm

Scenario	Pr(Eff)	Pr(Tox)	Pr(Eff & Tox)	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.15	0.20	0.030	88.41	9.77	11.5
2	0.30	0.10	0.030	34.21	65.36	23.0
3	0.30	0.25	0.075	86.01	12.85	12.5
4	0.10	0.30	0.030	98.89	0.69	7.8

8.4 Analysis Populations:8.4.1. Safety Population

All patients who receive at least 1 dose of the combination therapy will be included in the analysis of safety regardless of the duration of treatment. Patients who experience adverse events during the screening period but who do not start on study treatment due to reasons that include, but are not limited to ineligibility/screen failure, death or withdrawal of consent, will not be included in the safety population.

8.4.2. Efficacy Evaluable Population

All patients who complete at least one post-baseline disease status assessment or who discontinue study medication early due to study drug-related toxicity will be considered evaluable for efficacy. Patients who do not meet the aforementioned requirements will be considered non-evaluable for response and may be replaced.

In addition, we will perform a sensitivity analysis for the efficacy endpoint which will include all patients who have received at least one dose of the study treatment (i.e., those who drop off study early due to any reason will be counted as non-responders).

8.4.3. DLT-evaluable population:

Unless doses are missed in Cycle 1 due to DLT(s), a patient must receive at least 70% of the planned doses of venetoclax and omacetaxine to be considered evaluable for DLT. If a patient received fewer doses/days of treatment in the first cycle of treatment for reasons other than a DLT, the patient will be considered non-evaluable for DLT and replaced.

8.5 Analysis Plan:

Descriptive statistics including plots, mean, median and standard deviations will be used to summarize data. For the primary efficacy analysis, we will estimate the ORR for the combination treatment, along with the Bayesian 95% credible interval. The priors for ORR will be (0.2, 0.8) for AML cohort and (0.15, 0.85) for MDS cohort. Event-free survival (EFS) is defined as the time interval between the date of treatment start and the date of treatment failure, relapse or death from any cause. The Kaplan-Meier method will be used to estimate the probabilities of event-free survival (EFS) and overall survival (OS). Log-rank tests will be used to compare among subgroups of patients in terms of EFS or OS. Similar analyses will be performed for the duration of response. MRD negative status and exploratory biomarkers will be summarized graphically and with descriptive statistics. The association between molecular and cellular markers and overall response and/or resistance will be assessed through logistic regression analyses. Paired t-test or Wilcoxon signed rank test will be used to assess the marker change over time. Safety data will be summarized using frequency and percentage, by category and severity.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval

- Phase 1b
  After the first 3 evaluable patients, per arm, complete 1 cycle of study treatment, and every 3 evaluable patients thereafter, IND Office approval must be obtained prior to advancing/changing dose levels.

- Phase 2:
  After the first 10 evaluable patients, per arm, complete 3 cycles of study treatment, and every 10 patients thereafter.

  A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Appendix A: Sample List of Excluded and Cautionary Medication

Excluded
Strong CYP3A inducers – avasimibe, carbamazepine, enzalutamine, mitotane, phenobarbital, phenytoin, rifampin, St. john's wort **Strong CYP3A inhibitors** – Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, telithromycin **Sensitive CYP3A4 substrates with narrow therapeutic index** – alfentanil, astemizole, dihydroergotamine, ergotamine, pimozide, quinidine, everolimus, sirolimus, tacrolimus
Cautionary, Consider Alternative Medications, Additional Guidance Noted:
Moderate CYP3A inducers** – bosentan, efavirenz, etravirine, modafinil, nafcillin **Moderate CYP3A inhibitors‡** – Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* verapamil, isavuconazole, tofisopam
Cautionary
Warfarin and Coumarin derivatives **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** Asunaprevir, atrasentan, atorvastatin, cerivastatin, docetaxel,* ezetimibe, fluvastatin, glyburide, nateglinide, paclitaxel,* rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, azithromycin, captopril, carvedilol, felodipine, propafenone, quercetin, ronalzine, ticagrelor **BCRP inhibitors** Geftinib,* curcumin

* These are anticancer agents

** If subject requires use of these medications, use with caution

‡ If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 2-fold. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before venetoclax dose is increased back to the target dose.

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