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Department	Leukemia
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An Open-label Phase IB/II Study of Magrolimab in Combination with Azacitidine and Venetoclax for the Treatment of Patients with Acute Myeloid Leukemia (AML)

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IND number: 150858

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1.0 OBJECTIVES

1.1 Primary Objectives

1. To determine the safety and Maximum Tolerable Dose (MTD) of this combination in patients with AML.

2. To determine the response rate (RR) including CR (complete remission) + CRi (complete remission with incomplete count recovery) within 3 months of treatment initiation of this combination in patients with AML.

1.1 Secondary Objectives:

1. To assess the CR+CRh rate and morphologic leukemia free (MLF) rate within 3 months of treatment initiation of this combination in patients with AML.

2. To determine the duration of response (DOR), event-free survival (EFS), overall survival (OS), MRD status at response and best MRD response attained by flow-cytometry, 4- and 8-week mortality, and number of patients bridged to hematopoetic stem cell transplant (HSCT) and median duration to HSCT from the initiation of the combination.

3. To investigate correlations of response to this combination with a pre- therapy, on-therapy, and progression 81-gene panel of gene mutations in AML

1.2 Exploratory Objectives:

1. To investigate possible relationships between response and non-response to the combination with pretherapy, on-therapy, and progression gene expression signatures.

2. To investigate the characterization of genetic heterogeneity in tumor cell populations, by performing targeted single-cell sequencing on longitudinally collected AML tumor populations from patients using a novel microfluidic approach that barcodes amplified genomic DNA from thousands of individual leukemia cells confined to droplets (single cell sequencing). Targeted single-cell sequencing is able to sensitively identify cells harboring pathogenic mutations during complete remission and uncover complex clonal evolution within AML tumors that are not observable with bulk sequencing.

3. To identify individual cell populations (AML blasts, T-cells – both bulk and T-cell subsets and coreceptor/ligand expression, macrophages and their coreceptor/ligands) and how their signaling state in disease relates to clinical outcomes we will perform CyTOF (mass cytometry) using a customized CYTOF panel specifically developed for this study on patients' bone marrow samples and peripheral blood at diagnosis, remission and relapse and potentially other time-points on study.

4. To store and/or analyze surplus blood or tissue including bone marrow, if available, for potential future exploratory research into factors that may influence development of AML and/or response to the combination (where response is defined broadly to include efficacy, tolerability or safety).

BACKGROUND AND DRUG INFORMATION

2.1 Background

Venetoclax in AML (Brief Overview)

Bcl-2 overexpression has been implicated in maintaining the survival of AML cells and has been associated with resistance to chemotherapy and inferior overall survival (Konopleva M et al, *Cancer cell* 2006; **10**(5): 375-88). Venetoclax (VEN) is a potent and selective small-molecule inhibitor of Bcl-2 that has demonstrated cell-killing activity against a variety of leukemia cell lines, primary patient samples and leukemia stem/progenitor cells (Souers AJ et al, *Nat Med* 2013; **19**(2): 202-8; Pan R et al, *Cancer discovery* 2014; **4**(3): 362-75). VEN also has been found to synergize with agents known to down-regulate Mcl-1, including azacitidine (Tsao T et al, *Ann Hematol* 2012; **91**(12): 1861-70).

Venetoclax monotherapy in R/R AML: A phase II study has been completed evaluating single agent venetoclax in subjects with R/R AML and those unfit for intensive therapy. A total of 32 subjects were dosed. Exposure, safety, and efficacy data are available for this study (Konopleva M et al, *Cancer discovery* 2016; **6**(10): 1106-17). The most common adverse events observed in ≥ 30% of the subjects 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). No cases of TLS occurred during venetoclax treatment. In this phase II multicenter trial single agent venetoclax produced an overall response in 5/32 R/R AML patients (CR in 1 patient, CRi in 4 patients). Of the 5 patients with CR/CRi, 3 had IDH mutations suggesting that patients with IDH mutations may be particularly sensitive to venetoclax.

Venetoclax plus HMA in patients with newly diagnosed AML

An ongoing phase Ib/II study has reported promising safety and efficacy of venetoclax in combination with either azacitidine or decitabine in patients ≥65 years of age with previously untreated AML and who are ineligible for chemotherapy (DiNardo CD et al, Blood. 2019 Jan 3;133(1):7-17, attached as Appendix A). At the most recent update (Pollyea D et al ASH 2018 abstract #285, Oral presentation: full PowerPoint attached as Appendix B), 145 patients were treated with a median age of 74 years (range, 65-86 years). Cytogenetics were poor risk in 49% of patients. The 30-day and 60-day mortality rates were 3% and 8%, respectively. Tumor lysis syndrome was not observed. The CR/CRi rate for the entire cohort was 66% with a median duration of CR/CRi of 11.0 months. The median overall survival for the entire cohort was 17.5 months. These results represent the best survival data for older, unfit patients reported to date in newly diagnosed AML. In a parallel single arm study the CR/CRi rate for AML subjects (given venetoclax plus low dose ara-C) was 54% (Wei A et al J Clin Oncol. 2019 May 20;37(15):1277-1284). Based on these exciting results in this historically difficult-to-treat patient population, in November 2018 the US FDA approved venetoclax in combination with either LDAC, azacitidine or decitabine for patients with newly diagnosed AML who are ≥75 years of age or have comorbidities that preclude the use of standard intensive chemotherapy. Emerging clinical and exposure response data have suggested that the 400mg dose of venetoclax has the best risk-benefit profile, and a phase III study of venetoclax 400mg with azacitidine in the frontline setting is ongoing and has recently completed enrollment (VIALE A).

Unmet Need in AML and Need to Continue Improving HMA with Venetoclax
In spite of the encouraging efficacy of HMA with venetoclax in newly diagnosed older AML who are not good candidates for cytotoxic induction therapy, the median CR/CRi durations are </= 11 months and the 3-year OS is <45% (DiNardo CD et al, Blood. 2019 Jan 3;133(1):7-17, attached as Appendix A) suggesting that there is sufficient room for improvement by further improving the durability of CR/CRi's and thereby improving median OS. Similarly, MRD-negative rates with HMA with venetoclax are 40-50% in patients with CR/CRi and these may be further improved by the addition of an effective and tolerable third agent, potentially translating into more durable response and improved OS.

The long-term outcomes of patients with poor-risk disease features remain poor. Among high risk patients treated with HMA with venetoclax (defined as patients with TP53 and adverse cytogenetics) evaluated in both the MD Anderson Cancer Center internal data set (Shoukier M et al ASCO 2018, abstract #7034, attached as Appendix M) and in the multicenter phase Ib/II trial of HMA with venetoclax (DiNardo CD et al, Blood. 2019 Jan 3;133(1):7-17, attached as Appendix A) the CR/CRi rates were significantly lower at approximately 45-47%, median response durations were 4-6 months, median OS was 6-9 months, and only 14% of the patients achieving CR/CRi became MRD-negative.

Pre-clinical rationale for combination of venetoclax with immune therapies
Venetoclax was shown to decrease naïve but not memory T cells in *in vitro* studies of human lymphocytes (Mathew R et al. *Blood* 2018 132: 3704) In a mixed lymphocyte reaction assay, venetoclax did not affect IFN-gamma secretion by itself or when co-treated with the checkpoint inhibitor nivolumab. Similar findings were observed in a cytomegalovirus recall assay, suggesting that venetoclax does not impair immune response to infections. These findings suggest that venetoclax does not impair anti-tumor immune therapy and may synergize with immune checkpoint antibodies (T cell- or macrophage-based) therapy. Lasater et al demonstrated that significant venetoclax-induced cell death in the immune cell population at clinically relevant drug concentrations is limited to the B-cell subset and that BCL-2 inhibition is not detrimental to survival or activation of NK- or T-cell subsets (Lasater E et al, Blood 2018 132:1118).

2.2 Azacitidine (Vidaza®): Drug Information Summary

Please see attached azacitidine PI for detailed information.

Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism. Since the early 1970s, azacitidine has been investigated primarily in the US for the treatment of acute leukemia. Clinical studies have focused mainly on patients with disease refractory to conventional chemotherapy. Results of these investigations demonstrated activity of azacitidine in the treatment of AML. Clinical studies subsequently evaluated the effects of 5-azacitidine in a variety of other malignant and hematologic disorders, including solid tumors, hemoglobinopathies (e.g., thalassemia and sickle cell anemia), and MDS. In 1984, the Cancer and Leukemia Group B (CALGB) began a series of clinical studies with azacitidine in patients with MDS. These studies, in addition to other supportive data, led to the approval of Vidaza® (azacitidine) in May 2004 for the treatment of MDS.

Further details can be found in the azacitidine drug information (**Appendix L**), which contains comprehensive pharmacology, toxicology, pharmacokinetics, pharmacodynamics, metabolism, preclinical, and clinical efficacy and safety data information.

2.3 Venetoclax Drug Information Summary

See the Venetoclax Prescribing Label and Venetoclax IB(Appendix E) for additional details on nonclinical and clinical studies.

Bcl-2 overexpression has been implicated in maintaining the survival of AML cells and has been associated with resistance to chemotherapy and inferior overall survival (Konopleva M et al, *Cancer cell* 2006; **10**(5): 375-88). Venetoclax (VEN) is a potent and selective small-molecule inhibitor of Bcl-2 that has demonstrated cell-killing activity against a variety of leukemia cell lines, primary patient samples and leukemia stem/progenitor cells (Souers AJ et al, *Nat Med* 2013; **19**(2): 202-8; Pan R et al, *Cancer discovery* 2014; **4**(3): 362-75). VEN also has been found to synergize with agents known to down-regulate Mcl-1, including azacitidine (Tsao T et al, *Ann Hematol* 2012; **91**(12): 1861-70).

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. 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.

Summary of Venetoclax Clinical Data

Clinical Efficacy Data for Venetoclax: Preliminary efficacy results are available for subjects with a variety of hematological neoplasms; the drug is approved for the treatment of CLL patients whose cells have a 17p chromosomal deletion. Preliminary data indicate that venetoclax shows promising efficacy in AML.

- In Study M14-212 the CR/CRi rate for subjects treated with venetoclax monotherapy was 19% (Konopleva M et al, *Cancer discovery* 2016; 6(10): 1106-17).
- In Study M14-358 the CR/CRi rate for AML subjects (given venetoclax plus azacitidine or decitabine) was 66% (DiNardo CD et al, Blood. 2019 Jan 3;133(1):7-17).
- In Study M14-387 the CR/CRi rate for AML subjects (given venetoclax plus low dose ara-C) was 54% (Wei A et al J Clin Oncol. 2019 May 20;37(15):1277-1284).

For further details of venetoclax preclinical studies, clinical studies, toxicities, pharmacokinetics, and adverse events please see the venetoclax Prescribing Label (Appendix G).

2.4 Magrolimab Drug Information Summary

Magrolimab (formerly Hu5F9-G4 or 5F9) is a humanized IgG4 monoclonal antibody of the IgG4 kappa isotype containing a Ser-Pro (S-P) substitution in the hinge region (position 228) of the heavy chain to reduce Fab-arm exchange. It comprises a disulfide-linked glycosylated tetramer, consisting of two identical 444 amino acid heavy gamma chains and two identical 219 amino acid kappa light chains. Magrolimab targets the human CD47 antigen. Magrolimab drug product is a sterile, clear, colorless, preservative-free liquid intended for IV infusion.
Magrolimab active pharmaceutical ingredient is manufactured under current Good Manufacturing Practices.

Magrolimab is supplied in single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies.
Vials containing magrolimab should be stored under refrigeration at 2 to 8°C (36°F to 46°F) in an appropriate, locked room and/or locked refrigerator, accessible only to pharmacy personnel, the Principal Investigator, or a duly designated person. Magrolimab should not be frozen. Protect from light during storage. DO NOT SHAKE.

Additional details about magrolimab are provided in the Investigator Brochure (Appendix H) and Pharmacy Manual (Appendix I).

2.5 Rationale for the Protocol

In a phase II study of single-agent venetoclax in 32 patients with relapsed/refractory AML, the CR/CRi rate was 19%; another 19% of patients had a bone marrow blast reduction of >50% not meeting formal response criteria (Konopleva M et al, *Cancer cell* 2006; **10**(5): 375-88). Pre-existing and treatment-emergent mutations in FLT3-ITD and PTPN11 were identified as genomic mechanisms of primary and secondary resistance, respectively, on longitudinal whole-exome sequencing performed in patients treated with venetoclax monotherapy (Chyla B, Daver N et al Am J Hematol. 2018 May 17).

Subsequent studies have evaluated venetoclax in combination with low-intensity therapy in older adults with newly diagnosed AML deemed unfit for intensive chemotherapy. This is a population of patients in whom standard therapy over the last 10-15 years has comprised of either an HMA (e.g. azacitidine or decitabine) or low dose cytarabine (LDAC), with published CR/CRi rates of 15-28% and median OS of 6-10 months with HMA, and CR/CRi rates of 10-15% and median OS of 5-7 months with LDAC (Kantarjian H et al J Clin Oncol. 2012 Jul 20;30(21):2670-7; Dombret H et al, Blood. 2015 Jul 16;126(3):291-9). An ongoing phase Ib study has reporting promising safety and efficacy of venetoclax in combination with either azacitidine or decitabine in patients ≥65 years of age with previously untreated AML and who are ineligible for chemotherapy (DiNardo CD et al, Blood. 2019 Jan 3;133(1):7-17, attached as Appendix A). At the most recent update (Pollyea D et al ASH 2018 abstract #285, Oral presentation: full PowerPoint attached as Appendix B), 145 patients were treated with a median age of 74 years (range, 65-86 years). The 30-day and 60-day mortality rates were 3% and 8%, respectively. Tumor lysis syndrome was not observed. The CR/CRi rate for the entire cohort was 66% with a median duration of CR/CRi of 11.0 months. The median overall survival for the entire cohort was 17.5 months. Emerging clinical and exposure response data have suggested that the 400mg dose of venetoclax has the best risk-benefit profile. Based on these exciting results in this historically difficult-to-treat patient population, in November 2018 the US FDA approved venetoclax in combination with either low-dose cytarabine, azacitidine or decitabine for patients with newly diagnosed AML who are ≥75 years of age or have comorbidities that preclude the use of standard intensive chemotherapy.

Confirmatory phase III trials of azacitidine with or without venetoclax (VIALE A), and low-dose cytarabine with or without venetoclax (VIALE C) have completed enrollment and results are eagerly anticipated.

Despite the encouraging results observed with venetoclax-based regimens in AML, relapses are still common, and it is becoming clear that these regimens are unlikely to be curative in the vast majority of patients. The median CR/CRi durations are </= 11 months and median 2 year OS is approx 45% suggesting there is sufficient room for improvement by further improving the durability of CR/CRi's and thereby improving median OS. Furthermore, our data from MD Anderson Cancer Center showed that among among high risk patients treated with HMA with venetoclax, specifically patients with TP53 and adverse cytogenetics (n=40) the CR/CRi rates were significantly lower at approximately 45%, median OS 5.0 months, and only 14% of the patients achieving CR/CRi became MRD-negative (Shoukier M et al ASCO 2018, abstract #7034,

attached as Appendix M). MD Anderson Cancer Center has led the development of venetoclax based therapies in AML both preclinically and clinically and in addition to leading the national AZA/DAC with venetoclax combination, are now leading multiple novel doublet and triplet combinations of venetoclax based therapies to overcome mechanisms of resistance and to further improve outcomes in newly diagnosed older AML and relapsed AML including national/international ongoing studies of MDM2 inhibitor+venetoclax, FLT3-inhibitors (quizartinib and gilteritinib) with venetoclax, and immune therapies with venetoclax. We have also led the development of T-cell checkpoint therapies in AML and believe this combination triplet of HMA with venetoclax with macrophage unleashing agent magrolimab could be very important.

Preclinical Rationale: Venetoclax was shown to decrease naïve but not memory T cells in in vitro studies of human lymphocytes (Matthew R et al, Blood 2018 132:3704). In a mixed lymphocyte reaction assay, venetoclax did not affect IFN-gamma secretion by itself or when co-treated with the checkpoint inhibitor nivolumab. Similar findings were observed in a cytomegalovirus recall assay, suggesting that venetoclax does not impair immune response to infections. These findings suggest that venetoclax does not impair anti-tumor immune therapy and may synergize with immune checkpoint (T cell or macrophage based) therapy. These findings suggest that venetoclax does not impair anti-tumor immune therapy and may synergize with immune checkpoint (T cell or macrophage based) therapy. Lasater et al demonstrated that significant venetoclax-induced cell death in the immune cell population at clinically relevant drug concentrations is limited to the B-cell subset and that BCL-2 inhibition is not detrimental to survival or activation of NK- or T-cell subsets (Lasater E et al, Blood 2018 132:1118). Preclinical work combining CD47 and VEN and triplet of CD47+VEN+HMA is ongoing currently in Dr Konopleva's lab.

We have developed a great deal of expertise with venetoclax and developed, published optimized dosing schedules, assessment timepoints, safety monitoring, and biomarker assays. Additionally with >200 frontline HMA+VEN treated patients at MD Anderson Cancer Center we have developed and used robust internal controls for expected outcomes with HMA+VEN based therapies in older AML in each cytogenetic and molecular subset of AML to allow for rapid comparison with emerging triplets in this space to quickly decide "go" or "no go" signals. We have been impressed with the safety and efficacy profile of the AZA+magrolimab (Sallman D et al, ASH 2019 Oral presentation, Abstract #569: full PowerPoint attached as appendix J; Sallman D et al ASCO 2020, Oral presentation, Abstract #7507: full PowerPoint attached as appendix C) with a 64% ORR in 22 frontline older AML patients ineligible for intensive chemotherapy with a CR of 41% and CR/CRi of 55%, 8 week mortality was 0. No median duration of response had been reached with a median follow-up of 8.8 months. In addition, over 50% of patients achieved a cytogenetic CR and were minimal residual disease negative by multiparameter flow cytometry. Particularly in TP53 mutant AML patients, where available therapies have limited efficacy (including venetoclax+HMA), magrolimab+AZA led to a 78% CR/Cri rate. Magrolimab + AZA was well tolerated with no MTD reached and no significant exacerbation of azacytidine toxicities. Importantly, no deaths were observed in the first 60 days of therapy and the treatment discontinuation rate due to an AE was only 1.6%.

We believe that the combination of AZA+VEN+CD47 antibody warrants evaluation: the expected endpoints for us to consider this triplet superior to HMA+VEN and worthy of further development/registration pathways would predominantly be: CR/CRi duration >13 months (HMA+VEN 11months), median OS >22 months (HMA+VEN 17.5 months), and/or MRD-negative rate of >60% (HMA+VEN 40%) among CR/CRi patients, with 8-week mortality rate <10% (HMA+VEN 8%) in the older AML population not considered candidates for induction therapy. In the subset of patients with TP53, adverse cytogenetics, secondary AML the expected endpoints for us to consider this triplet superior to HMA+VEN and worthy of further development/registration

pathways would be CR/CRi>60% (HMA+VEN 45%), median OS >9months (HMA+VEN 5-6 months), and MRD-negative rate among CR/CRi of >40% (HMA+VEN 14%) again with 8-week mortality <10%. Furthermore, significant myelosuppression has not been observed with magrolimab monotherapy with the exception of an on target initial and transient anemia (generally observed with the first dose) due to the clearance of aging RBCs that are susceptible to magrolimab clearance. To this point, this anemia is mitigated with a priming/intra-patient dose escalation, which will be used for this study. Importantly, the average hemoglobin drop observed with the first dose of magrolimab + AZA was only 0.4 g/dL (Sallman ASH 2019, abstract #569) and 73% of AML patients achieved RBC transfusion independence at any timepoint. The lack of significant neutropenia and thrombocytopenia with magrolimab suggest that the combination of AZA+VEN with magrolimab may not result in severe and/or prolonged cumulative neutropenia/thrombocytopenia, and thereby be more feasible than a number of other ongoing combinations of other AML drugs with venetoclax that incorporate two myelosuppressive agents and encounter problems due to cumulative myelosuppression. This may be an added benefit for this combination.

Phase IB Cohort Update (Appendix N)

In summary the triplet of azacitidine, venetoclax and magrolimab was well tolerated. We had no 30- or 60-day mortality, no ICU stays in cycle 1, no sudden or unexpected AEs or SAEs with the combination, and no treatment discontinuations due to drug related toxicities. No drug related SAEs were documented. Drug related AEs included infusion related reactions in three patients (2 were Grade 2 and 1 Grade 1). The IRR was seen after first dose in the first patient and presented with a feeling of doom, depression and then resolved over 24-48 hours without interruption and did not recur. The other 2IRRs were transient and resolved with completion of infusion and did not recur. Drop in hemoglobin was frequently noted after the first, second and occasionally third dose of magrolimab and required close monitoring during the ramp-up.

Among the 6 patients treated, all R/R AML, median 1 prior salvage, all 6 with ELN 2017 adverse risk, 5 of6 with ELN adverse cytogenetics, 4 of 6 with TP53 mutations and median age 57 years (range, 42 – 77). Two patients (33%) achieved a response at end of C1 with CRp in both and one additional patient achieved an MLFS. One of the CRp's eventually went on to achieve CR after C2. Among the 4 TP53 mutated, one responded with CR that is ongoing at 3.5 months. Among 3 patients who had received prior VEN based therapies (Clad+LDAC with VEN in one, and HMA+VEN in two patients) we noted a response of MLFS in one patient, maintained for about 3 months.

Rationale for azacitidine, venetoclax and magrolimab in prior venetoclax exposed patients:
Patients who have relapsed or refractory disease post HMA+Venetoclax based therapy have dismal outcomes. Published data from the MDACC group for relapsed/refractory AML patients who had failed frontline venetoclax and hypomethylating agents (Maiti A et al, Haematologica. 2020 Jun 4; haematol.2020.252569) showed that this was a population of major unmet need. The median OS in 41 patients who had failed (relapsed or refractory) after prior venetoclax and hypomethylating agent was 2.4 months. Patients who received any salvage therapy (n=24) had longer OS compared to patients who could not or did not receive salvage therapy (n=17, 2.9 vs 1.3 months, hazard ratio [HR]=0.41, 95% confidence interval [CI] 0.19-0.88, p=0.003). Among the 24 patients in this group who had failed prior venetoclax based therapy and received subsequent salvage therapies a CR/CRi was noted in only 5 of 24 (22%). Post-venetoclax patients are a major referral population to our center and population in need of clinical trials. These patients often have emergent or pre-existing TP53 mutations and given the encouraging data of azacitidine with magrolimab in TP53m AML in the frontline setting we believe the combination of azacitidine with venetoclax and magrolimab is worth evaluating in patients relapsed/refractory to

HMA with venetoclax. Furthermore it is not known whether continuing venetoclax may leverage unique synergies in the triplet that were not present with the doublet of HMA with venetoclax. Among our initial phase 1B six patients we noted a response of MLFS maintained for about 3 months in 1 of 3 patients with prior venetoclax therapy for AML. Thus we believe it would be worthwhile to evaluate patients who are relapsed or refractory to venetoclax based therapies if they are not eligible for potentially curative therapy such as effective salvage therapy, targeted therapies or hematopoietic stem cell transplantation or who refuse these options at the time of enrollment.

3.0 STUDY DESIGN

- This will be a phase Ib/II study that will include a dose finding phase Ib portion and a phase II portion with three independent cohorts in the phase II:

  - **Dose Finding Phase IB:** A sample size up to 18 patients will be accrued into the Phase Ib part with AZA+VEN+Magrolimab. One dose level with dose de-escalation levels as needed, will be tested in this Phase Ib portion [see section 5.1]. The Phase Ib portion will enroll only R/R AML patients.

  - **Phase II, Frontline cohort:** The maximum number of patients that will be recruited for the phase II frontline AML part is 60. Phase II frontline will enroll newly diagnosed AML patients not fit for intensive induction therapy.

  - Phase II, Relapsed/Refractory prior Venetoclax naïve cohort: The maximum number of patients that will be recruited for the phase II relapsed/refractory prior venetoclax naïve cohort is 30.

  - Phase II, Relapsed/Refractory prior Venetoclax exposed cohort: The maximum number of patients that will be recruited for the phase II relapsed/refractory prior venetoclax exposed cohort is 30.

  Cycles will be repeated approximately every 28 days. It is planned that up to a total of 12 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 12 cycles of therapy may be considered on a case by case basis after discussion with the principal investigator.

4.0 PATIENT SELECTION

The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion Criteria

4.1.1 Diagnosis of 1) Pathology diagnosis of AML (excluding acute promyelocytic leukemia (APL)

4.1.2 Phase Ib dose finding cohort: Patients aged ≥18 years old with relapsed/refractory AML are eligible if they are not eligible for potentially curative therapy such as effective salvage therapy or hematopoietic stem cell transplantation or who refuse these options at the time of

enrollment. Patients must have received at least one prior therapy for AML. Patients may have received up to 2 prior therapies for AML (i.e. up to salvage 2 status allowed). Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2

4.1.3 Phase II (frontline cohort): Patients with newly diagnosed AML who are chemonaive (specified in 4.1.5) who are ineligible for intensive chemotherapy based on EITHER:
A. ≥75 years of age OR
B. <75 years of age with at least 1 of the following relevant comorbidities:
-Poor performance status (ECOG) score of 2.
-Clinically significant heart or lung comorbidities, as reflected by at least 1 of:
a. Left ventricular ejection fraction (LVEF) ≤50%.
b. Lung diffusing capacity for carbon monoxide (DLCO) ≤65% of expected.
c. Forced expiratory volume in 1 second (FEV1) ≤65% of expected.
d. Chronic stable angina or congestive heart failure controlled with medication.
e. Creatinine clearance ≥ 30 mL/min to < 45 ml/min calculated by the Cockcroft-Gault formula or measured by 24 hours' urine collection
-Other contraindication(s) to anthracycline therapy (must be documented).
-Other comorbidity the investigator judges incompatible with intensive remission induction chemotherapy, which must be documented and approved by the PI."

For patients with prior MDS or chronic myelomonocytic leukemia (CMML) or MPN who transformed to AML, therapy received for MDS, CMML, or MPN is NOT considered as prior therapy for AML. Patients with MDS or CMML treated with HMA therapies who progress to AML, and have no available therapies or are not candidates for available therapies, will be eligible at the time of progression to AML. Temporary prior measures such as apheresis, ATRA, steroids while diagnostic work-up of AML is being performed are allowed and not counted as a prior salvage

---Phase II (relapsed/refractory prior venetoclax naïve cohort): Patients aged ≥18 years old with relapsed/refractory AML are eligible if they are not eligible for potentially curative therapy such as effective salvage therapy or hematopoietic stem cell transplantation or who refuse these options at the time of enrollment. Patients must have received at least one prior therapy for AML. Patients may have received up to 2 prior therapies for AML (i.e. up to salvage 2 status allowed). Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2. Patients must not have received prior venetoclax for MDS or AML.

---Phase II (relapsed/refractory prior venetoclax exposed cohort): Patients aged ≥18 years old with relapsed/refractory AML are eligible if they are not eligible for potentially curative therapy such as effective salvage therapy, targeted therapies, or hematopoietic stem cell transplantation or who refuse these options at the time of enrollment. Patients must have received at least one prior therapy for AML. Patients may have received up to 1 prior therapies for AML (i.e. up to salvage 1 status allowed). Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2. Patients must have received prior venetoclax for MDS or AML.

4.1.4 Patients with newly diagnosed AML with poor risk karyotype or complex karyotype per ELN2017 and/or TP53 deletions/mutations of any age >/=18 years of age will be eligible for the Phase II (frontline cohort) regardless of eligibility or fitness for intensive chemotherapy

4.1.5 For Phase II (frontline cohort): Patients must be chemonaïve, i.e., not have received any chemotherapy (except hydrea or up to 2 doses of ara-C for transient control of hyperleukocytosis) for AML. They may have received transfusions, hematopoietic growth factors or vitamins for an antecedent hematological disorder (AHD) or for AML. Temporary prior measures such as apheresis, ATRA, steroids or hydrea while diagnostic work-up is being performed are allowed and not counted as a prior salvage. Supportive care therapy for MDS (growth factors, transfusions) will not be considered as prior therapy for MDS/AML and these patients will be enrolled to the frontline cohort of the study if they are otherwise eligible.

4.1.6 In the absence of rapidly progressing disease, the interval from prior treatment to time of initiation of protocol therapy will be at least 2 weeks or at least 5 half-lives (whichever is shorter). The half-life for the therapy in question will be based on published pharmacokinetic literature (abstracts, manuscripts, investigator brochure's, or drug-administration manuals) and will be documented in the protocol eligibility document. The toxicity from prior therapy should have resolved to Grade ≤1, however alopecia and sensory neuropathy Grade ≤2 not constituting a safety risk based on investigators judgement is acceptable. The use of chemotherapeutic or anti-leukemic agents is not permitted during the study with the following exceptions: (1) intrathecal (IT) therapy for patients with controlled CNS leukemia at the discretion of the PI. (2) Use of up to 2 doses of cytarabine (up to 2 g/m^2 each dose) for patients with rapidly proliferative disease is allowed before the start of study therapy and for the first four weeks on therapy. Since the effect of most IO-agents, HMA-therapies, venetoclax may be delayed, use of hydroxyurea for patients with rapidly proliferative disease is allowed on study and before the start of study therapy and will not require a washout. These medications will be recorded in the case-report form.

4.1.7 Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted. Patients with a known history of CNS disease or leukemic brain metastasis must have been treated locally, have at least 2 consecutive LPs with no evidence of CNS leukemia at the time of enrollment, and must be clinically stable for at least 4 weeks prior to enrollment and have no ongoing neurological symptoms that in the opinion of the treating physician are related to the CNS disease (sequelae that are a consequence of the treatment of the CNS disease are acceptable).

4.1.8 Serum biochemical values with the following limits:
Patients must have adequate renal function as demonstrated by a creatinine clearance (CrCl) ≥ 30 mL/min calculated by the Cockcroft-Gault formula or measured by 24 hours' urine collection.
For patients with BMI >23, Adjusted body weight and not Ideal Body Weight is the recommended parameter (Winter et al, Pharmacotherapy. 2012 Jul; 32(7):604-12; Brown et al, Ann Pharmacother. 2013 Jul-Aug;47(7-8): 1039-44).

-Total bilirubin <1.5 x ULN unless considered due to Gilbert's syndrome,

-Aspartate aminotransferase or alanine aminotransferase ≤2.0 x ULN (aspartate aminotransferase or alanine aminotransferase ≤3.0 x ULN if deemed related to leukemia by the treating physician)

4.1.9 White blood cell count <15 x 10^9/L. Patients must have a WBC count <15 x 10^9/L prior to each dose of magrolimab in Cycle 1. Hydroxyurea may be used to reduce the WBC count to ≤ 15x10^9/L.

4.1.10 Ability to understand and provide signed informed consent.

4.1.11 Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment.

4.1.12 Women of childbearing potential must agree to use an adequate method of contraception during the study and until 4 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

Adequate methods of contraception include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Combination of any of the two following (a+b or a+c or b+c)

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Male patients who are sexually active with a WOCBP and who have not had vasectomies must be willing to use a barrier method of contraception during the study and for 3 months after the last dose of magrolimab, venetoclax or azacitidine, whichever ends later.

Women who are pregnant or breastfeeding will not be eligible.

4.2 Exclusion Criteria

4.2.1 Patients with known allergy or hypersensitivity to magrolimab, venetoclax, azacitidine or any of their components.

4.2.2 Patients with any other known concurrent severe and/or uncontrolled medical condition including but not limited to diabetes, cardiovascular disease including hypertension, renal disease, or active uncontrolled infection, which could compromise participation in the study. Patients on active antineoplastic or radiation therapy for a concurrent malignancy at the time of screening. Maintenance therapy, hormonal therapy, or steroid therapy for well-controlled malignancy is allowed.

4.2.3 Prior organ transplantation including allogenic stem-cell transplantation within 3 months prior to planned enrollment, active graft versus host disease (GVHD) >Grade 1, or requiring transplant-related immunosuppression, excluding prednisone 10mg or equivalent steroid.

4.2.4 Known inherited or acquired bleeding disorders

4.2.5 Prior treatment with a CD47 or SIRPα targeting agent.

4.2.6 Patients with symptomatic CNS leukemia or patients with poorly controlled CNS leukemia.

4.2.7 Patients with a known HIV infection that is not well controlled (i.e. any detectable circulating viral load) at the time of enrollment.

4.2.8 Patients with known positive hepatitis B or C infection by serology, with the exception of those with an undetectable viral load within 3 months (Hepatitis B or C testing is not required prior to study entry). Subjects with serologic evidence of prior vaccination to HBV [i.e., HBs Ag-, and anti-HBs+] may participate.

4.2.9 Patients who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment.

4.2.10 Patients who have had any major surgical procedure within 14 days of Day 1.

4.2.11 Other severe acute or chronic medical conditions that is active and not well controlled including colitis, inflammatory bowel disease, or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

4.2.12 Active and uncontrolled disease (active infection requiring systemic therapy or fever likely secondary to infection within prior 48 hours): prophylactic antibiotics or prolonged course of IV antibiotics for controlled infection are allowed, uncontrolled hypertension despite adequate medical therapy, active and uncontrolled congestive heart failure NYHA class III/IV, clinically significant and uncontrolled arrhythmia) as judged by the treating physician.

4.2.13 Patients unwilling or unable to comply with the protocol.

5.0 TREATMENT PLAN

5.1 General

- All patients will be registered through CORe.

- The starting dose level for the study will be dose level 0.
    - 6 patients will initially be enrolled at dose level 0. If dose-limiting toxicities (DLT) is observed in ≤1/6, dose level 0 will be declared the MTD (and RP2D) and phase II portion will open with dose level 0.
    - If ≥2/6 in Dose Level 0 experience a DLT, the MTD has been exceeded. In this case, dose level 0 is too toxic and lower dose levels with subsequent cohorts of 6 patients each (dose level -1 and -2 in that order as dose de-escalation levels) will be sequentially examined.
    - If 2 or more patients experience DLT at dose level -2, in which case the MTD has been exceeded. In this case, dose level -2 is too toxic and amendment will be submitted to examine lower doses.

Rationale for the dose de-escalation design with cohorts of size 6:

We have extensive experience with both doublets azacitidine in combination with venetoclax (>200 patients treated at MDACC) as well as azacitidine in combination with magrolimab (>45 patients treated at MDACC). MDACC was one of the lead site for both these national studies: Dr Courtney DiNardo for azacitidine with venetoclax phase Ib/II registration study that led to US FDA approval of this combination for frontline older AML not suitable for intensive induction therapy, and Dr Naval Daver for the ongoing phase Ib/II azacitidine with magrolimab study in frontline higher risk MDS and for frontline older AML not suitable for intensive induction therapy. In our experience these regimens have non-overlapping toxicities and are well tolerated. Mechanistically we do not anticipate cumulative myelosuppression with this combination. The 60-day induction mortality at MDACC for azacitidine with venetoclax is 3%, and for azacitidine with magrolimab is 0, these are lower than with any other frontline AML therapies we have used in the past. All patients will be treated at MDACC and will be required to stay locally for the first cycle of therapy. Therefore, we believe the protocol size of 6 is reasonable for this triplet.

5.2 Schedule

5.2.0 Patients will be treated according to the following dose levels (Table 1);

Table 1: Dose levels for azacitidine, venetoclax, and magrolimab

Dose Level	Azacitidine (mg/m2)	Venetoclax (400mg or equivalent)	Magrolimab
-2	75 mg/m2 D1-7	D1-28*,#	1 mg/kg on Days 1 and 4 15 mg/kg on Day 8 15 mg/kg on Days 11,15, 22 15 mg/kg weekly for Cycle 2 15 mg/kg Q2weeks for Cycle 3+
-1	75 mg/m2 D1-7	D1-28*,#	1 mg/kg on Days 1 and 4 15 mg/kg on Day 8

			20 mg/kg on Days 11,15, 22 20 mg/kg weekly for Cycle 2 20 mg/kg Q2weeks for Cycle 3+
0 (Starting dose)	75 mg/m2 D1-7	D1-28*,#	1 mg/kg on Days 1 and 4 15 mg/kg on Day 8 30 mg/kg on Days 11,15, 22 30 mg/kg weekly for Cycle 2 30 mg/kg Q2weeks for Cycle 3+

* During cycle 1, venetoclax will be dose escalated daily to the goal dose of 400mg daily. Patients will receive 100mg on Day 1, 200mg on Day 2 and 400mg on Day 3 and onwards, or adjusted dose if on concomitant azoles. The goal is to administer 28 days of venetoclax in cycle 1 unless marrow remission with concomitant marrow hypocellularity and/or myelosuppression is confirmed earlier than cycle 1 Day 28. In this case the venetoclax may be stopped earlier to avoid venetoclax related myelosuppression or further marrow hypo/aplasia after discussion and approval from the PI. Venetoclax dose ramp-up as described in section 6.4.

If a bone marrow remission (</=5% blasts) or aplasia/hypoplasia (<10% cellularity or insufficient sample) is not confirmed on the Day 21 bone marrow, patients should continue venetoclax until day 28 and have a repeat bone marrow on Day 28 (+/- 5 days). If the Day 28 bone marrow shows >5% blasts proceed with cycle 2 if this is in the best interest of the patient (those with C1D28 bone marrow >5% are allowed to receive 21 days of venetoclax in cycle #2 after discussion and approval from the PI). If the Day 28 bone marrow shows </=5% blasts or aplasia/hypoplasia follow steps outlined in “a” and “b” below.

- Azacitidine (75 mg/m2/day) will be administered subcutaneously (SQ) or intravenously (IV) for the first 7 days of every cycle. The azacitidine may be given in a 5on - 2off - 2on or 4on - 2off - 3on or other similar modified schedule if the patient is not able to get weekend infusions. Azacitidine is administered in the clinic or chemotherapy administration area. Both SQ and IV forms of administration are FDA approved and are allowed and considered interchangeable. Patients may start receiving azacitidine by one route and changed to the other, and also administration schedules from one schedule and changed to the other at any time as needed based on patient and/or physician preference.

- Magrolimab will be administered IV using intrapatient ramp-up with a 1 mg/kg dose on Day 1 and 4, 15 mg/kg on Day 8, 30 mg/kg on Day 11, 15 and 22, followed by 30 mg/kg weekly for Cycle 2, then 30 mg/kg Q2 weeks Cycle 3 and beyond. Days 1, 4, 8, 11 (+/- 2 day) serve as the period of the ramp-up. After the dose ramp-up is completed magrolimab will be administered weekly for weeks 3 and 4 in Cycle 1 (+/- 2 days), then weekly in Cycle 2, and then once every 2 weeks from Cycle 3 onwards. Magrolimab should not be given on consecutive days. The hemoglobin must be documented at >/=8.5 g/dL on the day of administration, prior to the administration of the first, second, third and fourth dose of

magrolimab in Cycle 1.

- Magrolimab ramp-up will depend on the Dose Level being evaluated as specified in Table 1 above, All infusions will have a +/-2 day window,

- Venetoclax will be administered orally daily on Days 1-28 of the first cycle; and may be reduced to Venetoclax Days 1-21 or less for subsequent cycles after PI approval.

- In cycle 1, patients should undergo a bone marrow aspiration and biopsy on day 21 (+/- 4 days). Patients who achieve a confirmed marrow remission (i.e. bone marrow blasts </=5% by morphology) or marrow aplasia/hypoplasia (</=10% cellularity or insufficient sample) may discontinue venetoclax for the remainder of the cycle and be monitored for count recovery.

  a) If the Day 21 bone marrow shows </=5% blasts, the venetoclax may be held, and consider delaying cycle 2 till ANC>0.5 and platelets are >30K without platelet transfusion support for >5 days.

  b) If the Day 21 bone marrow shows aplasia/hypoplasia (</=10% cellularity or insufficient sample), the venetoclax may be held on Day 21 to avoid venetoclax related myelosuppression or further marrow hypo/aplasia, and a repeat bone marrow should be performed on Day 28 (+/- 4 days) to confirm response and MRD assessment. If the Day 28 bone marrow shows >5% blasts proceed with cycle 2 if this is in the best interest of the patient (those with C1D28 bone marrow >5% are allowed to receive 21 days of venetoclax in cycle#2). If the Day 28 bone marrow shows </=5% blasts, the venetoclax may be continued to be held, and consider delaying cycle 2 till ANC>0.5 and platelets are >30K without platelet transfusion support for >5 days. If the Day 28 bone marrow shows persistent aplasia/hypoplasia (</=10% cellularity or insufficient sample) venetoclax may be held to avoid venetoclax related myelosuppression or further marrow hypo/aplasia and consider repeating a bone marrow in approximately 10-14 days.

  c) If a bone marrow remission (</=5% blasts) or aplasia/hypoplasia is not noted on the Day 21 bone marrow, patients should continue venetoclax until day 28 and have a repeat bone marrow on Day 28 (+/- 5 days). If the Day 28 bone marrow shows >5% blasts proceed with cycle 2 if this is in the best interest of the patient (those with C1D28 bone marrow >5% are allowed to receive 21 days of venetoclax in cycle #2 after discussion with and approval from the PI). If the Day 28 bone marrow shows </=5% blasts or aplasia/hypoplasia follow steps outlined in “a” and “b” above.

  d) Treatment interruptions and dosing schedules other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale.

  e) Of note magrolimab antibody infusion will continue as scheduled and will not be impacted or adjusted based on venetoclax dosing schema or venetoclax related delays.

- Physicians should leukoreduce with hydroxyurea to reduce the peripheral white blood count to below 15,000/μL prior to the administration of the first dose of venetoclax. If the WBC is >15,000/μL the venetoclax should not be initiated till the white count is brought down to below 15,000/μL.

- The patient will be admitted to the hospital for at least the first 14 days of the 1st cycle of

concomitant azacitidine-venetoclax-magrolimab therapy (e.g., Days 1 through Day 14) of cycle 1, potentially admission will be longer if we encounter TLS, infections or other complications that would be better managed inpatient. To mitigate the risk for tumor lysis syndrome, patients must be receiving tumor lysis prophylaxis, including hydration (oral, intravenous) and treatment with a uric acid reducing agent (allopurinol, rasburicase) prior to the start of venetoclax therapy and continued during Cycle 1.

TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained prior to dosing and 5-8 hours after each new venetoclax dose during the venetoclax ramp-up period. TLS chemistry test results will be reviewed by the investigator in real time and prior to the subject receiving the next higher dose of venetoclax to ensure appropriate and timely management. If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax should be administered until resolution of the TLS. Venetoclax interruption for up to 72 hours following transient (< 48 hours) chemical changes and laboratory TLS will be allowed and will not require a dose reduction.

- See section 6.4 for details of TLS management.

- If azacitidine cycles are delayed, venetoclax therapy may continue on Days 1-21 or Days 1-28 of a 4-week cycle after discussion with the PI or Co-PI and documentation in the medical record. If azacitidine cycles are delayed, magrolimab may as scheduled during cycle 1 and continued weekly in cycle 2, then weekly in Cycle 2, then every 2 weeks from cycle 3 onwards) after discussion with the PI or Co-PI and documentation in the medical record.

5.2.1 DLT is defined as non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first 28 days on study that meets any of the following criteria:

• CTCAE Grade 3 AST (SGOT) or ALT (SGPT) for >/= 7 days or grade 3 hyperbiliribunemia for >/= 7 days. Patients with a Grade 3 indirect hyperbilirubinemia that resolves to Grade 2 or below within 14 days is excluded given the on target transient effect of extravascular hemolysis with magrolimab in clearing older RBCs.

• CTCAE Grade 3 AST (SGOT) or ALT (SGPT) accompanied by grade 2 bilirubin increase

• CTCAE Grade 4 AST (SGOT) or ALT (SGPT) of any duration

• All other non-hematological adverse events that are Grade 3 or 4 according to the NCI common terminology criteria version 5.0, with the following exceptions:

--Grade 3 or 4 nausea, vomiting and diarrhea will be considered DLT only if not controlled to Grade 2 or lower with optimal therapy within 72 hours.

--Grade 3 or 4 biochemical abnormalities (e.g., lipase or amylase elevation) will only be considered DLT if accompanied by clinical consequences.

--Grade 3 or 4 isolated electrolyte abnormalities must be without clinical consequence and resolve, with or without intervention, to < Grade 2 levels within 72 hours.

-- Grade 3 infusion reaction if successfully managed and which resolves within 72 hours

-- Grade 3 or 4 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage

- Results in discontinuation of therapy
- Any treatment-related death;

An inability to receive the full dose and schedule of azacitidine, magrolimab, and/or venetoclax or delays of subsequent cycles of more than 14 days due to drug related non-hematologic or hematologic toxicity/toxicities will be considered as DLTs.

Hematologic DLT is defined as grade 4 neutropenia and thrombocytopenia lasting for 42 days or more from Cycle 1 Day 1 in the absence of residual leukemia (i.e., </=5% blasts by morphology or residual leukemia by flow-cytometry). Anemia will not be considered for the definition of DLT.

5.2.2 Patients that are removed from study before day 28 for any reason other than toxicity and have not experienced DLT will be replaced. Patients who come off study earlier than 28 days during the DLT evaluation period may continue to receive protocol therapy if they are having clinical benefit, after discussion with the PI. The rationale for continuing therapy must be clearly documented in the patients chart.

5.2.3 Patients who do not receive venetoclax on day 1 due to logistical and/or financial reasons, the DLT period will be extended to 28 days from the first dose of venetoclax. For evaluation of neutropenia-related DLT, the DLT period will be 42 days from the first dose of venetoclax.

5.2.4 One cycle of therapy is defined as 28 days (+/- 4 days). Patients will receive one cycle of therapy every 28 days (+/- 4 days).

5.2.4.1 Cycles may be started early (but not earlier than day 21) for patients with active disease if judged in the best interest of the patient with the exception of cycle 1 during the DLT evaluation period which must be at least 28 days

5.2.4.2 Subsequent cycles may be delayed for recovery of toxicity. Delays in start of subsequent cycles greater than 2 weeks from the end of the cycle will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator and the sponsor of potential risk/benefit ratio and complete documentation of the degree of clinical benefit and reason for continuation on this regimen. In general dose delay of >2 weeks due to drug related toxicities in the absence of clear clinical benefit will result in discontinuation of study drug.

5.2.4.3 In instances where one drug has to be discontinued transiently because of safety, the administration of the other drug may continue as scheduled. If the drug that is held can resume at a later time, no doses will be made up and

the administration will follow the originally defined schedule calendar according to the drug that was continued.

5.2.4.4 Subsequent courses may be administered regardless of peripheral blood counts during the first 4 cycles and/or in the presence of residual leukemia. If prolonged myelosuppression defined as ANC $<0.5 \times 10^9$ and/or platelets $<20 \times 10^9$ (more than 56 days) with evidence of a hypocellular marrow (marrow cellularity less than 10% without evidence of leukemia) is observed, the subsequent courses of azacitidne and venetoclax may be given at the next lower dose. If there are persistent peripheral blood blasts, or the bone marrow shows persistent leukemia by morphology or flow-cytometry, patient may continue treatment regardless of neutrophil and platelet count. Subsequent cycles can be administered at the discretion of the treating physician not earlier than 3 weeks after the prior cycle.

5.2.4.5 Patients must receive at least 5 of 7 planned doses of azacitidine, 4 of 6 planned doses of magrolimab and 18 of 28 planned doses of venetoclax during the first 28 days on trial (i.e. during cycle 1) to be considered evaluable during the DLT phase. Patients who receive less than these planned number of doses of each drug during the first 28 days on trial will not be considered evaluable during the DLT phase. However, if such patients develop a toxicity that would normally be considered a DLT this will still be captured as a DLT. Any toxicity that meets the criteria for DLT during the first 28 days of trial in a patient who has received at least one dose of either azacitiidne, venetoclax or magrolimab will constitute a DLT. Patients not considered evaluable due to insufficient dosing and who do not develop a toxicity that is considered a DLT will be replaced. These patients may continue therapy on trial after discussion with the PI if they are having clinical benefit and the reasons for continuation and potential benefit/risk profile for the patient must be clearly documented in the medical records. In phase II, DLT will not be monitored.

5.2.4.6 For patients who discontinue therapy, the reason for treatment discontinuation will be documented.

5.2.4.7 Dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale.

5.2.5 Venetoclax Administration

5.2.5.1 If a dose is missed or vomited, the next dose should not be increased to account for missing a dose. The subject should take the next regular dose at the regularly scheduled time.

5.2.5.2 Day 1 of each cycle will be counted from the start of the azacitidine infusion. Treatment may be prolonged beyond the planned 28 days of each cycle if the start of the next course of azacitidne is delayed. However, if there are adverse events that mandate treatment interruption or it is considered in the best interest of the patient for safety reasons to interrupt magrolimab and/or venetoclax therapy, magrolimab and/or venetoclax administration can be transiently discontinued and re-started as per guidelines in section 6.0.

5.3 Discontinuation of Study Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease at any time on study (from cycle 1 onwards) or not achieving at least a PR response by the end of 4 courses of therapy.

2. Intercurrent illness that prevents further administration of treatment

3. Patient request

4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.

6. Patients who are eligible for hematopoietic stem cell transplantation are allowed to proceed and stop therapy when feasible.

It is planned that up to a total of 12 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 12 cycles of therapy may be considered on a case by case basis after discussion with the principal investigator.

5.4 Concomitant Medications

5.4.1 The use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted. Other leukemia directed therapy including systemic chemotherapy, radiation therapy, or biologic response modifiers are not permitted during the study with the exception of those specified in the eligibility criteria. No other investigational agent for the treatment of AML is allowed during the study. Antiemetics may be used for the prevention or treatment of nausea and vomiting.

5.4.2 Administration of other antineoplastic agents is prohibited for patients while on this study with the following exceptions: (1) intrathecal (IT) therapy for patients with controlled CNS leukemia at the discretion of the PI, (2) Use of 1-2 doses of cytarabine (up to 2 g/m^2 each dose) for patients with rapidly proliferative disease is allowed before the start of study therapy and for the first four weeks on therapy, (3) Since the effect of most IO-agents, HMA-therapies, venetoclax may be delayed, use of hydroxyurea (any dose) for patients with rapidly proliferative disease is allowed on study and before the start of study therapy and will not require a washout. These medications will be recorded in the case-report form.

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and MD Anderson Caner Center Leukemia Department guidelines (Table 2).

Table 2: Instructions for the use of concomitant medications and therapies

Category of Use	Medication	Comment on Use	Restriction on Use
Recommended	Prophylactic antibiotics, antifungal agents, and antiviral agents	Strongly encouraged	None
	Antiemetic agents	According to institutional standard of care	None
Allowed	Oral allopurinol or rasburicase	According to standard of care at MD Anderson Cancer Center	None
	Leukapheresis	According to standard of care at MD Anderson Cancer Center	Before induction 1 day 1 only
	Red blood cell transfusion	None	None
	Platelet transfusion	None	None
	White blood cell transfusion	At investigators discretion according to standard of care at MD Anderson Cancer Center	None
	Myeloid growth factors or platelet growth factor	At investigators discretion according to standard of care at MD Anderson Cancer Center	None
	Erythropoietin or darbepoetin	At investigators discretion according to standard of care at MD Anderson Cancer Center	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MD Anderson Cancer Center	None

Consistent with subject safety and comfort, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol during the clinical study.

If considered necessary for the subject's wellbeing, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the- counter, or illicit) before and during the course of the study.

Recommendations with regard to specific types of concomitant therapies, supportive care; diet and other interventions are as follows:

-Infections secondary to myelosuppression are common in patients with AML, and may be related to underlying disease, chemotherapy, or both. Therefore, the use of prophylactic antibiotics, antifungal agents, and antiviral agents is recommended according to institutional standards.

-All ongoing medications and therapies (including herbal products, nutritional supplements, and nontraditional medications) at screening will be considered prior medications. Concomitant medication data will not be collected or entered into the case report form other than hydroxyurea as mentioned above; however, the subject's medication record will contain a list of concomitant medications. If a prohibited medication is inadvertently administered/ taken by the patient, the patient may remain on study as long as the prohibited medication is discontinued as soon as feasible. If a prohibited medication is considered essential for the patient well being, continuation on study with concomitant administration of such medication(s) will need to be discussed with and approved by the principal investigator and sponsor.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Toxicity Directly Attributable to Study Drugs

Patients experiencing unacceptable toxicity directly attributable to the study drugs should temporarily stop treatment according to the guidelines in the dose adjustment schema.

6.2 Toxicity Grading

Toxicity grading will be according to the NCI CTCAE, v5.0. To prevent unnecessary morbidity, the following guidelines for dose adjustment for drug-related toxicities are recommended.

6.2.1 Dose adjustments for hematological drug- related adverse events (AE):

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE version 5.0 (**Appendix F**) and the guidelines provided below.

Patients with acute leukemias usually present with abnormal peripheral blood counts at the time therapy is started, and myelosuppression is an expected event during the course of therapy for acute leukemia. Thus, subsequent courses may be administered regardless of peripheral blood counts during the first 4 cycles and/or in the presence of residual leukemia. After cycle 4, treatment interruptions and dose adjustments may be considered according to the following guidelines when there is no evidence of active leukemia:

➢ Patients with a response (no evidence of any residual leukemia on bone marrow and/or peripheral blood by morphology or flow-cytometry) and pre-cycle counts of neutrophils >1x10^9/L and platelets >50 x10^9/L will have dose modifications for hematological toxicities as specified in the azacitidine and venetclax PIs and the magrolimab IBs (Appendices E and H).

➢ If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts or any evidence of residual leukemia by morphology or flow, treatment may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions of individual drugs in these patients should be considered on an individual case-by-case basis and discussed with the PI.

➢ Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce, as applicable. No dose reductions (only dose interruptions as needed) are permitted for the IO-agent magrolimab in this study.

6.2.2 Dose adjustments for non-hematologic drug- related AEs

Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce azacitidine, venetoclax, and/or interrupt magrolimab, as applicable (Table 3).

Dose reductions of azacitidine will be as follows: Baseline dose level: 75 mg/m^2 x 7 days, dose level -1 of azacitidine: 50 mg/m^2 x 7 days, dose level -2: 37.5 mg/m^2 x 7 days, dose level -3: 25 mg/m^2 x 7 days. Further reductions or modifications to schedule beyond what is shown above or alternative reductions (e.g. 75mg/m2 x 5 days) may be allowed if deemed in the patient's best interest by the treating physician.

Dose reductions of venetoclax will be as follows: Baseline dose level of venetoclax: 400mg, dose level -1 of venetoclax: 200mg, dose level -2: 100mg, dose level -3, 50mg. Alternatively, the duration of venetoclax administration can be decreased (e.g. decrease from 28-days per cycle to 21-days per cycle to 14-day per cycle to 10 days per cycle) rather the dose being reduced.

Dose reductions for magrolimab will be allowed if warranted by investigator and after discussion and approval by PI as follows: Baseline level of magrolimab: 30mg/kg, dose level -1: 20mg/kg, and dose level -2: 15mg/kg.

Table 3. Dose adjustments of azacitidine, venetoclax and magrolimab for non-hematologic drug-related AEs, clinically significant in the opinion of the investigator

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction

3 or 4 (Persistent grade 2: Consider similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician)	1st and 2nd time	Hold suspected drug. -Resume the held drug at prior dose if recovery to ≤ Grade 1 occurs within 14 days. -If toxicity persists for 15-28 days, hold the drug and resume at prior dose if recovery to ≤ Grade 1 OR resume the drug at ONE dose level below current dose if recovery to ≤ Grade 2. -If toxicity persists for >28 days, hold the drug resume the drug at ONE dose level below current dose if recovery to ≤ Grade 2. Dose re-escalation to prior dose of the drug is permitted in accordance with the dose-escalation guidelines in section 6.6.
	3rd.	Hold suspected drug. Follow until toxicity ≤ Grade 2. Resume the held drug at ONE dose level below current dose. Dose re-escalation of the drug to prior dose is permitted in accordance with the dose-escalation guidelines outlined below Patients who are experiencing ongoing dose delays >8 weeks due to unresolved grade ≥3 adverse events should be taken off treatment.
	4th time	Discontinue therapy

6.2.3 Magrolimab specific dose delay/interruptions and drug related AEs of interest

Dose Modifications

A dose delay for up to 3 days may be permissible if the patient's WBC count is greater than 15 × 109/L (which is applicable to Cycle 1), to allow for oral hydroxyurea treatment to reduce the WBC count. Further dose delay due to elevated WBC counts may be considered with the investigator on an individual patient basis. A dose delay up to 3 days is also permissible during the first 2 doses of Magrolimab if patient's hemoglobin count is < 8.5 mg/dL to allow for blood transfusions. Hemoglobin must be >/= 8.5 mg/dL prior to the first 4 doses of Magrolimab. Magrolimab may be withheld if treatment-emergent and/or magrolimab-related AEs occur. Dose reduction of magrolimab should generally be avoided as dose-dependent toxicities have not been observed with magrolimab to date. However, dose reduction of magrolimab may be considered on a case by case basis for AEs, in which a 50% dose reduction would be recommended. Patients with dose reduction in magrolimab may have their dose re-escalated back to the original dose based on clinical assessment and benefit by the investigator.

Treatment Interruption and Delays

Treatment interruption for up to 2 weeks will be allowed after the start of Cycle 3 at the discretion of the Investigator. An interruption is defined as a non-protocol-specified interruption from treatment, assessments, and procedures. Patients with an interruption of longer than 4 weeks (4 weeks is maximum allowed for an elective drug delay) or a treatment delay of longer than 4 weeks must undergo re-priming with the intra-patient dose escalation of magrolimab again based on their original dosing regimen (e.g., for patients on once-weekly dosing, 1 mg/kg priming dose on Days 1 and 4, 15 mg/kg on Day 8, and 30 mg/kg on Days 11, 15, and 22.
Magrolimab dosing at the start of a subsequent cycle may be delayed to start with the initiation of azacytidine and venetoclax at the subsequent cycle for study drug-related treatment delays.

Re-priming/Re-intrapatient dose escalation

Given the large CD47 antigen sink on normal cells, patients who have a long dose delay of magrolimab are required to be re-primed with magrolimab dosing to resaturate the CD47 antigen sink. For patients who had a dose delay of greater than 4 weeks for magrolimab, re-priming/re-escalation is needed with magrolimab. For patients who have not received at least one 30-mg/kg dose of magrolimab (ie, for patients who have either not received their first dose of 30 mg/kg or patients who have received doses <30 mg/kg), a dose delay of only 2 weeks is allowed until re-priming is needed.

New section: Magrolimab specific safety management guidelines

Pre-medication:

Premedication is required before administration of the first 4 doses of magrolimab with oral acetaminophen 650 to 1000 mg and oral or IV diphenhydramine 25 to 50 mg, or comparable regimen. It is also required in case of reintroduction with re-priming. In addition, premedications are to be used to manage infusion-related reactions as described below.

Anemia, Blood Crossmatching, and Packed Red Blood Cell Transfusion Procedures

MAgrolimab binds to red cells and leads to erythrophagocytosis. In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in hemoglobin observed in the first 1 to 2 weeks. Patients with low baseline hemoglobin level, especially those with cardiac history, should be monitored closely after initial administrations of magrolimab as preexisting anemia could be exacerbated. In general, a hemoglobin level of at least 8 g/dL or higher for patients with cardiac co-morbidities prior to the first magrolimab dose is recommended. Red blood cell transfusions are permitted during screening and prior to enrollment to ensure adequate hemoglobin level as per Investigator clinical judgement. This, coupled with anemia from other causes in patients with cancers, means that care
has to be taken with RBC crossmatching and packed RBC transfusions. There is a possibility that treatment with magrolimab may obscure assessment of RBC phenotyping, although this has not been observed in the patients treated to date.
During the screening period prior to initiation of magrolimab therapy, blood cell ABO phenotyping for minor antigens, type and screen (ABO/Rh), and direct antiglobulin test (DAT) will be performed for each patient. This, together with using the prior phenotype, will facilitate allocation of properly crossmatched blood should a blood transfusion be warranted.

For patients after exposure to magrolimab:

1. ABO, Rh, and DAT may be pan-reactive due to magrolimab binding to red cells. Therefore, if a non-urgent transfusion is ordered by the Investigator, perform the following procedures: a. Front Type: EGA treat cells (×2 maximum) and warm wash ×4 (minimum) with 0.9% saline.

b. Back Type: Perform reverse anti-human globulin for both A and B.

c. If a valid ABO type cannot be obtained, mark the final report as invalid and notify the transfusion service for the site.

2. Antibody screen: If a pan-agglutinin/warm autoantibody is present in low ionic strength solution (LISS), repeat the antibody screen with polyethylene glycol (PeG). Perform PeG adsorption studies and elution studies.

Blood Components for Transfusion

For all elective red cell transfusions, leukocyte-reduced units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all the specified blood groups proves impractical (e.g., for MNS blood group), local sites will decide on the best matched donor units to be used.
Cytomegalovirus (CMV) matching (i.e., CMV-seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.
If the crossmatch is incompatible, the RBC units that are Coombs crossmatch-incompatible will be selected (e.g., phenotype-matched or least incompatible) for issue at the discretion of the local site's Transfusion Service Medical Director or equivalent person, where available.
For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rhesus negative units if phenotyped units are not available.
Blood plasma therapy will be blood-type specific. Platelets will be blood type compatible whenever possible, and if not, will have been tested and found not to have high titer anti-A or anti-B.

Management of Infusion-related Reactions

Infusion-related reactions are defined by the NCI CTCAE (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances". For the purposes of this study, the time frame for infusion-related reaction assessment is the 24-hour period beginning from the start of the infusion. Recommendations for the management of infusion-related reactions are provided below.

• _For Grade 1 infusion-related reactions, described as mild transient reaction, infusion interruption is not indicated and intervention not indicated: o Remain at bedside and monitor patient until recovery from symptoms.

• _For Grade 2 infusion-related reaction , infusion interruption is indicated, but patient responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids); and prophylactic medications are indicated for ≤24 hours: o Stop the magrolimab infusion, begin an IV infusion of normal saline, and consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500-750 mg oral acetaminophen.

o Remain at bedside and monitor patient until resolution of symptoms.

o Corticosteroid therapy may also be given at the discretion of the Investigator.

o If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate.

o If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.

o If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further magrolimab will be administered at that visit.

o Premedications should be considered before any future infusions.

o The amount of magrolimab infused must be recorded on the electronic Case Report Form (eCRF).

o Patients who experience a Grade 2 infusion-related reaction during the post-infusion observation period that does not resolve to ≤Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.

• _For Grade 3 or Grade 4 infusion-related reaction, where: Grade 3 is described as prolonged infusion-related reactions (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4 is described as having life-threatening consequences and where urgent intervention is indicated. o Immediately discontinue infusion of magrolimab.
o Begin an IV infusion of normal saline, and consider treating the patient as follows: Administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.

o The patient should be monitored until the Investigator is comfortable that the symptoms will not recur.

o Patients who have Grade 4 infusion-related reactions occurring with the first dose (priming dose) will be permanently discontinued from study treatment.

o Patients who experience Grade 3 infusion-related reactions must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650-1000 mg), oral or IV diphenhydramine (25-50 mg), and IV dexamethasone (4-20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician.

o Patients who receive premedication and still experience a Grade 3 or 4 infusion-related reaction will be permanently discontinued from study treatment.

o For anaphylaxis, Investigators should follow their institutional guidelines for treatment.

o All patients with Grade 3 or greater infusion related reactions will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AEs.

Tumor Lysis Syndrome
In the case of evidence for tumor lysis syndrome associated with magrolimab, patients will be admitted to the hospital as clinically indicated. Standard management will include vigorous IV hydration; correction of acidosis, if present; hypouricemic agents; and close monitoring of serum uric acid, phosphorus, and electrolytes in accordance with local institutional guidelines.

6.3 CYP3A4 and P-gPInhibitors: Dose modifications

Venetoclax

6.3.1 Venetoclax should be administered at 50% dose reduction in the setting of moderate CYP3A inhibitor and at 75% dose reduction in the setting of strong CYP3A inhibitor for the duration of co-administration. The venetoclax dose will be reduced to 70mg PO Qday if patient is on posaconazole.

6.3.2 In the event the co-administered CYP3A inhibitor is discontinued, the assigned venetoclax dose should be resumed 2-3 days after discontinuation.

6.3.3 Every effort should be made to adhere venetoclax dose reduction. Variations in schedule of events such as late/missed interventions that do not affect the rights and safety of the patient will not be considered as deviations.

6.3.4 P-gp substrates: Concomitant use of venetoclax increases Cmax and AUCinf of P-gp substrates, which may increase toxicities of these substrates (please see Venetoclax US prescribing information – Appendix G). Avoid concomitant use

of venetoclax with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.

6.4 Tumor Lysis Prophylaxis (TLS)

6.4.1 The venetoclax dose titration scheme utilized in the AML studies performed to date to mitigate the risk of tumor lysis syndrome (TLS) will be employed. All patients will be hospitalized for the entirety of the venetoclax dose escalation starting at least on day 1 of treatment initiation and until 24 hours after the completion of venetoclax dose escalation. During cycle 1, venetoclax will be dose escalated daily to the goal dose of 400mg daily. Patients will receive 100mg on Day 1, 200mg on Day 2 and 400mg on Day 3 and onwards, or adjusted dose if on concomitant azoles (discussed below in section 6.3).

6.4.2 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) prior to start of venetoclax and at least during the first cycle of therapy.

6.4.3 TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained prior to dosing and 6-8 hours after each day of a new venetoclax dose. TLS chemistry test results will be reviewed by the investigator in real time and prior to the subject's next dose to ensure appropriate management. If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax should be administered until resolution.Venetoclax interruption for up to 72 hours following transient (< 48 hours) chemical changes and laboratory TLS will be allowed and will not require a dose reduction.

6.5 Meals and Dietary Requirements:

6.5.1 Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of a meal, preferably breakfast.

6.5.2 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.

6.6 Modifications of dose schedules other than the above will be allowed within the following guidelines:

---Dose adjustments by more than 1 dose level at a time for azacitidine or venetoclax (e.g., from azacitidine 75 mg/m2 to 25 mg/m2) can be considered when judged in the best interest of the patient (e.g. severe myelosuppression) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented in the medical record.

--A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above in Table 3 for at least 1 month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month. The dose of any agent must not exceed the RP2D dose for that agent in this protocol (i.e. azacytidine dose cannot exceed 75mg/m2 x 7 days, venetoclax dose cannot exceed 400 mg/day, and magrolimab dose cannot exceed 30 mg/kg).

--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/interruptions 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 (e.g., in patients with anemia or infusion reactions this would be likely secondary to the magrolimab, in patients with neutropenia this would be likely secondary to azacitidine and venetoclax). Patients in whom one agent is interrupted/discontinued for potential toxicity may be able to continue treatment on protocol if it is in the best interest of the patient to continue on protocol.

6.7 Treatment interruptions and dose modifications or delays other than the ones mentioned above can be considered after discussion with the PI or Co-PI and clear documentation of the rationale in the medical records

7.0 AGENT FORMULATION AND PROCUREMENT

7.1 Magrolimab

7.1.1 Description

Magrolimab is a humanized IgG4 monoclonal antibody of the igG4 kappa isotype that targets and blocks CD47, an anti-phagocytic signal. Its main mechanism of action is to enable phagocytic elimination of cancer cells through the blockade of signaling between CD47 and SIRPα. Magrolimab drug product is a sterolie, clear, coloreless, preservative-free liquid intended for IV infusion.

7.1.2 Clinical Pharmacology

No formal clinical pharmacology trials have been completed with magrolimab; however, preliminary PK data are available for magrolimab doses from 0.1 to 30 mg/kg for patients on the ongoing solid tumor Phase I study (SCI-CD47-001). In the solid tumor trial, patients have been treated with weekly magrolimab doses ranging from 0.1 to 30 mg/kg, with increasing plasma concentrations associated with increasing dose. Nonlinear PK consistent with target-mediated clearance has been observed over this dose range. However, at maintenance doses of 10 mg/kg and above, target-mediated clearance was saturated within the dosing regimen and trough levels associated with magrolimab efficacy in nonclinical studies have been achieved. Evidence of sustained target trough levels have been observed at doses 10 mg/kg weekly and higher. Two of 41 evaluable patients tested positive for anti-drug antibodies (ADA) against magrolimab, but the impact of ADA on PK could not be ascertained due to the limited amount of available PK data (after single and multiple doses).
For the Phase I AML study (SCI-CD47-002), initial PK data has been analyzed for the first 3 dose escalation cohorts (dose range from 0.1 mg/kg to 30 mg/kg twice weekly). Similar to the solid tumor Phase I study, nonlinear PK consistent with target-mediated clearance has been observed. PK sampling is continuing in the ongoing magrolimab Phase I trials. One of 13 evaluable patients tested positive for ADA against magrolimab, but did not exhibit clinical signs of immunogenicity.

The estimated terminal half-life of magrolimab after achievement of steady state is approximately 2 weeks.

7.1.3 Potential Indications and Usage

Magrolimab is currently being investigated for the treatment of various cancers as monotherapy or in combination. These indications include acute myeloid leukemia, myelodysplastic syndrome, Non-Hodgkin's lymphoma, ovarian cancer, bladder cancer

and colorectal cancer. Magrolimab is not approved by any regulatory agency for clinical use and is under clinical investigation.

7.1.4 Ongoing Clinical Trial (ClinicalTrials.gov)

ID	Setting	Phase	Clinical Trials	Identifier

MAgrolimab monotherapy or magrolimab in combination with azacitidine in patients with hematological malignancies. Phase Ib. NCT03248479

Trial of magrolimab in combination with cetuximab in patients with solid tumors and advanced colorectal cancer. Phase Ib/II. NCT02953782

A trial of magrolimab with avelumab in ovarian cancer. Phase Ib. NCT03558139

Trial of magrolimab in combination with rituximab in relapsed/refractory B-cell Non-Hodgkin's lymphoma. Phase Ib/II. NCT02953509

A Study evaluating the safety and pharmacokinetics of atezolizumab administered in combination with magrolimab to patients with relapsed and/or refractory acute myeloid leukemia. Phase I. NCT03922477

Platform study for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma (PRISM Study). Phase I. NCT03527147

A study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with locally advanced or metastatic urothelial carcinoma after failure with platinum-containing chemotherapy (MORPHEUS mUC). Phase I/II. NCT03869190

7.1.5 Dosing

Magrolimab is administered intravenously with an initial intra-patient dose escalation as shown below.

Table 4

Dose concentration/route	Cycle 1	Cycle 2	Cycle 3 and beyond
Magrolimab 1 mg/kg IV	Days 1 and 4	-	-
Magrolimab 15 mg/kg IV	Day 8	-	-
Magrolimab 30 mg/kg IV	Days 11, 15, 22	Days 1, 8, 15, 22	Days 1, 15

The duration of each magrolimab infusion will be 3 hours (± 30 minutes) for the first 4 weeks of treatment. After 4 weeks of treatment, the magrolimab infusion will be 2 hours (± 30 minutes).

7.1.6 Selection and Timing of Dose

The frequency of dosing of magrolimab is listed above. When both magrolimab and azacytidine are given on the same visit day, magrolimab will be administered at least 1 hour after the completion of azacytidine administration.

7.1.7 Packaging and Labeling

Magrolimab is supplied in single-use, 10 mL vials containing 200 mg of the antibody in a formulation of 10 mM sodium acetate, 5% (w/v) sorbitol, 0.01% (w/v) polysorbate 20, at pH of 5.0.

The labeling complies with the requirements of the applicable regulatory agencies.

7.1.8 Study Drug Preparation

Vials containing magrolimab should be stored under refrigeration at 2 to 8°C (36°F to 46°F) in an appropriate, locked room and/or locked refrigerator, accessible only to pharmacy personnel, the Principal Investigator, or a duly designated person. magrolimab should not be frozen. Protect from light during storage. DO NOT SHAKE.

Additional details about magrolimab are provided in the Pharmacy Manual.

7.2 **Azacitidine**: It is commercially available and will be handled as per the packet insert and standards in the MD Anderson Cancer Center standard institutional pharmacy.

7.3 **Venetoclax**: It is commercially available and will be handled as per the packet insert and standards in the MD Anderson Cancer Center standard institutional pharmacy

International Non-proprietary name venetoclax (formerly ABT-199)
Manufacturer Abbvie/Genentech
Dose 100 - 400 mg daily
Route of Administration oral
Formulation Capsule formulation (10 mg, 50 mg and 100 mg)
Venetoclax will be obtained from commercial source. For further details, please refer to the prescribing information (Appendix G).

7.4 **Disposition of unused drug:** all unused drug will be disposed of per institutional guidelines and procedures.

7.5 Variations in infusion times of drugs due to minor differences in IV bag overfill/under fill and institutional procedure on flushing chemotherapy lines will not result in protocol deviation. All infusion times are considered approximate.

7.6 For further details on drug formulation, reconstitution, administration, infusion related instructions, concern and plan of management for infusion related topics please the respective agents IB and/or Pharmacy Manuals (Appendices)

8.0 CORRELATIVE/SPECIAL STUDIES

1. All patients are also routinely monitored for MRD by flow cytometry and RT-PCR or NGS (in some cases) at the time of bone marrow assessments. This will allow an analysis of response beyond hematologic criteria and correlation with long-term outcome.
2. All patients will be evaluated by a pretherapy and on-treatment 81-gene molecular panel to investigate correlations of mutations with long-term outcome, and to identify molecular characteristics of residual or recurrent clones.
3. Identification of clonal subsets in AML almost entirely been done using genomics, in which cellular populations are inferred. In order to effectively characterize and ultimately treat these cells, we need tools to identify therapy resistant cell populations as they arise in patients. Flow cytometry is a useful tool for tracking cells in patients but traditional fluorescent cytometry is limited by panel size and scope. CyTOF (Cytometry by Time of Flight), is a variation of flow cytometry in which antibodies are labeled with heavy metal ion tags rather than fluorochromes. This allows for the combination of many more

antibody specificities in a single cell with greater depth and breadth of phenotypic and functional cytometric profiling. CyTOF will enable us to identify individual treatment-resistant cell populations and their signaling state in disease relate to clinical outcomes. In collaboration with Dr. Marina Konopleva and Padmanee Sharma's lab, we will perform CyTOF on patients' bone marrow samples and peripheral blood at diagnosis, remission and relapse..

4. To enable the characterization of genetic heterogeneity in tumor cell populations, we will use novel microfluidic approach that barcodes amplified genomic DNA from thousands of individual leukemia cells confined to droplets. The barcodes are then used to reassemble the genetic profiles of cells from next-generation sequencing data. By using this approach, we will sequence longitudinally collected AML tumor populations from patients and genotype disease relevant loci across thousands of individual cells. Targeted single-cell sequencing is able to sensitively identify cells harboring pathogenic mutations during complete remission and uncovered complex clonal evolution within AML tumors that are not observable with bulk sequencing. We anticipate that this approach will make feasible the routine analysis of AML heterogeneity, leading to improved stratification and therapy selection for the patients. In collaboration with Dr. Marina Konopleva's lab, we will perform single cell sequencing on patients' bone marrow samples at diagnosis, remission and relapse.

8.0 .1 PATIENT EVALUATION

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule, occasional missed required research samples such as correlative assays.

8.1 Pre-Treatment Evaluation

All pretreatment studies should be obtained within 14 days of entry into any of the study arms, unless otherwise stated.

8.1.1 A complete history and physical, documentation of all measurable disease, concomitant medications and performance status.

8.1.2 CBC, platelet count, differential (differential can be omitted if WBC is ≤0.4 $x10^9$/L).

8.1.3 Creatinine, total bilirubin, ALT or AST, electrolytes, glucose, uric acid, creatinine, direct bilirubin, calcium, magnesium, alkaline phosphatase, BUN.

8.1.4 Pregnancy test (urine or plasma) in females of childbearing potential should be performed within 72 hours before initiation of protocol therapy.

8.1.5 Bone marrow aspirate during the last 28 days (+/- 7 days) preceding study initiation.

Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose).

8.1.6 Electrocardiogram EKG at baseline.

8.1.7 Pretreatment optional correlative studies (see below)

8.1.8 RBC genotyping for all patients at baseline

8.2 Evaluation During Treatment

8.2.1 Physical exam at the start of each cycle (± 4 days).

8.2.2 CBC, platelet count, differential at least two times per week for the first 3 cycles, then one to two times per week in subsequent cycles (differential can be omitted if WBC is ≤0.5 $x10^9$/L). Lower frequency of laboratory evaluations may be considered on a case by case basis after cycle 6 in patients in remission, after discussion and approval from PI.

8.2.3 Creatinine, total bilirubin, ALT, or AST, electrolytes, glucose, uric acid, creatinine, direct bilirubin, calcium, magnesium, alkaline phosphatase, BUN at least two times per week for the first 3 cycles, then one to two times per week in subsequent cycles. Lower frequency of laboratory evaluations may be considered on a case by case basis after cycle 6 in patients in remission, after discussion and approval from PI.

8.2.4 TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained same day prior to dosing and 6-8 hours on each day after a new venetoclax dose during cycle 1.

8.2.5 Bone marrow aspiration on Cycle 1 Day 21 (+/- 4 days), then on Day 28 (+/- 4 days) of cycles 3, 6, 9 and progression. Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC < 0.3 if the bone marrow test is considered noncontributory by the investigator at any time point.

8.2.6 Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea; however, the subject's medical record will contain a list of concomitant medications.

8.2.7 **Correlative Studies relating to immunologic response (Optional):** Tumor tissue, blood samples and bone marrow aspirate for correlative research will be collected in patients who consent to participate in the optional procedures. Correlative laboratory studies will be conducted under this clinical trial as described: Patients may participate in the clinical study protocol irrespective of whether they choose to participate in the correlative studies. **Proposed correlative studies to be performed are discussed in Section 8.0 above**

Peripheral blood up to 40 mL (within 24 hours) will be collected in patients who consent to the correlative studies for testing of biomarkers at the following time points: Baseline (prior to day 1 dose of drug), and on day 21 (+/- 4) on cycle 1 (done at MD Anderson), at day 28 (+/- 4 days) of cycles 3, 6, 9, and at progression (if possible).

Additional timepoints may be collected as needed.
Bone marrow samples will be collected in patients who consent to the correlative studies for testing of biomarkers at baseline, on day 21 (+/-4 days), at day 28 (+/- 4 days) of cycles 3, 6, 9, and at progression (if possible). Additional timepoints may be collected as needed.

All correlative samples and proposed correlative analysis are optional.
Missed samples for correlative studies will not constitute protocol deviations.

- For patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluations during study may be modified after discussion with the principal investigator. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated), correlative studies to every 6-12 months (or suspension of sample collection for correlative studies), other laboratory tests to once every cycle.

- All treatments with the investigational agent magrolimab must be administered at the Main MD Anderson Cancer Center, either inpatient or in the outpatient infusion center. The first cycle of azacitidine must be administered at the MD Anderson Cancer Center, either inpatient or in the outpatient infusion center. Subsequently, patients will have the option of receiving azacitidine injections or infusions at the MD Anderson Cancer Center outpatient clinic or their local ambulatory treatment center/outside physician's office. We do not intend for the subjects to receive magrolimab at any time at an outside physician's office. During the first cycle all the laboratory evaluations will be done at MD Anderson and the patients must stay locally within easy access of MD Anderson Cancer Center. Subsequently, the patient may have the laboratory work done at a local clinic and the results reported and filed by the MD Anderson Cancer Center research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MD Anderson Cancer Center or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

8.3 Outside Physician Participation During Treatment

1. MD Anderson Physician communication 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 will request local physician agreement to supervise the patient's care (**Appendix K**).
3. Protocol required evaluations outside MD Anderson Cancer Center will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MD Anderson physician, indicating that they have reviewed it. Changes in drug dose and/or schedule must be discussed with and approved by the MD Anderson Cancer Center physician investigator, or they're representative prior to initiation, and will be documented in the patient record.
4. A copy of the informed consent, and treatment schema and evaluation during treatment will be provided to the local physician.
5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
6. The home physician will be requested to report to the MD Anderson Cancer Center physician investigator all life threatening events within 24 hours of documented occurrence.
7. All protocol required follow-up visits will be performed at MD Anderson Cancer Center.
8. Changes in drug dose and/or schedule must be discussed with and approved by the MD

Anderson Cancer Center physician investigator, or they're representative prior to initiation, and will be documented in the patient record.

9. Patients with an objective response at completion of active study treatment will be followed for survival at MD Anderson Cancer Center (MD Anderson) every 3 to 6 months for up to 5 years after completion of active treatment and while still on study. If the patient is unable to return to MD Anderson Cancer Center the duration visits may be conducted via telephone.

Data regarding adverse events will be collected during the study. Protocol specific data will be entered intothe electronic case report form (eCRF). The eCRF used for this protocol will be Prometheus. AEs will be recorded in the Case Report Form (eCRF as described under section 11.0).
Treatment may be discontinued for a variety of reasons, including patient withdrawal, investigator decision, and reasons specified by the protocol. Reasons for discontinuation of treatments are described in section 10.0.

9.0 CRITERIA FOR RESPONSE:

Response Criteria for AML

Responses will be assessed by the International Working Group for AML (Cheson B et al, J Clin Oncol. 2003 Dec 15;21(24):4642-9) and the ELN2017 (Dohner H et al, Blood. 2017 Jan 26;129(4):424-447). Responders are patients who obtain a CR, CRp, CRi, or PR, with or without cytogenetic response, hematologic improvements, and a morphologic leukemia-free state.

Complete remission (CR):

- Peripheral blood counts: No circulating blasts

Neutrophil count >1.0 $x10^9$/L Platelet count >100 $x10^9$/L

- Bone marrow aspirate and biopsy:

≤5% blasts No Auer rods
No extramedullary leukemia

Complete Remission with Incomplete Platelet Recovery (CRp):

For patients to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery (<100 × 10^9/L).

Complete remission with incomplete blood count recovery (CRi):

- **Peripheral blood counts:**
  No circulating blasts
  Neutrophil count <1.0 x10^9/L,
  OR
  Platelet count <100 x10^9/L

- **Bone marrow aspirate and biopsy:**
  </= 5% blasts
  No Auer rods
  No extramedullary leukemia

CRh

- All CR criteria if abnormal before treatment except neutrophil count >/=0.50 x10^9/L and platelet count >/=50 x10^9/L

Partial remission:

- All CR criteria if abnormal before treatment except:
- >/=50 % reduction in bone marrow blast but still >5%

Morphologic leukemia-free state:

- Bone marrow: </=5% myeloblasts, no neutrophil or platelet recovery parameters required

Hematologic Improvement (HI): Hematologic responses will be additionally collected and assessed by the MDS IWG response criteria (Cheson et al., Blood 2006)

- Erythroid response (E) (pretreatment Hgb <11 g/dL)
  Hgb increase by >/=1.5 g/dL

- Platelet response (P) (pretreatment platelets <100 x10^9/L)
  Absolute increase of >/=30 x 10^9/L for patients starting with > 20 x 10^9/L platelets
  Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%

- Neutrophil response (N) (pretreatment ANC <1.0 x10^9/L)
  At least 100% increase and an absolute increase > 0.5 x 10^9/L

- Blast response (B)
  >/=50% reduction in peripheral blood or bone marrow blasts but still >5%

10.0 DISCONTINUATION OF TREATMENT

10.1 Discontinuation Criteria for Individual Patients

10.1.1 Patient Withdrawal

Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. “For patients who withdraw consent, the Investigator may search publically available records (where permitted) to ascertain survival status.” Their withdrawal will not jeopardize their relationship with their healthcare providers or affect their future care. Patients may also choose to withdraw from study treatment, but agree to remain in the study for follow-up procedures.

10.1.2 Investigator Discontinuation of Patient

The investigator may exercise medical judgment to discontinue study treatment if clinically significant changes in clinical status or laboratory values are noted.

10.1.3 Criteria for Protocol-Defined Required Discontinuation of Treatment

The protocol requires discontinuation of study treatment for the following reasons:

1. Patient requests discontinuation.
2. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.
3. Clinically significant progressive disease.
4. Investigator discretion.

10.1.4 Follow-Up at Treatment Discontinuation or Early Withdrawal

Patients who discontinue treatment for any reason should complete end-of-treatment procedures when possible. End of treatment procedures will include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all patients who do not withdraw consent for follow-up, die, or become lost to follow-up, will remain on study for follow-up evaluations. Subject will be followed for toxicity for at least 30 days after the last protocol treatment. The 100-day follow-up visit (+ or – 5 days) will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MD Anderson Cancer Center clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MD Anderson Cancer Center. The research nurse will contact the patient by telephone and get a verbal assessment of the patient’s condition. The phone conversation will then

be documented in the patient's charts.

10.2 Study Stopping Rules

The principal investigator and MD Anderson Cancer Center IND office have the right to terminate this clinical study at any time. The principal investigator and MD Anderson Cancer Center IND office, as appropriate, will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

10.3 Protocol Violations and Deviations

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities (missed evaluations or visits) except for those allowed per protocol
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay; or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

11.0 ADVERSE EVENT REPORTING

11.1 Monitoring, recording and reporting adverse events

An Adverse Event is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study.

Adverse event reporting will be as per the NCI criteria. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting (http://ctep.cancer.gov/reporting/ctc.html).

Of note, all adverse reactions, irrespective of attribution will be recorded. This includes hematologic and non-hematologic AEs of all grade, irrespective of attribution.

Serious Adverse Event Reporting (SAE)
A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity – a substantial disruption of a person's 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 for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the eSAE system in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, 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.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:
Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) 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 (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

AEs of Special Interest (AESIs)
AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Supporter is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Supporter to other parties (e.g., Regulatory Authorities) may also be warranted.

The Venetoclax Events of Special Interest are:
Adverse events of special interest for this study include the following:

- Tumor Lysis Syndrome (irrespective of causality and seriousness)
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
  - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
  - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Pregnancy reports
While such reports are not serious AEs or Adverse drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to venetoclax, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug.

Investigators must report all Serious Adverse events (SAEs), AEs of Special Interest (AESIs) pregnancy reports and special situation reports (if applicable) adequately to Genentech using the MDACC SAE form within 24 hours of the knowledge of the event. All Adverse Events will be reported to Genetech every 3 months. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed immediately upon completion to Genentech Drug Safety at:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

STUDY CLOSE-OUT

Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study and to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

10.1 Regulatory and eporting requirements to IND Office as Sponsor

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug.

12.0 STATISTICAL CONSIDERATIONS

Phase Ib

The primary objective of the Phase Ib is to determine the MTD of the combination drugs. Only relapsed/refractory AML patients are eligible for phase Ib part. The MTD is the highest dose level in which we have treated 6 patients with at most 1 experiencing the DLT. See section 5.1 for details. A sample size up to 18 patients will be accrued into the Phase Ib part.

Phase II

The primary objective for the phase II part is to further evaluate the safety and efficacy of the combination within 3 months of treatment initiation The phase II will have 3 independent cohorts as follows:

A. Phase II, Frontline cohort: The maximum number of patients that will be recruited for the phase II frontline AML part is 60. Phase II frontline will enroll newly diagnosed AML patients not fit for intensive induction therapy.

B. Phase II, Relapsed/Refractory prior Venetoclax naïve cohort: The maximum number of patients that will be recruited for the phase II relapsed/refractory prior venetoclax naïve cohort is 30.

C. Phase II, Relapsed/Refractory prior Venetoclax exposed cohort: The maximum number of patients that will be recruited for the phase II relapsed/refractory prior venetoclax exposed cohort is 30.

A. Phase II, Frontline cohort: The response rate (CR +CRi) and toxicity within 3 months of treatment initiation will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M D Anderson Cancer Center was used to generate the stopping boundaries and operating characteristics for futility and toxicity monitoring. Toxicities are defined as drug-related non-hematological Grade ≥3 AEs.

Historical data for frontline patients treated with venetoclax and hypomethylating agents (DiNardo CD et al, Blood. 2019 Jan 3;133(1):7-17, attached as Appendix A and Pollyea D et al ASH 2018 abstract #285, Oral presentation attached as Appendix B) show CR/CRi of 60-65%. It is expected for the current trial that the three-drug combination will improve the RR by 20%, while the toxicity rate is maintained at or below 20%. A sample size of 60 patients ensures that, if the trial is not terminated early, a posterior 95% credible interval for RR will be (0.69, 0.88) under the assumption of a 80% of RR and a prior of Beta (1.2, 0.8). The prior probabilities of RR and toxicity for the experimental regimen are modeled by beta distributions *Beta* (1.2, 0.8) and *Beta* (0.4, 1.6), respectively. Denoting the historical proportion of response rate and toxicity rate by {p(RR, H) = 0.60, p(TOX, H) = 0.20}, the following decision criteria will be applied:
1) Stop if Prob{p(RR, H) + δ_{RR} > p(RR, E) | data} > 0.975, where δ_{RR} = 0.2
2) Stop if Prob{p(TOX, H) + δ_{TOX} < p(TOX, E) | data} > 0.80, where δ_{TOX} = 0

Patients will be monitored in cohorts of 10 according to the following stopping boundaries for response and toxicity.

# Patients Evaluated	Stop this cohort if ≤ this # RR	Stop if ≥ this # toxicities
10	0-5	4-10
20	0-12	6-20
30	0-19	9-30
40	0-26	11-40
50	0-34	13-50
60	Always stop with this many patients	Always stop with this many patients

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True RR	PROB(Stop Early)
0.10	0.60	0.9282
	0.70	0.5304
	0.80	0.0985

True Toxicity Rate	True RR	PROB(Stop Early)
	0.85	0.0369
	0.90	0.0231
0.20	0.60	0.9509
	0.70	0.6788
	0.80	0.3834
	0.85	0.3413
	0.90	0.3319
0.30	0.60	0.9888
	0.70	0.9270
	0.80	0.8599
	0.85	0.8503
	0.90	0.8482
0.40	0.60	0.9994
	0.70	0.9961
	0.80	0.9925
	0.85	0.9920
	0.90	0.9919
0.50	0.60	0.9999
	0.70	0.9999
	0.80	0.9999
	0.85	0.9999
	0.90	0.9999

B. Phase II, Relapsed/Refractory prior Venetoclax naïve cohort:
The response rate (CR +CRi) and toxicity within 3 months of treatment initiation will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M D Anderson Cancer Center was used to generate the stopping boundaries and operating characteristics for futility and toxicity monitoring. Toxicities are defined as drug-related non-hematological Grade ≥3 AEs.

Published data from our group for relapsed/refractory AML who had not been previously exposed to venetoclax based therapies for AML or MDS and were treated with venetoclax and hypomethylating agents in salvage (DiNardo CD et al, Lancet Haematol. 2020 Oct;7(10):e724-e736) showed a CR/CRi rate of 40-42%. It is expected for the current trial that the three-drug combination will improve the RR by 15%, while the toxicity rate is maintained at or below 20%. A sample size of 30 patients ensures that, if the trial is not terminated early, a posterior 95% credible interval for RR will be (0.37, 0.71) under the assumption of a 55% of RR and a prior of Beta (0.80, 1.20). The prior probabilities of RR and toxicity for the experimental regimen are modeled by beta distributions Beta (0.80, 1.20) and Beta (0.4, 1.6), respectively. Denoting the historical proportion of response rate and toxicity rate by {p(RR, H) = 0.40, p(TOX, H) = 0.20}, the following decision criteria will be applied:
1) Stop if Prob{$p(RR, H) + \delta_{RR} > p(RR, E) \mid data\} > 0.975$, where $\delta_{RR} = 0.15$

2) Stop if Prob{p(TOX, H) + δ_{TOX} < p(TOX, E) | data} > 0.80, where δ_{TOX} = 0

Patients will be monitored in cohorts of 5 according to the following stopping boundaries for response and toxicity.

# Patients Evaluated	Stop this cohort if ≤ this # RR	Stop if ≥ this # toxicities
5	Never stop with this many patients	3-5
10	0-1	4-10
15	0-2	5-15
20	0-3	6-20
25	0-5	7-25
30	Always stop with this many patients	Always stop with this many patients

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True RR	PROB(Stop Early)
0.10	0.40	0.0997
	0.50	0.0434
	0.55	0.0354
	0.60	0.0322
	0.65	0.0310
0.20	0.40	0.3568
	0.50	0.3165
	0.55	0.3108
	0.60	0.3085
	0.65	0.3076
0.30	0.40	0.7456
	0.50	0.7296
	0.55	0.7274
	0.60	0.7265
	0.65	0.7261
0.40	0.40	0.9488
	0.50	0.9456
	0.55	0.9452
	0.60	0.9450
	0.65	0.9449
0.50	0.40	0.9952
	0.50	0.9949
	0.55	0.9948
	0.60	0.9948
	0.65	0.9948

Efficacy assement after the first 15 patients are enrolled

The target response rate (RR) for cohort B is 55%. The posterior probability for the RR will be calculated after after the first 15 patients are enrolled and evaluated, we will expect the RR to be 55% or higher (≥8 responses/15 patients evaluated). The prior probability of RR rate is denoted by P_{RR}. We assumed P_{RR} ~ beta (0.80, 1.20). The stopping efficacy rule is given by the following probability statement: Stop if Prob{RR > 55% | data} > 0.975. That is, we will stop the study if, after the first 15 patients are enrolled and evaluated for efficacy, we determine that the data suggest that it is unlikely (i.e., probability > 97.5%) that RR of the treatment is greater than the target RR. Cohort B will be considered worthy of further investigation if it elicits an increase in RR to 55%.

C. Phase II, Relapsed/Refractory prior Venetoclax exposed cohort:
The response rate (CR +CRi) and toxicity within 3 months of treatment initiation will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M D Anderson Cancer Center was used to generate the stopping boundaries and operating characteristics for futility and toxicity monitoring. Toxicities are defined as drug-related non-hematological Grade ≥3 AEs.

Published data from our group for relapsed/refractory AML patients who had failed frontline venetoclax and hypomethylating agents (Maiti A et al, Haematologica. 2020 Jun 4; haematol.2020.252569) showed that this was a population of major unmet need. The median OS in 41 patients who had failed (relapsed or refractory) after prior venetoclax and hypomethylating agent was 2.4 months. Patients who received salvage therapy (n=24) had longer OS compared to patients who could not or did not receive salvage therapy (n=17, 2.9 vs 1.3 months, hazard ratio [HR]=0.41, 95% confidence interval [CI] 0.19-0.88, p=0.003). Among the 24 patients in this group who had failed prior venetoclax based therapy and received various salvage therapies a CR/CRi was noted in only 5 of 24 (22%). It is expected for the current trial that the three-drug combination will improve the RR by 15%, while the toxicity rate is maintained at or below 20%. A sample size of 30 patients ensures that, if the trial is not terminated early, a posterior 95% credible interval for RR will be (0., 0.) under the assumption of a 37% of RR and a prior of Beta (0.44, 0.56). The prior probabilities of RR and toxicity for the experimental regimen are modeled by beta distributions Beta (0.44, 0.56) and Beta (0.4, 1.6), respectively. Denoting the historical proportion of response rate and toxicity rate by {p(RR, H) = 0.22, p(TOX, H) = 0.20}, the following decision criteria will be applied:
1) Stop if Prob{p(RR, H) + δRR > p(RR, E) | data} > 0.975, where δRR = 0.15
2) Stop if Prob{p(TOX, H) + δTOX < p(TOX, E) | data} > 0.80, where δTOX = 0

Patients will be monitored in cohorts of 5 according to the following stopping boundaries for response and toxicity.

# Patients Evaluated	Stop this cohort if ≤ this # RR	Stop if ≥ this # toxicities
5	Never stop with this many patients	3-5
10	0	4-10
15	0	5-15

20	0-1	6-20
25	0-1	7-25
30	Always stop with this many patients	Always stop with this many patients

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True RR	PROB(Stop Early)
0.10	0.22	0.1302
	0.30	0.0611
	0.37	0.0405
	0.45	0.0329
	0.52	0.0310
0.20	0.22	0.3785
	0.30	0.3291
	0.37	0.3144
	0.45	0.3090
	0.52	0.3077
0.30	0.22	0.7542
	0.30	0.7347
	0.37	0.7288
	0.45	0.7267
	0.52	0.7262
0.40	0.22	0.9506
	0.30	0.9466
	0.37	0.9455
	0.45	0.9450
	0.52	0.9449
0.50	0.22	0.9953
	0.30	0.9949
	0.37	0.9948
	0.45	0.9948
	0.52	0.9948

Efficacy assement after the first 15 patients are enrolled

The target response rate (RR) for cohort B is 37%. The posterior probability for the RR will be calculated after after the first 15 patients are enrolled and evaluated, we will expect the RR to be 37% or higher (≥6 responses/15 patients evaluated). The prior probability of RR rate is denoted by P_{RR}. We assumed P_{RR} ~ beta (0.44, 1.56). The stopping efficacy rule is given by the following probability statement: Stop if Prob{RR > 37% | data} > 0.975. That is, we will stop the study if, after the first 15 patients are enrolled and evaluated for efficacy, we determine that the data suggest that it is unlikely (i.e., probability > 97.5%) that RR of the treatment is greater than the target RR. Cohort B will be considered worthy of further investigation if it elicits an increase in RR to 37%.

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 Ib:
This should be submitted after the first 6 evaluable patients complete 1 cycle of study treatment, and every 6 evaluable patients, thereafter. Approval must be obtained prior to advancing/changing dose levels.

Phase II Relapsed/Refractory cohorts

Efficacy and Toxicity summary will be submitted after the first 5 evaluable patients, per cohort, complete 3 months of study treatment, and every 5 evaluable patients, per cohort, thereafter, until enrollment is complete.
Phase II, Frontline cohort:Efficacy and Toxicity summary will be submitted after the first 10 evaluable patients, complete 3 months of study treatment, and every 10 evaluable patients, thereafter, until enrollment is complete

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

Statistical Analysis Plan

All patients who received at least one dose of study drug will be included in the intent-to-treat analysis for efficacy and safety. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency using frequency tables. Demographic/clinical characteristics (such as duration of response) will be summarized using descriptive statistics such as mean, standard deviation, median and range. Response rate, CR+CRh rate and MLF rate within 3 months of treatment initiation will be estimated along with 95% credible intervals. Chi-square tests or Fisher's exact test will be used to evaluate the association between patient's prognostic factor and response. Kaplan-Meier method will be used to estimate the event-free survival (EFS), duration of response, and overall survival. EFS is defined as the time duration from the start of treatment to disease progression/death or censored at last follow-up while on the drug. Paired t-tests will be used to determine the gene expressions and other clinical variables changes from pre-therapy to the predefined time-points.

13.0 PROTOCOL ADMINISTRATION

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Protocol amendments

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by the IND office and IRB of the study center.

Archival of data

MD Anderson-IND study must retain all records *indefinitely*.