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A Phase Ib/II Study of Venetoclax in Combination with Quizartinib in FLT3-mutated Acute Myelogenous Leukemia (AML)

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1.0 OBJECTIVES

1.1 Primary Objectives

Phase Ib

1. To determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of the combination of venetoclax with quizartinib in FLT3-ITD mutated patients with relapsed/refractory acute myeloid leukemia (AML).

Phase II

1. To determine the composite CR (CRc) rate including CR (complete remission) + CRp (complete remission with incomplete platelet recovery) + CRi (complete remission with incomplete count recovery) within 3 months of treatment initiation in FLT3-ITD mutated patients with relapsed/refractory AML.

1.2 Secondary Objectives

Phase Ib

1. To determine the composite CRc rate including CR + CRp + CRi within 3 months of treatment initiation in FLT3-ITD mutated patients with relapsed/ refractory AML.
2. To determine the overall response rate (ORR) including CRc + partial remission (PR) within 3 months of treatment initiation in FLT3-ITD mutated patients with relapsed/ refractory AML.
3. To determine the duration of response (DOR), progression free survival, event-free survival (EFS), overall survival (OS), and number of patients bridged to hematopoietic stem cell transplant (HSCT) and median duration to HSCT from the initiation of the combination in FLT3-ITD mutated patients with relapsed/ refractory AML.
4. To characterize the pharmacokinetic (PK) profiles of combination therapy of venetoclax and quizartinib in FLT3-ITD mutated patients with relapsed/refractory AML..

Phase II

1. To determine the ORR within 3 months of treatment initiation in FLT3-ITD mutated patients with relapsed/ refractory AML.
2. To determine the DOR, PFS, EFS, OS, and number of patients bridged to HSCT and median duration to HSCT from the initiation of the combination in FLT3-ITD mutated patients with relapsed/ refractory AML.
3. To determine the safety and tolerability of the combination in FLT3-ITD mutated patients with relapsed/ refractory AML.

1.3 Exploratory Objectives

1. To investigate possible relationships between baseline next generation gene sequencing and clinical response to the combination.
2. To investigate quantitative changes of FLT3-ITD allelic burden with time and the extent of pharmacodynamics biomarker (such as p-FLT3, p-p70S6K, pERK, pSTAT) inhibition, and the induction of apoptosis in the bone marrow and peripheral blasts in patients treated with the combination.

3. To investigate possible relationships between baseline gene expression signatures, Bcl-2 family mRNA and protein levels of AML blasts and/or stem cell sub-population, BH3 profiling of Bcl-2 family member dependency and ex vivo functional screen and clinical response to the combination.
4. To analyze immune modulation including alterations in total and percent of CD3+ T-cells, total and percent of various T-cell subsets (CD4-effector, CD4-regs, CD8 cytotoxic T-cells), and total and percent of T-cell/T-cell subsets expressing specific checkpoint receptors/ligands with the combination.
5. To store and/or analyze surplus blood or tissue including bone marrow, if available, for potential future exploratory research into molecular and immune factors that may influence response to venetoclax and/or quizartinib (where response is defined broadly to include efficacy, tolerability or safety).

2.0 BACKGROUND

2.1 FLT3-mutated AML

FLT3 (FMS-like tyrosine kinase III) belongs to the Class III family of receptor tyrosine kinases (RTKs; other members of this family include receptors for KIT, FMS, and PDGF) (1). Signaling via RTKs is frequently dysregulated in hematological malignancies (2). FLT3 is activated following binding of FLT3 ligand, which causes receptor dimerization leading to increased kinase activity and activation of downstream signaling pathways including Stat5, RAS, and PI3-kinase.(3-5) FLT3 plays a role in the regulation of survival and proliferation of hematopoietic progenitor cells, in particular by synergy with other RTKs and cytokine receptors.(6-8) FLT3 is also expressed in acute myeloid leukemia cells from approximately 90-95% of patients and stimulates survival and proliferation of leukemic blasts.(9-11). Additionally, activating mutations in *FLT3* are observed in 30% of adult AML patients (12). The two FLT3 mutations found in AML include internal tandem duplications in the juxta-membrane domain (ITD, 17–34%) and mutations in the tyrosine kinase domain (TKD) activation loop (7%) (13). FLT3-ITD mutations are associated with adverse prognosis. Patients with FLT3-ITD have significantly elevated peripheral blood white cell counts, increased bone marrow blasts, increased relapse risk, inferior event-free survival (EFS), and decreased overall survival (OS) (14-16). The FLT3-TKD mutations have unknown prognostic significance in AML (16).

Several small-molecule *FLT3* targeted tyrosine kinase inhibitors (TKIs) that are undergoing evaluation in phase I, II, and III trials have shown promising activity as single agents and in combination with hypomethylating agents or chemotherapy. These include quizartinib (AC220), sorafenib, midostaurin (PKC412), lestaurtinib, gilteritinib, and crenolanib(17). These TKIs act as direct inhibitors of *FLT3* via competitive inhibition of the ATP-binding sites in the FLT3 receptor kinase domain (KD)(18, 19).

Several multitargeted tyrosine kinase inhibitors (TKIs) such as lestaurtinib, sunitinib, sorafenib, and midostaurin had activity against FLT3 and have been investigated in *FLT3*-mutated AML. These agents have limited single-agent activity with marrow remission response rates of <10% with single-agent midostaurin(20) or sorafenib(21). On the other hand, second generation FLT3 inhibitors such as quizartinib and gilteritinib have demonstrated potent anti-leukemic activity and improved outcomes in

patients with relapsed/refractory AML and *FLT3-ITD* mutations(22). About 40-50% of such patients achieve marrow responses to the second generation *FLT3* inhibitors such as quizartinib(23-25) and gilteritinib(26), with 20-30% bridged to allogeneic stem cell transplant. Although the response rates are high, the responses to both first and second generation *FLT3* inhibitors are invariably transient, lasting 8-18 weeks (except among patients who undergo transplantation) due to the emergence of resistance(27, 28). The primary cause of resistance is the acquisition of point mutations in the *FLT3* KD. Heidel et al first to identified point mutations in the *FLT3-ITD* KD as a mediator of resistance to the *FLT3* inhibitor midostaurin. They reported a single amino acid substitution at position 676 (N676K) within the *FLT3* KD as the sole cause of resistance to midostaurin in a patient with AML(29). Acquired point mutations in the KD may be preexisting or acquired after exposure to the *FLT3* inhibitors as has been shown with midostaurin(29). Homology modeling has identified two main types of *FLT3* mutations, namely TKD1 mutations involving the ATP-binding (hinge regions) and the TKD2 mutations involving the activation loop(30). Non-mutational mechanisms of resistance include up-regulation of compensatory pathways including the MAPK/ERK, *PI3K/Akt/mTOR*, *FOXO3A*, *SYK*, and *STAT5/PIM* pathways, up-regulation of the *FLT3* ligand or receptor, mutations in other kinases (e.g. *CBL*), activation of anti-apoptotic proteins *BCL2*, *MCL1* and *BCL-x(L*), and tumor microenvironment mediated resistance(31, 32).

2.2 Quizartinib

Quizartinib is a novel second-generation Class III RTK inhibitor with potent and highly efficacious FLT3 activity in vitro and in vivo. Activating gene mutations in the RTK FLT3 (FLT3 mutant) are present in approximately 30% of patients with AML. These patients with FLT3-mutants have a significantly worse prognosis than patients with FLT3 wild type (FLT3 WT), suggesting that the activated kinase is a driver of AML and a potential target for kinase inhibitor therapy.

Toxicology studies with quizartinib in rats, dogs, and monkeys up to 90 days in duration have shown that the principle toxicological target organs were the bone marrow and lymphoid organs in rat, dog, and monkey. These findings are consistent with the presumed FLT-3 and c-KIT kinase inhibition mechanism of action of the drug. In addition, toxicological effects were observed in the kidney, the liver and the ovary, vagina, and testes. Target-organ toxicity appears to be dose-, and time-dependent, and most findings were reversible following a 28-day reversal period. Bioavailability and exposure were good across species, ranging from 15% in monkeys to 40% in dogs. Plasma protein binding with quizartinib was high (> 99%) in all 5 species examined (mouse, rat, dog, monkey, and human) and the compound has been shown to penetrate the brain poorly. In vitro CYP450 studies demonstrate that quizartinib is neither an inhibitor nor inducer of major human CYP isoforms. Quizartinib qualifies as P-gp substrate and has weak potential to inhibit P-gp. Evidence from rat toxicokinetic studies indicate that quizartinib does not accumulate nor does it induce its own metabolism. A major pharmacologically active metabolite, termed AC886, has been identified in the plasma of rat, dog, monkey, and humans.

Quizartinib Clinical Pharmacology and Pharmacokinetics

Absorption: The time for quizartinib to reach maximum observed plasma concentration (Tmax) is approximately 4 hours in healthy volunteers and 2 hours in AML subjects. Food has minimal effect on the bioavailability of quizartinib: peak concentrations (Cmax) decreased by approximately 8% while area under the curve (AUC) values increased by approximately 5% to 8%. Food increased Tmax by approximately 2 hours. Quizartinib can be administered without any restriction on fed status. The proton pump inhibitor lansoprazole modestly decreased the absorption of quizartinib with Cmax decreased by 14% and AUC decreased by 5% to 6% Quizartinib can be coadministered with gastric acid reducing agents (i.e. proton pump inhibitors, H2 blockers, and antacids).

At steady state in AML patients, the geometric mean (%CV) AUC0-24h for 30 mg QD and 60 mg QD were 3370 (72.5) and 8276 (95.7) ng·h/mL, respectively. The geometric mean (%CV) for Cmax at steady state for 30 mg QD and 60 mg QD were 186 (66.0) and 487 (80.8) ng/mL, respectively.

Distribution: Both quizartinib and its active metabolite, AC886, are highly plasma-protein bound with measured values >99% in all species tested. Both quizartinib and AC886 partition to red blood cells in a temperature-dependent manner. Blood samples must be processed at room temperature for accurate measurement of plasma quizartinib and AC886.

Metabolism: Reaction phenotyping using human liver microsomes and recombinant human CYP enzymes revealed that both quizartinib and AC886 were substrates of CYP3A, with little or no contribution of CYP2D6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP1A2. The in vitro studies showed that quizartinib is metabolized to AC886 by CYP3A. The metabolite AC886 is, in turn, metabolized by CYP3A.

Steady state simulations of quizartinib coadministered with ketoconazole predicted that quizartinib Cmax and AUCtau increase by 86% and 96%, respectively, compared with quizartinib administered alone. Similarly, steady state simulations for quizartinib coadministered with fluconazole showed Cmax and AUCtau increases of only 20.1% and 20%, respectively. These results indicate that quizartinib should be dose reduced by approximately half when coadministered with a strong CYP3A inhibitor, but not a moderate or weak CYP3A inhibitor.

The major circulating moeities are unchanged quizartinib and AC886 (> 10% of the total radioactivity exposure in plasma). AC886 has similar potency and selectivity to quizartinib and has been measured in all clinical studies with quizartinib PK assessments. The median Tmax for AC886 ranged from approximately 5 to 8 hours across studies in healthy volunteers. The ratio of AC886 to quizartinib (AUCinf) was approximately 0.5 at steady state.

Elimination: The principal route of excretion was hepatobiliary, estimated as > 90%. Renal excretion was a minor route of elimination (< 2%). The terminal elimination half-lives for quizartinib and AC886 are approximately 100 hours. For quizartinib 60 mg QD, the observed geometric mean accumulation ratios (AUC0-24h) for quizartinib and AC886 were 5.7 and 8.2, respectively.

Safety

A cardiovascular safety pharmacology study in cynomolgus monkeys demonstrates that single oral doses of quizartinib result in prolonged QTc interval at ≥10 mg/kg doses and biologically significant increased systolic blood pressure at ≥100 mg/kg doses. It should be noted that increases in blood pressure were not observed in the Phase 1 dose-escalation study, Protocol AC220-CP0001; henceforth called Study CP0001(33). No QTc interval prolongation was evident in monkeys dosed with 3 mg/kg quizartinib. It is suggested that quizartinib and AC886 induced blockade of human ether-à-go-go-related gene (hERG) current and I_{Ks}, and therefore caused QT prolongation by a decrease in the net repolarization currents. The effect on I_{Ks} was more dominant than that on hERG. There were no apparent electrocardiogram (ECG) abnormalities in the dog (28- and 90-day) or monkey (28- and 90-day) general toxicology studies. In addition, there were no apparent toxicologically relevant quizartinib-related heart microscopic changes in the rat, dog, or monkey general toxicology studies.

Results from Study CP0001 have shown that quizartinib has been well tolerated in the 76 patients (23). The majority of adverse events (AEs) observed in the study were those associated with the underlying disease. In addition, the safety profile was similar between patients receiving continuous dosing (28 days continuous dosing as 1 cycle) and those on the intermittent schedule (14 days dosing and 14 days rest as 1 cycle). In spite of limitations of the Phase 1 design, e.g., limited evaluation of response and the potentially suboptimal intermittent dosing schedule, encouraging preliminary evidence of clinical activity has been observed in the first 76 patients treated with quizartinib. The overall response (complete remission [CR] + partial remission [PR]) observed in all quizartinib-treated patients was 32% (24/76). Responses were defined per modified Cheson criteria (34). Ten patients achieved a CR defined as a decrease of < 5% blast in bone marrow: 2 complete hematological recovery, 4 with incomplete platelet recovery (CRp), and 4 with incomplete platelet and neutrophil recovery (CRi). One of these patients also had complete resolution of leukemia cutis. Fourteen patients had PR, defined as a decrease of ≥ 50% blasts to levels of 5% to 25% in the bone marrow but with incomplete peripheral recovery of neutrophils and platelets. Most of the patients had best bone marrow responses (14/22, 64%) during the first 28 days of treatment (defined as Cycle 1). Median duration of response was 14.1 weeks (range, 4 to 61+ weeks). Consistent with the proposed mechanism of action, the response in the FLT3-ITD mutant population was the highest with an overall response rate of 61% (11/18) including 6 PR, 3 CRi, 1 CRp, and 1 CR.

The dose-limiting toxicity (DLT) as per protocol in Study CP0001 was National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3 (v3) Grade 3 QTcF (corrected QTc by Fridericia's correction factor) interval prolongation at the 300-mg dose of quizrtinib administered continuously, and considered to be possibly drug related. It should be noted that this study did not exclude high risk cardiac patients, including those with abnormal baseline QTcF prolongation, nor did it exclude the administration of QT/QTc-prolonging concomitant medications, and patients were sometimes in a state of electrolyte imbalance with low serum potassium and/or magnesium levels. These patients with Grade 3 QTcF interval prolongation have been asymptomatic, with no evidence of arrhythmias and have had reversal of QTcF prolongation when quizartinib dosing was interrupted. The ECGs were originally analyzed by the sites, however they were subsequently re-read

using a centralized digital analysis system employed by a central ECG laboratory (EResearch Technology in Philadelphia, PA) and a formal analysis was performed. This determined that the ECG data in Study CP0001 did not demonstrate any clear signal of any clinically important effect on heart rate, PR (atrioventricular conduction), or QRS interval duration (depolarization) or morphology. The primary finding in this first-in-human study with limited cardiac safety data was that quizartinib appears to have a marked effect on cardiac repolarization, which is best defined by the Fridericia's corrected QT data (QTcF). The time-averaged mean change from baseline for QTcF duration for the intermittent dose groups showed no QTcF effect for the 12- to 60-mg dose groups. Starting with the 90-mg dose, however, the QTcF interval change from baseline was > 20 ms and tended to increase with dose, up to 30 to 38 ms for the 300- to 450-mg doses. For the continuous treatment dose groups, the QTcF interval change from baseline for 200 mg was 26 ms and for 300 mg was 54 ms. During the first 14 days of dosing, the intermittent and continuous treatment dose groups at 200 mg and 300 mg experienced the same exposure to quizartinib, and therefore, the data over this time period may be considered together. Taken together, the QTcF interval change from baseline for the 200-mg dose was 22 ms to 26 ms, and for the 300-mg dose was 38 ms to 54 ms, and the incidence of new cases (not seen at baseline) of Grade 3 QTcF interval prolongation (> 500 ms) was 9.5% (2/21 patients) at 200 mg and 30% (3/10 patients) at 300 mg. This demonstrates a clear dose-related and marked QTcF interval change at the ≥200-mg dose level. The QTcB (Bazett's correction factor) results were comparable. The onset of increase to > 500 ms QTcF occurred as early as 2 hours after the first dose and by Cycle 1 Day 8 of dosing in the cases that were observed. Additional observations were made in women and patients of > 62 years, as is usual in these settings. The pharmacokinetic-pharmacodynamic (PK-PD) relationship for parent and metabolite was also indicative that quizartinib caused a positive QTc response of a magnitude that was observed by the ECG data.

The results of a randomized phase 2 trial comparing two lower doses of quizartinib have been reported (35, 36). In this trial, patients with relapsed or refractory AML with FLT3 mutation were randomized to receive quizartinib 30 mg or 60 mg orally, daily. A total of 76 patients were enrolled (38 to each arm). The overall composite response rate (CRc, which was the primary endpoint) was identical for the two arms (47%). The overall response rate was slightly higher with 60 mg daily (71%) than with 30 mg daily (61%) because of a higher rate of partial responses in the 60mg arm (24%) compared to the 30 mg arm (13**%).** QTc prolongation to >500 msec (the dose limiting toxicity for quizartinib) occurred in 3% with 60 mg and 5% with 30 mg. When comparing these results with a prior study (37) exploring higher doses (90 mg, 135 mg, and 200 mg) it is clear that the rate of CRc is identical at all dose levels with some increase in PR with progressively higher doses. However, QTc prolongation is clearly dose dependent and prolongations >60 msec from baseline occur in 40% or more of the patients treated at doses of 90mg or above, exceeding the threshold of acceptable grade 3 toxicity for the standard definition of MTD.

	2689-CL-2004		AC220-002 (Cohort 2)

	30 mg/day (N = 38)	60 mg/day (N = 38)		90 mg/day (N=57)	135 mg/day (N=67)	200 mg/day (N=12)
Best Response						
CRc Rate	47%	47%		47%	45%	42%
PR Rate	13%	24%		25%	28%	50%
Maximum change in QTcF from baseline (msec)						
≤ 30	50%	44%		9%	9%	0%
> 30 to ≤ 60	47%	36%		46%	51%	8%
> 60	3%	19%		46%	39%	92%

In a recently reported phase I/II study, quizartinib and low intensity chemotherapy combination was shown to be safe and effective in patients with FLT3+ AML(38). In the phase I, patients with relapsed/refractory high-risk MDS, chronic myelomonocytic leukemia (CMML), or AML were eligible irrespective of FLT3 mutation and salvage status. The phase II enrolled patients age >60 years with untreated MDS/CMML/AML or patients of any age receiving first salvage treatment for AML with FLT3-ITD were eligible. Other requisites: performance status ≤2, adequate organ function and normal electrolytes (potassium, calcium and magnesium). Exclusions include: QTcF>450 msec, administration of drugs that prolong QT/QTc or strong CYP3A4 inhibitors or inducers.

Each treatment cycle was 28 days and comprised azacytidine (AZA) 75 mg/m2 subcutaneously (SQ) or intravenously for 7 days per cycle, or low-dose cytarabine (LDAC) 20 mg SQ twice daily for 10 days per cycle along with quizartinib at 2 planned dose levels: 60 mg (dose level 1) or 90 mg orally daily (dose level 2), uninterrupted. Patients were assigned to AZA or LDAC arm by physician choice.

Sixty-one (Phase I=12, phase II=49) patients were enrolled: 38 to AZA arm and 23 to LDAC arm, and 59 were evaluable for response (2 too early). Median age was 68 years (range, 23-84), 27 (44%) were female. Forty-three patients [14 in LDAC arm (67%) and 29 in AZA arm (76%)] of the 59 evaluable had responded with an ORR of 73 % (CR=10, CRp=6, CRi=20, PR=2); 5/43 (12%) patients were negative for minimal residual disease (MRD). **Twelve patients were previously untreated, and 11 responded (ORR 92%) (CR-6, CRi-1, CRn-1, CRp-2, HI-P-1). The median overall survival (OS) for previously untreated patients was 18.6 months (range, 3.91-43.5).** ORR among the 47 previously treated was 68% (CR-4, CRi-19, CRp-4, HI-2, HI-E-1, PR-2), and the median OS was 11.25 months (range, 1.15 – 38.93). ORR was 75% among all patients (frontline and salvage 1) harboring a FLT3-ITD mutation (N=55), and 5 (9%) had no MRD detectable (4 AZA, 1 LDAC)(38).

For additional details please see the quizartinib Investigator's Brochure (IB) (Appendix) for additional details on nonclinical and clinical studies.

2.3 Overview of BCL-2 and venetoclax in AML

2.3.1 Venetoclax

See the Venetoclax Investigator's Brochure (IB) (Appendix) 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 (39). 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 (40, 41). VEN also has been found to synergize with agents known to down-regulate Mcl-1, including azacytidine. (42)

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.

2.3.2 Summary of Venetoclax Nonclinical Pharmacology

Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of Bcl-2 that binds with > 1,000-fold higher affinity for Bcl-2 (dissociation constant [K_i] < 0.010 nM) than for Bcl-X_L (K_i - 48 nM or Mcl-1 (K_i > 444 nM).(40) In vitro, venetoclax has demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines(40). Venetoclax has demonstrated potent killing of AML cell lines, primary patient samples, and leukemic stem/progenitor cells ex vivo, and has also exhibited anti-tumor efficacy in vivo, inhibiting the growth of AML cells systemically engrafted into immunocompromised mice.

2.5.3 Summary of Venetoclax Nonclinical Pharmacokinetics

The pharmacokinetics of venetoclax was evaluated in mice, rats, monkeys, and dogs. Venetoclax pharmacokinetic (PK) profile was characterized by low plasma clearance and low to moderate volumes of distribution. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). Blood to plasma ratios showed that venetoclax does not partition preferentially into the red blood cells. Following oral administration of venetoclax to nonclinical species and humans, parent compound and metabolites were mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance.

Venetoclax is predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. In addition, venetoclax is also a substrate for P-gp and BCRP. Active uptake of venetoclax was not observed in cells overexpressing OATP1B1, OATP1B3 or OCT1. In vitro studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9, and UGT1A1 in vitro, but it is not predicted to cause clinically relevant inhibition due to high plasma protein binding.

Venetoclax is a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro. In vitro, venetoclax is metabolized by CYP3A4 and is a moderate inhibitor of CYP2C8. Definitive in vitro experiments showed that venetoclax is not predicted to be an inducer or inhibitor of the metabolism of CYP2C9 substrate compounds. Venetoclax is not a reversible inhibitor of CYP1A2, CYP2B6, CYP2D6, CYP2C19 or CYP3A4 (IC_{50} > 30 μM) in vitro and does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM.

2.5.4 Summary of Nonclinical Toxicology

Venetoclax has been assessed in repeated-dose general toxicology studies and in genetic, developmental/reproductive, and safety pharmacology studies. The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice and dogs, the male dog reproductive system (testicular germ cell depletion), and embryo-fetal toxicity in mice.

2.5.5 Summary of Venetoclax Clinical Data

Clinical Efficacy Data for Venetoclax: Preliminary efficacy results are available for subjects with a variety of hematological neoplasms; venetoclax is approved for the treatment of CLL patients whose cells have a 17p chromosomal deletion and venetoclax in combination with rituximab is approved for the treatment of CLL or small lymphocytic lymphoma (SLL) patients, with or without 17p deletion, who have received at least one prior therapy.

. Preliminary data indicate that venetoclax shows promising efficacy in AML.

- In Study M14-212 the ORR for subjects treated with venetoclax monotherapy was 19%.(43)
- In Study M14-358 the ORR for AML subjects (given venetoclax plus azacitidine or decitabine) was 68%.(44)
- In Study M14-387 the ORR for AML subjects (given venetoclax plus low dose ara-C) was 75%.(45)

Venetoclax Clinical Pharmacology and Pharmacokinetics: Venetoclax clinical pharmacology is being evaluated in several Phase I to III clinical trials, and data are available from three Phase I studies (M12-175, M13-367, M12-630), four Phase Ib studies (M13-365, M12-901, GO29440, GP28331), one Phase II study (M14-212) and five dedicated clinical pharmacology studies (Study M13-364, M14-497, M13-363, M14-253 and M15-101).

In the Phase 1 Study M14-358, preliminary pharmacokinetic results in 31 treatment-naïve AML subjects were available for venetoclax doses ranging from 400 mg to 800 mg when given in combination with decitabine (Arm A) or azacitidine (Arm B) and with or without posaconazole (Arm C). For Arm A and Arm B, venetoclax steady-state mean Cmax and AUC24 (Cycle 2 Day 5) ranged from 1.77 – 3.36 μg/mL and 24.7 – 59.5 μg/mL, respectively. Based on the limited preliminary pharmacokinetic data, there was no evidence to suggest a marked effect of the co-administration of decitabine and azacitidine on the pharmacokinetics of venetoclax. In Arm C of this study, preliminary pharmacokinetic results from 6 subjects were available on Cycle 1 Day 20 (venetoclax 400 mg alone QD until Day 20) and Cycle 1 Day 28 (venetoclax 100 mg QD with posaconazole given from Day 21 to Day 28). Venetoclax Cmax and AUC following co-administration of venetoclax 100 mg with posaconazole were 2.1- and 2.7-fold higher respectively, compared to venetoclax 400 mg alone.

Preliminary pharmacokinetic results of venetoclax are available from 12 treatment-naïve subjects with AML in Cohorts 1 (600 mg) and 2 (800 mg) from the ongoing Phase 1 combination study of venetoclax and low dose cytarabine (Study M14-387). On Cycle 1 Day 10 (with cytarabine), venetoclax mean Cmax and AUC24 values ranged from 2.25 – 2.56 µg/mL and 34.7 – 44.6 µg•hr/mL, respectively. On Cycle 1 Day 18 (venetoclax alone), mean Cmax and AUC values of venetoclax ranged from 2.38 – 2.89 µg/mL and 37.9 – 45.3 µg•hr /mL. Dose-normalized Cmax and AUC24 of venetoclax on Cycle 1 Day 10 (with cytarabine) were comparable to dose normalized Cmax and AUC24 on Cycle 1 Day 18 (venetoclax alone), suggesting that co-administration of cytarabine did not markedly affect venetoclax exposures.

Clinical Safety Data for Venetoclax: As of 05 June 2017, three Phase 1/2 studies have been conducted in the AML indication as described below.

Overview of Phase 2 Study M14-212: Venetoclax Monotherapy in AML
This is a completed study with 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.[43] The most common adverse events observed in ≥ 30% of the subjects in Study M14-212 were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., 1 event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia). No cases of TLS occurred during venetoclax treatment.

In this phase II multicenter trial single agent VEN produced an overall response in 5/32 relapsed/refractory AML patients (CR in 1 patient, CRi in 4 patients) (46). Of the 5 patients with CR/CRi, 3 had *IDH* mutations suggesting that patients with *IDH* mutations may be particularly sensitive to VEN.

Two ongoing trials are evaluating VEN combination regimens in treatment naïve patients with AML who are ≥65 years of age and who are not eligible for standard induction: (a) to evaluate the efficacy and tolerability of the combination of VEN with a methyltransferase inhibitor (azacytidine or decitabine) (ClinicalTrials.gov Identifier: NCT02203773); (b) to evaluate VEN with low-dose cytarabine (ClinicalTrials.gov Identifier: NCT02287233).

Overview of Ongoing Phase 1b Study (M14-358): Venetoclax in Combination with HMA in Treatment Naïve AML
As of 09 March 2016, a total of 45 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled into the escalation stage at 3 dose levels of venetoclax at 400 mg, 800 mg, and 1200 mg. Venetoclax was administered daily during the 28-day cycles in combination with decitabine (20 mg/m^2 intravenously on Days 1 – 5 once every 28 days) or azacitidine (75 mg/m^2 intravenously

or subcutaneously on Days 1 – 7 once every 28 days). Preliminary safety and efficacy data are available from the ongoing dose escalation stage of this trial.(45, 47)

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

As of 09 March 2016, the ORR, as assessed by the investigators for the subjects enrolled into the 3 dose levels, was 62.2% (28 of 45), with CR in 12 (26.7%), CRi in 15 (33.3%), and PR in 1 (2.2%). Four subjects (8.9%) were reported to have morphologic leukemia-free state (less than 5% blasts in bone marrow aspirate sample with at least 200 nucleated cells) after completion of Cycle 1. Eight patients (17.8%) had resistant disease. However, all of the patients with resistant disease had evidence of blast reduction at completion of Cycle 1. The patients enrolled into the 1200 mg dose level had a shorter follow-up at the time of this analysis.

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

Study M14-387: Study M14-387 titled, "A Phase 1/2 study of venetoclax in combination with low-dose cytarabine in treatment naïve subjects with acute myeloid leukemia who are ≥ 65 years of age and who are not eligible for standard anthracycline-based induction therapy," is an ongoing, open-label, multicenter safety and pharmacokinetics study. The primary objectives of the Phase 1 portion are to assess the safety profile, characterize pharmacokinetics, and determine the dose schedule, the MTD, and the RPTD of venetoclax in combination with low-dose cytarabine (LCD) in treatment-naïve AML subjects. The primary objectives of the Phase 2 portion of the study are to evaluate preliminary estimates of efficacy (including ORR and TTP) and to characterize the toxicities of the combination at RPTD. Secondary objectives of the Phase 2 portion include evaluating leukemia response (rates of CR, CRi, PR, RD, and HR including transfusion support needs) and DOR. An additional exploratory objective includes the evaluation of biomarkers that may serve as surrogate or predictors for clinical outcomes for future studies.
Of the 25 subjects in Study M14-387, 24 (96.0%) experienced at least 1 treatment-emergent adverse event. The most common adverse events for all subjects in Study M14-387 were: nausea (54%), febrile neutropenia (41%), diarrhea (44%), decreased appetite (33%), and peripheral edema (31%). Adverse events leading to study drug discontinuation occurred in 4 (16.0%) subjects, including 1 event each of disease progression, acute hepatic failure, Candida pneumonia, and subdural hemorrhage. Fatal adverse events occurred in 5 (20.0%) subjects: 2 events of malignant neoplasm progression and 1 event each of acute hepatic failure, Candida pneumonia, and lung infection.(44)

For further details of venetoclax preclinical studies, clinical studies, toxicities, pharmacokinetics, and adverse events please see the venetoclax Investigator Brochure (attached).

Experience with Venetoclax in combination therapy in relapsed and refractory myeloid malignancies

Efficacy of venetoclax combinations in the salvage setting will be presented at ASH 2017. Twenty-seven patients treated at our institution with relapsed/refractory AML (n=24), MDS (n=2) or BPDCN (n=1) received combinations including with decitabine (n=16) or azacitidine (n=5). Objective responses were achieved in 22% (n=6) of patients after a median of 1 cycle (range 1-4), including 11% with CRi and 11% with MFLS. 4 of the 6 responding patients received decitabine + venetoclax combinations, including 2 patients treated on the 5-day schedule and 2 patients treated on the 10-day schedule.

2.4 RATIONALE FOR STUDY

Second generation FLT3 inhibitors such as quizartinib and gilteritinib demonstrate potent anti-leukemic activity and improve outcomes in patients with relapsed/refractory AML with *FLT3-ITD* mutations(22). About 40-55% of FLT3-mutated patients not previously exposed to FLT3-inhibitors achieved marrow responses (CRc) to the second generation FLT3 inhibitors quizartinib(23-25) and gilteritinib(26), with 20-30% bridged to allogeneic stem cell transplant. Of note, recent FDA approval of midostaurin in combination with 7+3 induction chemotherapy in newly diagnosed FLT3-mutant AML signifies that essentially all relapsed FLT3-mutated AML patient will likely been exposed to at least one FLT3 targeting TKI. In this setting, the marrow response (CRc) rates with second generation FLT3 inhibitors such as crenolanib, gilteritinib and quizartinib have been reported to be lower than in prior FLT3 TKI naïve patients and are in the range of 20-25% (26, 48, 49) and Daiichi Sankyo unpublished communication).

Although response rates are high, the responses to single agent second generation *FLT3* inhibitors are almost invariably transient, maintained for 14-17 weeks, except among patients who undergo transplantation, due to the emergence of resistance(27, 28). The causes of resistance include the acquisition of point mutations in the *FLT3* KD (in 30-40% of resistant cases) and non-mutational mechanisms of resistance (in 50-60% of resistant cases) including up-regulation of compensatory pathways including the activation of anti-apoptotic proteins *BCL2*, *MCL1* and *BCL-x(L)*, *PI3K/Akt/mTOR*, *FOXO3A*, *SYK*, *RAS* and *STAT5/PIM* pathways, up-regulation of the *FLT3* ligand or receptor, mutations in other kinases (e.g. *CBL*), and tumor microenvironment mediated resistance(31).

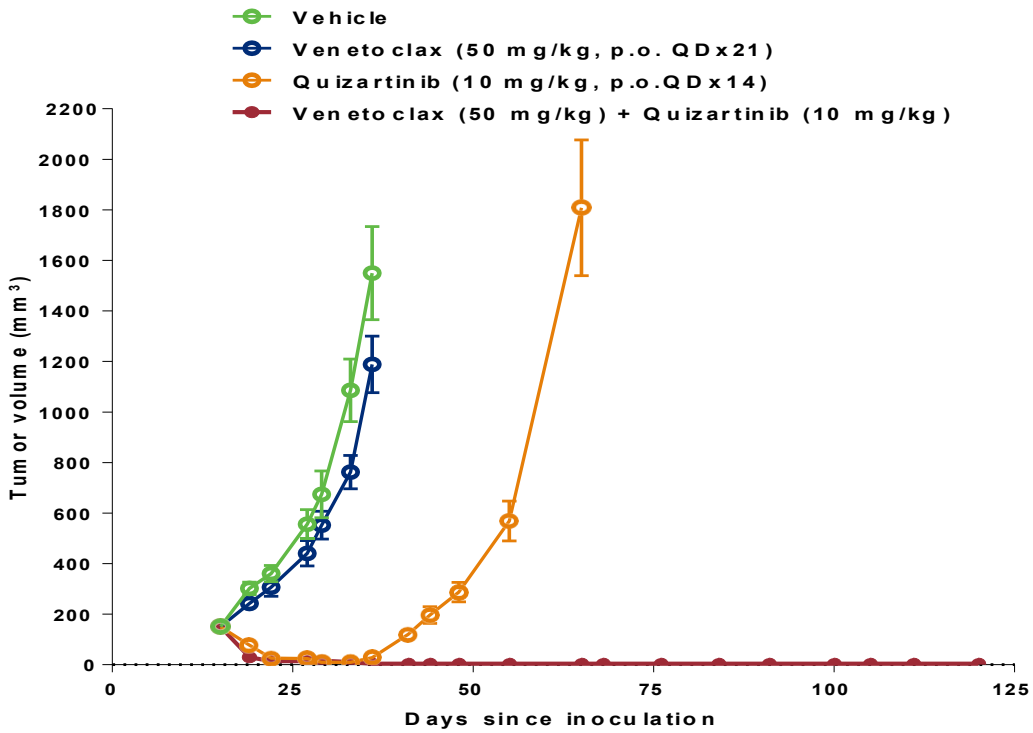
MCL-1 was reported as an essential effector of FLT3-ITD-mediated drug resistance (50) and a number of FLT3 inhibitors down-regulate MCL1 thereby reducing the propensity to resistance to BCL2 inhibitors. Combination of ABT-737 and FLT3 inhibitors was synergistic in FLT3-ITD-mutated AML(51).

Furthermore, our recent data shows that FLT3-ITD activation/mutations may play a major role in primary and secondary resistance to ABT-199 (Popovic R, Daver N et al, manuscript accepted to *American Journal of Hematology May 2018).* A phase 2 trial evaluated the efficacy and safety of venetoclax monotherapy in 32 patients with

relapsed/refractory acute myeloid leukemia (AML) or those unfit for intensive therapy(46). Venetoclax demonstrated activity and a tolerable safety profile in these patients with a CR/CRi in 6/32 (19%) of patients and biological activity defined as any measurable reduction in bone marrow blast counts after initiation of venetoclax therapy observed in 17/32 (53%) of patients. Occurrence of genetic mutations known to be associated with myeloid malignancies was investigated by next generation sequencing on blood and bone marrow specimens collected at baseline (32 patients) and relapse (20 patients). Eleven of 17 (65%) patients with biological activity had blasts containing mutations in the splicing factor genes *SRSF2/ZRSR2*, among them 6 patients also had blasts with mutations in *IDH1/IDH2*. Of the remaining 6 patients with biological activity, 1 patient had an *IDH2* mutation and the remaining 5 patients were wild-type for *SRSF2/ZRSR2/IDH1/IDH2*. Four of 15 patients (27%) without biological response to venetoclax had blasts with *FLT3-ITD* mutation prior to therapy. Four of the 17 patients (24%) with initial biological response to venetoclax acquired a new *FLT3-ITD* or *PTPN11* mutation at loss of response. Previous studies have shown that both these genetic alterations affect the expression of BCL-2 family members, suggesting that *FLT3-ITD* mutations may be responsible for primary and acquired resistance to venetoclax in AML patients by deregulating anti-apoptotic proteins. Furthermore, pretreatment and/or acquisition of FLT3 mutations correlated with decreased time on study.

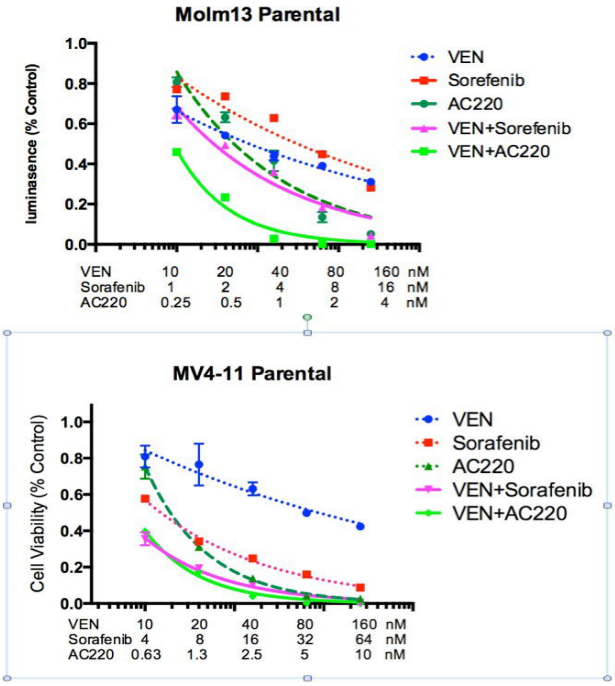
Based on our sequencing findings, we assessed the combination of venetoclax with the small-molecule FLT3 inhibitor quizartinib in the *FLT3-ITD*+ mutant xenograft model MV-4-11. *In vitro*, the MV-4-11 cells were sensitive to BCL-2 inhibition by venetoclax.[3] However, similar to our clinical observations, venetoclax did not inhibit the growth of these tumors when implanted in vivo. Although daily dosing of quizartinib induced tumor regressions in this model, the tumors eventually regrew. Strikingly, co-treatment with venetoclax and quizartinib induced similar tumor regressions as quizartinib alone but with significantly increased durability, preventing tumor re-emergence for up to 3 months post-cessation of treatment (Figure 1). These data suggested that combining venetoclax with FLT3 inhibitors such as quizartinib could be highly effective for the treatment of FLT3-mutated AML (and potentially in non FLT3-mutated AML as well) and may also prevent the emergence of FLT3-mutated, venetoclax-resistant sub-clones in patients who do not have an already detectable FLT3 mutation.

Figure 1: Tumor growth inhibition by venetoclax plus quizartinib in mice xenografted with *FLT3-ITD*$^+$ MV-4-11 cells.



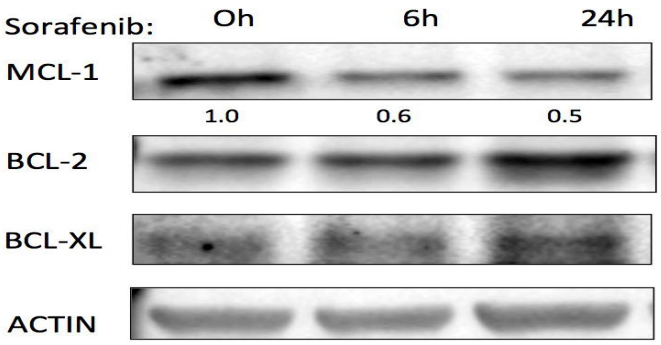
BCL-2 over-expression has also been implicated in maintaining the survival of FLT3-mutated AML cells. BCL-2 inhibition pre-clinically has been shown to potentiate the effects of FLT3-inhibitors, especially quizartinib (see attached prelim data from our lab) (Figure 2).

Figure 2: Venetoclax with FLT3-inhbiitor in cell lines



Combination Index (CI) for Parental cells

CI / Cell line	VEN+ Sorafenib	VEN+ AC220
MV4-11	0.64	0.66
Molm 13	0.71	0.69



Molm13 were treated with 8nM Sorafenib for 0/6/24 hours.

Our collaborator Jeff Tyner (Drug sensitivity testing for individualized therapies in hematologic malignancies. Jeffrey W. Tyner, OHSU Knight Cancer Institute, Portland, OR. AACR major symposium, 2016) has performed functional ex vivo screening of primary patient samples to identify effective small molecule drug combination strategies based on IC50 evaluation. In his study the combination of quizartinib with venetoclax revealed a higher percentage of sensitive samples than to venetoclax alone or quizartinib alone. This was one of the most potent small molecule combinations of multiple evaluated TKI combinations

3.0 STUDY DESIGN:

3.1 General

The study will be a phase Ib/II, single-institution, open label, non-randomized, single arm, clinical trial. All patients will be registered through CORe/PDMS.

- **Phase Ib**
  - This will include FLT3-ITD mutated patients with relapsed/refractory AML (up to four prior therapeutic regimens for AML i.e. up to salvage 4 status), including patients who may have been previously exposed to one prior FLT3-inhibitor other than quizartinib. Relapsed/ refractory status defined by the failure of at least one prior cycle of therapy for active AML (including but not limited to cytotoxic chemotherapy, hypomethylator therapy, immune-based therapy, stem cell transplant or stem cell therapy,

one prior FLT3-inhibitor therapy exposure allowed, investigational therapy, and others).

- The DLT assessment period will be only during Cycle 1 of the Phase Ib (DLT assessment period = 28 days).

3.2 Study Design

- The phase Ib portion is aimed at finding the MTD and RP2D of the two drugs in this combination. The target dose is dose level +1, and the starting dose will be dose level 0. The first 6 patients on study will receive dose level 0.

- The Investigator is responsible for completing the cohort summary template and submitting to the IND office Medical Monitor for review and approval prior to advancing subjects to the next protocol specified cohort/dose level. A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence". This should be submitted after the first six patients.

- The dosing schema is shown in Table 1 below.

Table 1: Dosing schema

Dose level	Quizartinib	Venetoclax
+1 (Target dose)	60 mg daily	400 mg daily
0 (Starting dose, n=6)	30 mg daily	400 mg daily
-1	20 mg daily	400 mg daily

3.3 Dosing algorithm

The goal of the lead-in phase Ib is to determine the MTD and RP2D. We will first treat 6 patients at dose level 0 in the phase Ib. If DLT occurs in >/=2/6 patients, this dose level would exceed the MTD, and 6 patients will be treated at the next lower dose level (i.e. dose level -1). If DLT occurs in <2/6 patients at dose level 0, the next cohort of 6 patients will be treated at the next higher dose level (i.e. dose level +1). The dose escalation or de-escalation (Table 1) will continue in cohorts of 6 until we reach the highest dose level at which <2/6 patients experience a DLT in the first 28 days. The highest dose level at which 0-1/6 patients experience a DLT in the first 28 days of treatment will be the MTD. The RP2D will be selected from among the doses evaluated after reviewing the efficacy, safety, pharmacodynamics data. The RP2D selected may be lower than the MTD. The RP2D will be used to treat an additional 20 patients in the phase II expansion portion of the study.

If >/=2/6 patients experience DLT at dose level -1, the study may be revised to consider additional lower dose levels.

Patients that are removed from study before day 28 for any reason other than toxicity and have not experienced DLT will be replaced.

*With up to1 potential dose escalation level (+1) to be studied and up to 6 patients to be treated at a given dose, the target maximum number of patients projected to be enrolled in the phase Ib part of the trial will be 12.

3.4 Definition of dose-limiting toxicity (DLT)

DLT is defined as a grade 3 or higher, clinically significant non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle on study, with the following exceptions:

- Grade 3 or 4 nausea, vomiting, or diarrhea that can be managed to ≤ grade 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 7 days of onset.
- Electrolyte abnormalities of Grade 3 or higher which can be corrected to grade 2 or less within 48 hours will not be considered as DLT only if the abnormalities are asymptomatic and corrected by optimal replacement therapy within 48 hours. Symptomatic grade 3 or higher electrolyte abnormalities will be considered DLT even if correctable within 48 hours.
- Grade 3 or 4 biochemical abnormalities of amylase or lipase without evidence of clinical pancreatitis.
- Grade 3 or 4 anorexia or fatigue.
- Grade 3 QTc prolongation will constitute DLT as follows: The QTc interval will be calculated by Fridericia's correction factor (QTcF). If the QTcF is > 500 msec the EKG must be evaluated within 4 hours in triplicate and if persistent ≥ grade 3 QTc prolongation is confirmed this will be considered a DLT. Note: Grade 4 QTc prolongation will be considered a DLT.
- All other clinically significant non-hematological adverse event that is Grade 3 according to the NCI CTCAE version 5.0 will be DLTs.

- Myelosuppression and cytopenias are expected outcomes of leukemia treatment and per se will not constitute DLT. Only prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, i.e. marrow cellularity < 5% with grade 4 neutropenia or thrombocytopenia on Day 42 or later from start of therapy without any evidence of leukemia, will be considered in defining DLT. In case of a normocellular bone marrow with no evidence of leukemia, 8 weeks with grade 4 neutropenia or thrombocytopenia will be considered a DLT. Anemia will not be considered for the definition of DLT.

  Any patients who stop treatment prior to completing evaluation for the DLT observation period (first 28 days) due to disease progression or refusal for further participation for reasons other than

toxicity during the DLT defining phase Ib portion of the study will be replaced for DLT evaluation. Patients who come off study earlier than 28 days during the DLT evaluation period may continue therapy off protocol if they are having clinical benefit, after discussion with the PI. The rationale for continuing therapy must be clearly documented in the patients chart.

Patients must receive at least 75% of the scheduled doses of quizartinib and at least 75% of the scheduled doses of venetoclax, respectively, in any given cohort to be eligible for DLT evaluation. Patients who receive <75% of the scheduled dose of either quizartinib or venetoclax will not be eligible for DLT evaluation and must be replaced. However, subjects who are unable to complete at least 75% of the prescribed dose of venetoclax and quizartinib in Cycle 1 (28 days) due to clinically significant non-hematologic adverse event or abnormal laboratory values that meet the definition of DLT in section 3.4 will be considered to have a DLT. Such patients 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 patient's chart.

3.5 Phase II expansion

Once MTD is defined, the RP2D will be selected based on efficacy, safety, and pharmacodynamics data evaluation from the phase Ib in discussion with the PI, Co-PI, sponsor and supporting companies (Daiichi-Sankyo, Abbvie and Genentech). The PI is responsible for completing the cohort summary template prior to advancing subjects to the phase II portion. The phase II portion will have 20 patients. Any patients still on study from the phase I portion at a dose lower than RP2D can be dose escalated up to RP2D in accordance with the dose escalation guidelines in section 5.2.3.
However, the dose for any patient may never exceed the RP2D.

4.0 PATIENT SELECTION

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to initiating treatment or any study-specific procedures. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion Criteria:

A subject will be eligible for study participation if he/she meets the following criteria within 14 days prior to the first day of therapy.

1. FLT3-ITD mutated patients with relapsed/refractory AML (up to four prior therapeutic regimens for AML i.e. up to salvage 4 AML), including patients who may have been previously exposed to prior FLT3-inhibitor/s other than quizartinib (SCT or stem cell therapy for patients who previously underwent SCT/stem cell therapy in remission will not be considered a salvage regimen).

2. Patients must be ≥18.

3. Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 2.

4. Potassium, magnesium, and calcium (normalized for albumin) levels should be within institutional normal limits.

5. Adequate hepatic (serum direct bilirubin </= 1.5 x upper limit normal (ULN) (or </= 3.0 x ULN if deemed to be elevated due to leukemia), alanine aminotransferase and/or aspartate transaminase </= 2.5 x ULN (or </= 5.0 x ULN if deemed elevated due to leukemia). Note: Subjects with documented Gilbert's Syndrome may have a total bilirubin > 1.5 × ULN.

6. Adequate renal function as demonstrated by a serum creatinine </=1.8

7. Patients must provide written informed consent.

8. With the exception of patients with rapidly proliferative disease, the interval from prior treatment to time of initiation of venetoclax and quizartinib administration will be at least 14 days or at least 5 half-lives (whichever is shorter) for cytotoxic/noncytotoxic agents. Patients with rapidly proliferative disease will not be required to wait for a washout and can start therapy at any time. 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 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. Controlled CNS leukemia is defined by the absence of active clinical signs of CNS disease and no evidence of CNS leukemia on the most recent 2 simultaneous CSF evaluations. (2) Use of one dose of cytarabine (up to 2 g/m^2) or hydroxyurea for patients with rapidly proliferative disease is allowed before the start of study therapy and on therapy. These medications will be recorded in the case-report form.

9. Baseline ejection fraction by ECHO or MUGA must be ≥ 50%.

10. Women of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectory..

11. Women of childbearing potential must agree to have a negative serum or beta human chorionic gonadotropin (Beta-hCG) pregnancy test result within 7 days prior to the first dose of study drugs and must agree to use an effective contraception method during the study and for 90 days following the last dose of the study. Men who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 90 days following the last dose of study drug.

4.2 Exclusion Criteria

1. Subject has t(8;21) or inv(16) karyotype abnormalities.

2. Subject has acute promyelocytic leukemia (French-American-British Class M3 AML).

3. Prior exposure to quizartinib at any time in the past.

4. Serum potassium < 3.5 mEq/L despite supplementation, or > 5.5 mEq/L. Serum magnesium above or below the institutional normal limit despite adequate management. Serum calcium (corrected for albumin levels) above or below institutional normal limit despite adequate management.

5. Patients with known allergy or hypersensitivity to quizartinib, venetoclax or any of their components.

6. Subject with a known history of being HIV positive (due to potential drug-drug interactions between antiretroviral medications and venetoclax, as well as anticipated venetoclax mechanism-based lymphopenia that may potentially increase the risk of opportunistic infections). Note: HIV testing is not required.

7. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit within 3 days prior to the initiation of study treatment.

8. Subject has a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or any other medical condition that in the opinion of the investigator and/or the PI would adversely affect his/her participating in this study. Patients who have had any major surgical procedure within 14 days of Day 1.

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

10. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:

a. Uncontrolled systemic infection requiring IV therapy (viral, bacterial or fungal). Infections controlled on concurrent anti-microbial agents are acceptable, and anti-microbial prophylaxis per institutional guidelines is acceptable. Patients with neutropenic fever considered infection related should be afebrile for at least 72 hours prior to first dose.

11. Subject has a history of other malignancies within 1 year prior to study entry, with the exception of:
a. Adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast;
b. Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
c. Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
d. Patients on active antineoplastic or radiation therapy for a concurrent malignancy, with curative or palliative intent, at the time of screening. Maintenance therapy, hormonal therapy, or steroid therapy for well-controlled malignancy is allowed.

12. Patients with a 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.

13. Female subjects who are pregnant or breastfeeding.

14. Impaired cardiac function including any of the following:

    -Screening ECG with a QTc >450 msec. The QTc interval will be calculated by Fridericia's correction factor (QTcF) at Screening and on Day 1 prior to the first dose of quizartinib. The QTcF will be derived from the average QTcF in triplicate. If QTcF >450 msec on Day 1, quizartinib will not be given.

    -Patients with congenital long QT syndrome

    -History or presence of sustained ventricular tachycardia requiring medical intervention within 3 months prior to starting study drug

    -Any history of clinically significant ventricular fibrillation or torsades de pointes

    -Known history of second or third degree heart block (may be eligible if the patient currently has a pacemaker) within 3 months prior to starting study drug

    -Sustained heart rate of <50/minute on screening or Day 1 ECG

    -Right bundle branch block + left anterior hemiblock (i.e. bifascicular block). Isolated RBBB will not be an exclusion criterion.

    -Complete left bundle branch block

    -Patients with myocardial infarction or unstable angina within 6 months prior to starting study drug

    -CHF NY Heart Association class III or IV within 3 months prior to starting study drug

-Atrial fibrillation documented within 2 weeks prior to first dose of study drug.

-Patients who are actively taking CYP3A inducers. CYP3A4 inducers should be stopped at least 3 days prior to the first dose of quizartinib and are prohibited at any time on study

-Patients who are actively taking a strong CYP3A inhibitors medication [see section 5.5.2 for the list of moderate and strong CYP
CYP3A4 inhibitors should be stopped at least 3 days p
quizartinib and are prohibited anytime during study. Mo
CYP3A4 inhibitors may be used with the below dose re
Patients may receive weak CYP3A4 inhibitors at an
venetoclax and quizartinib doses do not need to be adju
inhibitors.

Daver,Naval
2020-02-25 21:44:00

Rationale: Moderate CYP3A4 inhibitors have been safely administered with venetoclax with appropriate dose reduction as per US label. Moderate CYP3A4 inhibitors have been safely administered with Quizartinib. Based on this we are allowing moderate CYP3A4 inhibitors on protocol

Assigned Venetoclax Dose	Venetoclax Dose If Co-Administered with a Moderate CYP3A Inhibitor/Inducer
100mg	50mg
200mg	100mg
400mg	200mg

-Patients who require treatment with concomitant drugs that prolong QT/QTc interval [see section 5.5.2 for the list of strong drugs that prolong QT/QTc]. QT/QTc prolonging drugs should be stopped at least 3 days prior to the first dose of quizartinib and are prohibited at any time on study.

-Known family history of congenital long QT syndrome

5.0 TREATMENT PLAN:

5.1 Schedule

All patients will be registered through CORe.

The Phase Ib dose escalation stage of the study will evaluate the safety, tolerability, PD and PK of venetoclax in combination with quizartinib, with the objectives of identifying the MTD and RP2D for each combination.

Quizartinib will be administered orally daily continuously staring on cycle 1 day 1. Patients will self-administer quizartinib tablets orally QD. 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. Patients will receive one cycle of therapy every 28 days (+/- 7 days). Cycle 1 Day 1 of each cycle will be counted from the start of the quizartinib dosing. Quizartinib dose escalation criteria will be maintained as suggested in quizartinib Investigational Brochure (IB) as follows:

1. If the target dose for the given patient in the phase IB or phase II portion is quizartinib 30mg the patient will start the dosing on C1D1 at quizartinib 30mg per day
2. If the target dose for the given patient in the phase IB or phase II portion is quizartinib 60mg the patient will start the dosing on C1D1 at quizartinib 30mg per day and can increase to quizartinib 60mg per day on C1D12 only if QTcF on triplicate ECG is <450 msec on the Day 12 post-dose EKG

The initiation of venetoclax will be deferred for 7 days in cycle 1 to allow clinical and correlative evaluation of quizartinib single agent activity, and to debulk tumor burden thereby reducing the risk of tumor lysis syndrome (TLS). The intent is to initiate venetoclax on cycle 1 day 8. Blood samples will be collected at pre-dose, 2 (+/- 30 minutes) , 4 (+/- 30 minutes) , 6(+/- 30 minutes) , 8 (+/- 30 minutes) and 24 (+/- 30 minutes) hours post-dose on cycle 1 day 14 to measure venetoclax, quizartinib and AC886 concentrations in patients enrolled in the dose-escalation period (n=12). The WBC count must be <10K prior to the initiation of venetoclax dosing. Note: Hydroxyurea can be used if needed during these initial 7 days to control WBC count, if needed.

It is suggested that each dose of venetoclax be taken with approximately 240 mL of water within 30 minutes after the completion of a low-fat breakfast. Examples of a low-fat breakfast include 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jam, and 8 ounces/240 mL of skim milk (319 calories and 8.2 g fat) or 1 cup/30 g of cereal, 8 ounces/240 mL of skim milk, 1 slice of toast with jam, 1 cup/240 mL of apple juice, and 1 cup/240 mL of coffee or tea (520 calories and 2 g fat). If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be taken. Otherwise, no replacement dose is to be taken. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken with food within 8 hours after the missed dose. Otherwise, the dose should not be taken. Patient compliance with the assigned daily dose of venetoclax will be assessed by standard pill counts. Bottles containing venetoclax tablets will be given to patients at regular scheduled visits. Previously distributed bottles will be returned to the clinic and tablets counted and returned study drug destroyed per institutional policy. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Any overdose or incorrect administration of Venetoclax and Quizartinib should be noted within Prometheus. Adverse events associated with an overdose or incorrect administration of study drug should be recorded as an Adverse Event within Prometheus.

5.1.1.1 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.

*For the phase Ib, DLT defining period is 28 days. As such, cycle 2 should not be started before 28 days for the patients being treated on the phase Ib cohort to allow for adequate evaluation of DLTs.

5.1.1.2 Subsequent cycles may be delayed for recovery of toxicity or other medical conditions. Delays in start of subsequent cycles greater than 8 weeks 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.

5.1.1.3 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.

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

5.2 Dose Adjustments

5.2.1 Venetoclax and quizartinib dose adjustments for drug-related hematological adverse events (AEs) **(all dose adjustments to follow guidelines in section 5.2.2)**

Dose reduction/interruption/discontinuation decisions should be based on the CTCAE version 5.0 of the toxicity 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 leukemias. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 cycles and/or in the presence of residual leukemia. After that, treatment interruptions and dose adjustments may be considered according to the following guidelines only when there is no evidence of residual leukemia.

    - Patients with a response (no marrow evidence of leukemia) and pre-cycle counts of neutrophils >1.0 x 10^9/L and platelets >50 x 10^9/L who have sustained low counts of neutrophils <0.5 x 10^9/L or a platelet count <20 x 10^9/L for more than 2 consecutive weeks in the current cycle, are recommended to have the treatment with

venetoclax and/or quizartinib interrupted or dose-reduced by one dose level after discussing with the PI until neutrophils recover to ≥0.5 x10^9/L and platelets to ≥20 x 10^9/L. If prolonged myelosuppression defined as ANC < 0.5 x 10^9/L and platelets <20 x10^9/L (more than 8 weeks) with evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of leukemia) is observed in these patients, both venetoclax and quizartinib will be discontinued. Delays in start of subsequent cycles greater than 8 weeks will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio and complete documentation of the degree of clinical benefit and reason for continuation on this regimen.

- If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts or evidence of leukemia by other assays, treatment may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions of venetoclax and/or quizartinib in these patients should be considered on an individual case and discussed with the PI and the sponsor.

- Patients with a response (no marrow evidence of leukemia) and pre-cycle counts of neutrophils <1x10^9/L and platelets <50 x10^9/L may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions in these patients should be considered on an individual case and discussed with the PI.

- Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce venetoclax and/or quizartinib, as applicable.

5.2.2 Venetoclax and quizartinib dose adjustments for non-hematologic drug-related AEs

Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce venetoclax and/or interrupt quizartinib, as applicable. Thus, if dose level +1 is established as the MTD (Table 1), one dose level reductions of quizartinib will be quizartinib 30 mg daily, two dose level reductions of quizartinib will be 20 mg daily, three dose reductions of quizartinib will be 15 mg daily, respectively. If the RP2D is lower than dose level +1 (Table 1) further dose reduction levels of quizartinib will be defined before moving to the phase II portion of the study.

Dose reductions of venetoclax for non-hematologic drug-related AEs will be as follows: assuming the starting dose = venetoclax 400 mg daily: one dose level reduction = 200 mg daily, two dose level reductions= 100 mg daily, three dose level reductions = 50 mg daily. The venetoclax dose will not be reduced beyond 50 mg daily. Reductions in the number of days of venetoclax, i.e. going from 28 day continuous dosing per cycle to 21-days on/7-days off schedule or a 14-days on/14-days off schedule will be allowed if this is felt to be in the best interest of the patient only after discussion and approval from the PI and clearly documenting the reason for the change in the schedule in the medical records of the patient.
During the dose escalation phase 1B dose-reductions will be allowed and will follow the schema outlined above.

Table 2 Dose adjustments for non-hematologic drug-related AEs, clinically significant in the opinion of the investigator (all dose adjustments to follow guidelines in section 5.2.2)

(The list of QTc prolonging medications is not comprehensive)

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction.
3 (Persistent grade 2: Consider similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician)	1st time	Hold venetoclax and/or quizartinib. Resume venetoclax and/or quizartinib at prior dose if recovery to ≤ Grade 1 or baseline occurs within 14 days. If toxicity persists for 15-28 days, hold therapy and resume at ONE dose level below current dose for venetoclax OR quizartinib OR both based on which medication is likely causing the toxicity ONLY after recovery of toxicity to ≤ Grade 2. Dose re-escalation to prior dose of venetoclax OR quizartinib OR both is permitted if tolerated and no recurrent Grade 3 or 4 toxicities occur over 4 weeks while on the lower dose level.
	2nd time	Hold venetoclax and/or quizartinib. Follow until toxicity ≤ Grade 2. Resume at TWO dose level below current dose for venetoclax OR quizartinib OR both based on which medication is likely causing the toxicity ONLY after recovery of toxicity to ≤ Grade 2. Dose re-escalation by one dose level every 4 weeks of venetoclax OR quizartinib OR both is permitted if tolerated and no recurrent Grade 3 or 4 toxicities occur over the 4 weeks while on the lower dose level.

	3rd time	Stop venetoclax and quizartinib and discontinue patient. (For patients with clinical benefit/response from the combination we will consider continuation if toxicities resolve to ≤ grade 1 within 28 days and with proper dose adjustments after consultation with the PI and the sponsor.)
4	1st time	Hold venetoclax and/or quizartinib. Resume venetoclax and/or quizartinib at prior dose if recovery to ≤ Grade 1 or baseline occurs within 14 days. If toxicity persists for 15-28 days, hold therapy and resume at ONE dose level below current dose for venetoclax OR quizartinib OR both based on which medication is likely causing the toxicity ONLY after recovery of toxicity to ≤ Grade 2. Dose re-escalation to prior dose of venetoclax OR quizartinib OR both is permitted if tolerated and no recurrent Grade 3 or 4 toxicities occur over 4 weeks while on the lower dose level.
	2nd time	Stop venetoclax and quizartinib and discontinue patient. (For patients with clinical benefit/response from the combination we will consider continuation if toxicities resolve to ≤ grade 1 within 28 days and with proper dose adjustments after consultation with the PI and the sponsor.)
Cardiac Toxicity	Grade 1 QTc ≥ 450 and ≤ 480 msec	Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Continue quizartinib at the same dose.
Cardiac Toxicity	Grade 2 QTc> 480 and ≤ 500 msec	Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. The dose of quizartinib will be reduced one level without interruption of dosing. Following dose reduction, the quizartinib dose may be resumed at the previous level in the next cycle if the QTc has decreased to within 30 msec of baseline or <450 msec but subject must be monitored closely for QT prolongation for the first cycle at the increased dose. Subjects who experience >480 msec QTc prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTc prolongation and then weekly thereafter until the QTc prolongation is resolved.

Cardiac Toxicity	Grade 3 QTc interval >500 msec (at least on two separate EKGs) or >60 ms change from baseline	Check magnesium and potassium levels and correct any abnormalities. Interrupt quizartinib and if possible any medications that may prolong the QTc interval. Quizartinib dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or <450 msec within 14 days, quizartinib administration may be resumed at a reduced dose (reduce by one level). Subjects who experience >500 msec QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTc prolongation is resolved.
Cardiac Toxicity	Grade 4 , and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia (i.e., grade 4)	Quizartinib dosing will be permanently discontinued

- If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

- Patients in whom the toxicity occurs or persists beyond the planned completion of drug administration for the cycle will have the dose reductions for either venetoclax or quizartinib or both agents (based on attribution of the specific toxicity to venetoclax or quizartinib or both) implemented in subsequent cycles provided the toxicity has resolved as specified in Table 2 above.

- These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the PI in specific cases.

- Guidelines for dose adjustment for toxicities that are may be reasonably related to venetoclax are given below.

5.2.3 Intra-patient dose escalation

Intra-patient dose escalation of venetoclax and quizartinib (in accordance with the dosing schema in Table 1) will be permitted provided:

- Patient has completed ≥1 cycle at their current dose level
- Patient has not experienced any grade 3 or higher non-hematologic drug-related toxicity (including Grade 3 QTcF prolongation), and
- Patient has not experienced hematologic DLT, and
- At least 6 patients have been treated at the next higher dose level and followed for at least 28 days without experiencing DLT and this dose level has been deemed safe and does not exceed the RP2D.
- The dose may be escalated by one dose level per cycle (per Table 1) provided such dose level does not exceed RP2D.
- Dose escalation of only one of the two agents is allowed if judged in the best interest of the patient (e.g., in patients with neutropenia this would be likely secondary to venetoclax, in patients with QTc changes this would be likely secondary to quizartinib).
- However, the dose of any agent cannot be escalated beyond the established RP2D for the combination.

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

5.2.4.1 Further dose reductions can be made to keep clinically significant toxicities grade ≤ 2.

5.2.4.2 Dose adjustments by more than 1 dose level at a time (e.g., from quizartinib 60 mg daily to 20 mg daily) can be considered when judged in the best interest of the patient (e.g. severe myelosuppression or other toxicity attributable to one of the agents) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented in the medical record.

5.2.4.3 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 for at least 1 month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month.

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

prolonged neutropenia this would be likely secondary to venetoclax, in patients with QT changes this would be likely secondary to quizartinib).

5.3 Duration of 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, or
2. Grade 4 QTc prolongation (based on average of triplicate).
3. Intercurrent illness that prevents further administration of treatment, or
4. Patient request, or
5. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
6. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy. This includes patients with grade 4 non-hematological toxicity unless it reverses to grade ≤ 1 on or before 8 weeks of interrupting quizartinib and/or venetoclax.

5.3.1 It is planned that up to a total of 24 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 24 cycles of therapy may be considered on a case-by-case basis after discussion with the principal investigator.

5.3.2. All patients receiving at least one dose of either of the two drugs will be considered evaluable for toxicity.

5.4 Drug administration

5.4.1 Venetoclax administration

a. Dosage Form

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by Abbvie as oral film-coated tablets of 10-mg, 50-mg, and 100-mg strength. Venetoclax tablets will be packaged in high-density polyethylene (PE) plastic bottles to accommodate the study design.

Venetoclax is an investigational agent supplied to investigators of this study by Abbvie Inc at no cost.

Each bottle of venetoclax tablets will be labelled in accordance with current International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), FDA and specific national requirements.

Sites must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy. The Investigator (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

The Investigational medicinal product should not be used for any purpose outside the scope of this protocol, nor can Investigational medicinal product be transferred or licensed to any party not participating in the clinical study. Venetoclax's data for Investigational medicinal product are confidential and proprietary and shall be maintained as such by the Investigators.

b. Drug Storage

Venetoclax must be stored at 15°C – 25°C (59°F – 77°F) in a locked and secured area with restricted access. The tablets should not be stored at freezer temperatures or allowed to freeze. All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

c. Accountability and Destruction of Investigational Medicinal Product

The Principal Investigator (or an authorized designee) at each participating institution must maintain a careful record of the inventory of the Investigational medicinal product received using the Drug Accountability Form. The study drug will be destroyed as per the institutions destruction policies and documentation of study drug destruction will be provided to Abbvie Inc. Both used and unused study drug may be returned to Abbvie Inc if requested.

For information on the formulation and handling of venetoclax, see the Venetoclax IB.

5.4.2 Quizartinib administration

a. Description

The chemical name of the investigational product, quizartinib, is N-(5-tert-Butyl-isoxazol-3-yl)-N′-[4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl] urea dihydrochloride salt.

Quizartinib is supplied as tablets each containing 15 mg, 20 mg or 30 mg quizartinib. The tablets also contain microcrystalline cellulose, magnesium stearate, and Opadry® II 85F18422 white film coating. They are packaged in high density polyethylene bottles, each containing 30 tablets, with child-resistant caps.

c. Potential Indications and Usage

Quizartinib + Chemotherapy: Ongoing Clinical Trial (ClinicalTrials.gov 10/26/17)

ID	Setting	Phase	Clinical Trials	Identifier
AC220-A-U302	Frontline	Phase 3	Quizartinib + standard chemotherapy (Quantum-First)	NCT02668653
AC220-A-J102	Frontline	Phase 1	Quizartinib + 7 + 3 (in Japan)	NCT02834390
2012-1047	Both	Phase 1/2	Quizartinib + LDAC or AZA	NCT01892371
AML005	Both	Phase 2	Quizartinib and Omacetaxine	NCT03135054
AC220-007	Relapsed	Phase 3	Quizartinib versus LDAC, or MEC or FLAG-IDA (Quantum-R)	NCT02039726

d. Dosing
Each patient will receive or be instructed to take quizartinib oral tablets at the assigned dose once a day on in the morning for 28 consecutive days as 1 cycle of treatment.

e. Selection and Timing of Dose
Each treatment cycle consists of 28 consecutive days. Quizartinib will be taken orally once a day in the morning.

f. Packaging and Labeling
Please refer to the Investigational Brochure for packaging and labeling information.

5.4.3 Disposition of unused drug
All unused drug will be disposed of per institutional guidelines and procedures.

5.5 Concomitant medication

5.5.1 In general, the use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted. Since the effect of both venetoclax and quizartinib may be delayed for up to 4 weeks, patients with high WBC counts may receive hydroxyurea and up to 1 dose of cytarabine (up to 2 g/m^2) prior to study entry, and while on therapy. Hydroxyurea and cytarabine use would be recorded in the CRF. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted as defined in inclusion criteria. With the exception of these agents, concomitant systemic chemotherapy is not permitted.

5.5.2 Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are allowed for managing myelosuppression as shown in Table 3.

The administration of drugs known to prolong QTc interval is strictly prohibited on this protocol. QT/QTc prolonging drugs should be stopped at least 3 days prior to the first dose of quizartinib and are prohibited at any time on study.

See Section 5.2.2 (Table 2) for guidelines on monitoring and managing QTc prolongation.

Category	**Drug Name**
QT prolonging drugs with a known risk to induce Torsades de Pointes (TdP)	amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisaprideC, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidonel, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, ibogaine, ibutilide, levofloxacin, levomepromazinel, levomethadyl, levosulpiride, mesoridazine, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl, pentamidine,pimozide, probucol, procainamide, quinidine, roxithromycin, sevofluran, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib

Propofol is allowed on this study.

Strong CYP3A4 inhibitors should be stopped at least 3 days prior to the first dose of quizartinib and are prohibited anytime during the study. Moderate (but not strong) CYP3A4 inhibitors may be used with the below dose reductions of venetoclax. Patients receiving weak CYP3A4 inhibitors at any time on study will receive quizartinib doses do not need to be adjusted. The venetoclax and inhibitors.

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Rationale: Moderate CYP3A4 inhibitors have been safely administered with venetoclax with appropriate dose reduction as per US label. Moderate CYP3A4 inhibitors have been safely administered with Quizartinib. Based on this we are allowing moderate CYP3A4 inhibitors on protocol

Assigned Venetoclax Dose	Venetoclax Dose If Co-Administered with a Moderate CYP3A Inhibitor/Inducer
100mg	50mg
200mg	100mg
400mg	200mg

Strong CYP3A inducers – avasimibe, carbamazepine (Tegretol®), enzalutamine, mitotane, phenytoin (Dilantin®), rifampin (Rifadin®), St. john's wort

Moderate CYP3A inducers – bosentan, efavirenz, etravirine, modafinil, nafcillin

Strong CYP3A inhibitors – Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir,

posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole

Moderate CYP3A inhibitors – Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem†, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil

* These are anticancer agents; excluded on study as per protocol.
† Moderate CYP3A inhibitor per venetoclax FDA USPI.

Note: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Table 3: 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 standard of care at MDACC	None
Allowed	Oral allopurinol or rasburicase	At investigators discretion	None
	Leukapheresis	According to standard of care at MDACC	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 MDACC	None
	Myeloid growth factors or	At investigators discretion according to standard of care at MDACC	None

		At investigators discretion according to standard of care at MDACC	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MDACC	None

5.5.3 Use of Blood Products

During the administration of venetoclax, patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines.

Myelosuppression is expected in patients with AML due to underlying disease, as well as due to therapies (such as venetoclax and sorafenib), or both. Most patients have neutropenia, thrombocytopenia, or both at study entry. Significant or life-threatening myelosuppression may be managed with growth factor support including G-CSF, GM-CSF and erythropoietin/darbepoetin/blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.

5.5.4 Tumor Lysis Prophylaxis

There is a potential for TLS in patients treated with venetoclax, especially in those with elevated pretreatment LDH levels, elevated leukocyte count, renal dysfunction, and dehydration. To mitigate the potential risk of TLS, patients will be required to have WBC count <10K prior to initiating venetoclax on C1D8 and will receive TLS prophylaxis prior to venetoclax initiation on C1D8 and prior to venetoclax dose escalation. Patients will be hospitalized on Day -1 (C1D7) of venetoclax through at least 24 hours post target cohort dose. Thus it is projected that if WBC is <10K on C1D7, patients will be hospitalized C1D7 (day -1 venetoclax) through C1D12 (24 hours post venetoclax dose escalation completed).

Venetoclax will be administered at a dose of 50 mg on day 8, 100 mg on day 9, 200 mg on day 10, and 400mg on days 11-28 of the first cycle. All subsequent cycles, Venetoclax will begin on Day 1. For toxicities that could be attributed to either drug, Venetoclax or Quizartinib or both could be held or modified, based on perceived contribution (as per treating physician, in discussion with PI) of respective drug to the toxicity. This schedule may need to be adjusted if we see any signs of TLS. If this occurs it should be discussed with the PI and the new schedule documented in the patients chart.

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) at least 24 hours prior to the first dose of venetoclax and during the venetoclax ramp up period of Cycle 1.

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.

5.5.5 Prohibited Food

Use of the following foods is prohibited during the study and for at least 7 days prior to initiation of study treatment:
Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days prior to the initiation of study treatment

Patients who consume any of these foods will be discontinued from study treatment and followed for safety outcomes for 4 weeks after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever comes first.

5.5.6 P-glycoprotein substrates

There is a narrow therapeutic index for interactions between venetoclax and P-glycoprotein substrates. A list of p-glycoprotein substrates is provided via link below. Patients who are taking a p-glycoprotein substrate and venetoclax should take the p-glycoprotein substrate 6 hours before the venetoclax.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Note: Every effort will be made to adhere to the quizartinib and 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.

5.5.7 DRUG DRUG INTERACTION ASSESSMENT

Both quizartinib and venetoclax are CYP3A and Pgp substrates. Both quizartinib and ventoclax are Pgp inhibitors, and the latter also inhibits BCRP. Therefore, the potential for a two way drug drug interaction will be assessed in a substudy of the first 12 subjects enrolled in the Phase 1b. Specifically this substudy will assess the effect of venetoclax on quizartinib PK (i.e. Cmax and AUC0-24h) and the effect of quizartinib on venetoclax PK (i.e. Cmax and AUC0-24h) as summarized in section 5.1.

6.0 CORRELATIVE/SPECIAL STUDIES (Optional)

Biomarker assessments may include:

6.1 81-gene sequencing in all patients

As a standard of care all AML patients at MDACC are evaluated for karyotype and molecular mutation profile using a CLIA-certified next-generation 81-gene panel sequencing platform. The effects of the combination will be compared not only to historical outcomes in matched groups of patients, but also at the molecular and cellular level by correlating with karyotype and molecular mutation profile. The 28-gene panel will be performed on the screening BM aspirate and the progression BM aspirate.

6.2 Minimal Residual Disease assessment by flow-cytometry

As a standard of care all BM aspirates including but not limited to the screening BM, end of cycle 1 BM, end of cycle 3 BM, will be evaluated for MRD by validated 17-color multiplanar flow-cytometry at MDACC.

6.3 Gene expression signatures by RNA sequencing and/or RT-PCR

This will be performed on the pretreatment BM aspirate and when available, the progression/relapse BM aspirate.

6.4 Cytof analysis

We will analyze BCL-2 family expression, stem cell surface markers and intracellular signaling markers in AML cells by CyTOF (mass cytometry) assay established in Dr Konopleva's laboratory. This will be done on mononuclear cells obtained from BM aspirate and when available from PB at all time points specified in 7.1.8 and 7.2.9.

6.5 Immune assays

To analyze immune modulation including alterations in total and percent of CD3+ T-cells, total and percent of various T-cell subsets (Cd4-effector, CD4-regs, CD8 cytotoxic T-cells), and total and percent of T-cell/T-cell subsets expressing specific checkpoint receptors/ligands with single-agent quizartinib and with the combination. This will be done on peripheral blood and BM aspirate at all time points specified in 7.1.8 and 7.2.9.

6.6 BH3 profiling of BCL-2 family member dependency

BH3 profiling will be performed on PB samples at pre-treatment, pre venetoclax dose 1 (cycle 1 day 7), and at progression.

6.7 Single Cell Genotyping

To precisely monitor mutant clones and address clonal heterogeneity on a single cell level, we will utilize a high-throughput ***single-cell genomics platform*** for targeted sequencing, in collaboration with Catherine Smith (UCSF) on PB at all time-points in 7.1.8 and 7.2.9

7.0 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 correlative assays.

7.1 Pre-Treatment Evaluation

All pretreatment studies should be obtained within 14 days from time of first dose of the study drug administration, unless otherwise specified:

7.1.1 A complete history and physical, concomitant medications and performance status.

7.1.2 CBC, platelet count, hemoglobin, differential (differential can be omitted if WBC is ≤0.5 $x10^9$/L).

7.1.3 Creatinine, total bilirubin, ALT, potassium, magnesium, calcium, sodium, chloride, CO_2 (HCO3), uric acid, phosphorus, and BUN.

7.1.4 Serum or urine pregnancy test in females of childbearing potential, should be performed within 72 hours before the initiation of therapy.

7.1.5 Bone marrow aspirate with or without biopsy within the last 21 days preceding study initiation.

7.1.6 Evaluation of FLT3, NPM1, IDH1 & 2 should have been done within 60 days preceding study initiation.

7.1.7 12-lead EKG (in triplicate) and ECHO and/or MUGA.

7.1.8 Pretreatment optional correlative studies (see section 6.0)

Peripheral blood (up to 40 cc) – (1) Cytof and gene expression signatures by RNA sequencing and/or RT-PCR, (2) BH3 profiling, (3) immune panel in the blood prior to first dose of quizartinib at baseline (Cycle 1 Day 1)

- Bone marrow samples (up to 15 cc): (1) Mutation analysis of leukemia associated genes by deep sequencing; (2) Cytof (3) immune panel prior to first dose of quizartinib at baseline (Cycle 1 Day 1)

7.2 Evaluation During Treatment

7.2.1 During Cycle 1 Day 7-12 patients will be admitted to the inpatient service and have labs done at least daily to monitor closely for TLS, proliferative disease, and electrolyte changes. Patient can be treated as an outpatient if WBC <10,000 with approval from the PI.

7.2.2 Physical exam on day 1 of each cycle (± 1 days) for the first 4 cycles.

7.2.3 CBC, platelet count, hemoglobin, differential at least twice weekly for the first 3 cycles, then at least once a week (differential can be omitted if WBC is ≤0.5 x10^9/L). Outside labs may be used, but the PI/Treating physician must review all protocol specific outside lab results and determine the clinical significance of abnormal values then sign/date the results or dictate this process in the medical record.

7.2.4 Creatinine, total bilirubin, ALT, K, Mg, Ca, sodium, chloride, and CO2 (HCO3) on day 1 prior to start of quizartinib, at least twice weekly for the first 3 cycles, then at least once a week. For initial labs and initial management of electrolyte imbalances and prevention of tumor lysis syndrome patients will be admitted and monitored inpatient for cycle 1 Days 7-12 (section 5.5.4).

7.2.5 Laboratory tests can be ordered more frequently if mandated by development of peripheral blast/blood counts or electrolyte/liver function test abnormalities.

7.2.6 Bone marrow aspiration for differential and PCR for FLT3 on day 28 (±7 days) of cycle 1, day 28 of cycle 3 (±7 days), then every 2 cycles. 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.

7.2.7 Concomitant medication data will not be collected or entered into the case report form (Prometheus is the case report form for this study). Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea if administered during the first cycle; however, the subject's medication record will contain a list of concomitant medications.

7.2.8 EKG will be performed on day 1, day 5, day 8, and day 12 of the first cycle (all ±2 days) Day 1 and day 8 ECG are collected pre-dose; day 5 are collected pre-dose and 4 hrs (+/- 2 hrs) post-dose; day 12 are collected 4 hrs (+/- 2 hrs) post-dose. Then ECG to be done on day 1 of each cycle for cycles 2, 3, 4 and 5 before initiation of quizartinib and 4 hr (+/-2 hrs) post dose, then pre-dose every 2 subsequent cycles. EKG may be omitted if patient has not received study drug (quizartinib) in the 48 hrs preceding the time when EKG is done. EKG at screening and for the first 3 cycles will be done in triplicate. Subjects **should rest in the supine position or semi-recumbent, with the same position used for an individual subject for the duration of the study, for at least 5 minutes before each 12-lead ECG recording is started. The ECGs should be reviewed, signed,**

and dated by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. The results will include heart rate, PR interval, QRS interval, QT interval, and QTcF interval. QTcF is calculated using the formula, (QT)/3√ (RR). All screening and on study ECGs should be obtained in triplicate (10 seconds for each ECG over the 5-minute period).

A. On patients who increase the dose of Quizartinib or start therapy with a drug that is a moderate CYP3A4 inhibitor, an EKG will be required 24 hrs (±6 hrs), 7 days (±2 days) and 14 days (±2 days) after the dose increase or after the start of the moderate CYP3A4 inhibitor.

B. Patients who had their dose reduced because of QTc prolongation and have their dose re-escalated as described in section 5.2.3 will have an EKG repeated 24 hrs (±6 hrs) and 7 days (± 2 days) after re-escalation.

C. The QTc interval will be calculated by Fridericia's correction factor (QTcF). The 12–lead EKG evaluation will consist of 3 separate EKGs obtained at least 5 minutes apart.

7.2.9 Peripheral blood (up to 40 cc each time) and bone marrow (up to 15 cc each time) for pharmacodynamic studies (Optional) as defined in section 6.0 on

Peripheral blood:

- Prior to first dose of quizartinib at baseline (Cycle 1 Day 1).
- Cycle 1 Day 8: prior to the first dose of venetoclax
- Cycle 1 Day 15: prior to the dose of quizartinib and venetoclax (steady state)
- Cycle 1 Day 28 (+/- 4 days): prior to the dose of quizartinib and venetoclax
- At progression/relapse (if sample available)

Bone marrow samples:

- At screening (within 14 days preceding study initiation) as per section 7.1.8 – This BM will be done after the patient is consented to the study
- Cycle 1 day 8 (prior to the first dose of venetoclax)
- At the time of disease assessment on day 28 (+/- 4 days)
- At response assessment pre-cycle 4 (EOC 3)
- At progression/relapse (if sample available)

- Missed samples or cycles outside the provided time windows for correlative studies and/or for PK analysis will not constitute

protocol deviations. These studies are optional on this protocol.

7.2.10 All treatment prescriptions for quizartinib and venetoclax must be written by the patient's attending physician at MDACC or the PI of the study. We do not intend for the subjects to receive prescriptions for quizartinib or venetoclax at an outside physician's office. During the first cycle all the protocol required laboratory evaluations will be done at MDACC. Subsequently, the patient may have the laboratory work done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MDACC or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

Outside Physician Participation During Treatment

1. MDACC Physician communications 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.

3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. The PI/treating physician must review the labs, determine clinical significance and sign and date the report.

4. A copy of the informed consent, protocol abstract, 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 MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

7. All follow-up visits that correspond with drug dispensation will be performed at MDACC.

8. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

7.2.11 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 PI. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated) and other laboratory tests to once every cycle.

7.2.12 Pregnancy test (urine or serum) in females of childbearing potential every 3 months (±2 weeks).

7.2.13 Patients will be followed for survival at MD Anderson Cancer Center (MDACC) every 3 to 6 months after the end of treatment visit for up to 5 years after completion of active treatment. If the patient is unable to return to MDACC the follow-up visits may be conducted via telephone.

8.0 CRITERIA FOR RESPONSE

Response criteria will be modified from the International Working Group for AML(52). Responders are patients who obtain a Composite Complete Remission Rate (CRc) with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. CRc rate is defined as the confirmed remission rate of all complete and incomplete CRs (i.e., CR+ CRp + CRi).

8.1 Complete Remission (CR)

For patients to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an ANC > 1×10^9/L and platelet count ≥ 100×10^9/L, and normal marrow differential with < 5% blasts, and patients will be red blood cell (RBC) and platelet transfusion independent (defined as 4 weeks without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia.

8.2 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).

8.3 Complete Remission with Incomplete Hematological Recovery (CRi)

For patients to be classified as being in CRi, they must fulfill the criteria for CR except for incomplete hematological recovery with residual neutropenia (ANC ≤ 1×10^9/L) with or without thrombocytopenia (platelet count < 100×10^9/L). In addition, patients do not need to be RBC or platelet transfusion independent (modification to Cheson criteria).

8.4 Partial Remission (PR)

For patients to be classified as being in PR, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25% and meet the criteria for CR.

8.5 Morphologic leukemia-free state:

≤

8.6 Hematologic Improvement (HI): Hematologic response must be described by the number of positively affected cell lines.

- **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 bone marrow blasts but still >5%

8.7 Recurrence of Disease
Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia. Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

8.8 Best Response measurement
Response will be measured and defined for primary endpoints as the best response achieved during the first 3 cycles of therapy, or at time off study, for those patients discontinuing treatment before the completion of 3 cycles of therapy. Best response is defined to be the best-measured response (CRc=CR+CRp+CRi, PR, or marrow clearance) post-treatment up to that time. Best response will also be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

9.0 DISCONTINUATION OF TREATMENT:

9.1 Discontinuation Criteria for Individual Patients

9.1.1 Patient Withdrawal
Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. 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.

9.1.2 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.

9.1.3 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.

9.1.4 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 30-day (+/-7 days) follow-up visit will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MDACC. 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.

9.2 Study Stopping Rules

The principal investigator, the MDACC IND office (Sponsor) and the supporting companies (Daiichi-Sankyo and Abbvie) have the right to terminate this clinical study at any time. The principal investigator and MDACC 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

9.3 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

10.0 ADVERSE EVENT REPORTING

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

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

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

The Investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs.

10.2 Adverse Events (AEs) will be evaluated against the most current version of the venetoclax and quizartinib IBs for expectedness. Adverse Events (AEs) will be evaluated according to the latest CTCAE version 5.0 and documented in medical record. AEs will be recorded in the Case Report Form (CRF). The Leukemia-specific Adverse Event Recording and Reporting Guidelines (Appendix G) will be used for reporting.

10.3 Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form, unless the event is considered a DLT as listed in section 3.4.

10.4 Serious Adverse Event Reporting (SAE)

An adverse event (AE) or suspected adverse event is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse 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 might have caused death if it had occurred in a more severe form.

- Inpatient hospitalization or prolongation of existing hospitalization, not to include planned hospitalization for ramp-up portion of the therapy
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol that meet the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “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 Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC 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 is related to the study treatment must be reported to

the IND Office, Abbvie Inc and Daiichi-Sankyo. This may include the development of a secondary malignancy.

- All cases of venetoclax or quizartinib overdose (defined as accidental or intentional ingestion of any dose of the product that is considered excessive and medically important) must be reported as an SAE to the Sponsor (MDACC IND office) and to the supporting company on the SAE Form.

- Pregnancy alone is not considered an AE. However, if a patient becomes pregnant or causes a pregnancy during treatment or within 6 months of ending treatment, even if the subject is withdrawn from the study, the pregnancy must be reported immediately to the sponsor (MDACC IND office) on the MD Anderson SAE Form and to the supporting company within 1 days of the Investigator's knowledge of the pregnancy. The investigator should abide by necessary regulation for medical release from a female partner of a male subject prior to obtaining follow up. The investigator will follow the pregnancy to term or termination, will collect data on both the maternal and fetal outcome and will report all outcomes as a follow-up report to the initial pregnancy notification to the supporting company, Daiichi-Sankyo and Abbvie Inc.
Notwithstanding, all pregnancy outcomes that meet the regulatory definition of serious (i.e. spontaneous abortion, neonatal death, congenital anomaly in an aborted fetus or neonate) will be reported on the MD Anderson SAE Form to the sponsor (MDACC IND office) and the supporting companies within 24 hours of Investigator knowledge of the outcome.

10.4.1 Adverse Events of Special interest (AESI):

a. **QTc Prolongation, TdP, and Other Ventricular Arrhythmias**Subjects who experience >480 msec QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved, as described in Section 5.2.2.(dose modification section).
    a. QTcF prolongation ≥ Grade 3, either serious or non-serious and whether or not causally related, must be recorded as AE or SAE in the [Electronic Data Capture (EDC)], with the Investigator's assessment of seriousness, causality, and a detailed narrative.
    - Electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range;
    - Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects (section 5.5.2);
    - Subjects who experience >480 msec QTcF prolongation and undergo dose interruption and/or reduction must be

monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved.**b. .Combined Elevations of ATs and Bili**
Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case [ALT or AST ≥3 x ULN with simultaneous TBL ≥2 x ULN] should always be recorded as an AE or SAE within 24 hours of awareness, with the Investigator's assessment of seriousness, causality, and a detailed narrative. Subjects will be monitored as described below:

Evaluation may include the following depending on the clinical situation:
• Medical history and physical exam, including focus on medications and substances used: alcohol, acetaminophen, azole antifungals, change in medication dosages, new medications added, over the counter medication use and recreational drug use. Check for change in diet or use of dietary supplements;
• Abdominal ultrasound;
• Hepatitis A, B, C, and E screening (anti-hepatitis A virus immunoglobulin M, hepatitis B surface antigen, anti-hepatitis C virus plus viral titer, and evaluation for Hepatitis E), antinuclear antibody and anti-Smith antibody, cytomegalovirus, Epstein Barr virus;
• Additional evaluations as deemed appropriate by the Investigator to exclude other causes of liver enzyme and bilirubin elevations;
• All laboratory results, including local laboratory reference ranges are to be recorded.

10.5 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.

10.6 Serious Adverse Event Reporting to Abbvie Inc and Daiichi-Sankyo.

All SAEs, whether related or unrelated to venetoclax and/or quizartinib, Quizartinib , pregnancies and reports of overdose regardless of suspected causality and expectedness will be reported immediately but not later than 24 hours of the PI becoming aware of the SAE to Abbvie's and Daiichi-Sankyo's SAE Management team who will ensure data is

captured in Abbvie's and Daiichi Sankyo Pharmacovigilance systems. The PI will forward completed SAE and pregnancy forms by fax to 617-224-9420 (Abbvie) and 732-906-9621 (Daiichi-Sankyo).

Address and phone number of person responsible for SAE management at Abbvie:
PPDINDPharmacovigilance@abbvie.com

The Alliance Pharmacovigilance Agreement executed on February 2018 between Daiichi Sankyo, Plexxikon and MDACC describes all Safety Information-related exchange obligations and will govern all ICSR case report exchanges between MDACC and Daiichi Sankyo. Any serious suspected unexpected adverse reaction (where SAE is not reported in the Investigator Brochure and is considered to be related to study drug) will be reported by the Investigator via email immediately to CSPV-Clinical@dsi.com.

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. For any event of TLS, serious or non-serious, additional details maybe requested.

11.0 STATISTICAL CONSIDERATIONS

The primary objectives of the study are to evaluate safety and efficacy of venetoclax in combination with quizartinib in patients with FLT3-ITD mutated AML. The total accrual is 32 patients (Phase Ib: 12 patients and Phase II: 20 patients).

11.1 Phase Ib (Lead-in Phase)

The phase Ib portion is aimed at finding the MTD and RP2D of the two drugs in this combination. We plan to select a RP2D based on efficacy, toxicity, and PD data from the phase 1b dose-escalation. 3 patients at each dose level may not be sufficient to get a good estimate of efficacy and PD changes, and thus 6 patient dose escalation schema is proposed.
Patients will be enrolled in cohorts of 6 patients in the phase Ib portion of the study. The target dose is dose level +1, and the starting dose will be dose level 0. The first 6 patients on study will receive dose level 0.
The MTD is defined as the highest dose level with </= 1 out of 6 patients experience a DLT during the first 28 days of treatment. DLT is defined in section 3.4. The planned dosing algorithm is presented in section 3.3 and the dosing schema for the combination treatment is shown in Table 1. The RP2D will be selected at the end of the phase I portion based on reviewing the safety, efficacy, and PD data of quizartinib and venetoclax after discussion between the PI/Co-PI, the sponsor (MDACC IND office), and the supporting companies (Daiichi-Sankyo and Abbvie Inc). The Investigator is responsible for completing the cohort summary template prior to advancing subjects to the phase II part. Once RP2D has been established, any patients still on study at a dose lower than RP2D can be dose escalated up to RP2D in accordance with the dose-escalation guidelines in section 5.2.3.

The PK of quizartinib will be summarized statistically as n, geometric mean, %CV, median, minimum and maximum as Cmax and AUC0-24h of quizartinib and AC886 collected on Cycle 1 Day 7 (quizartinib alone) and Cycle 1 Day 8 (quizartinib + venetoclax) for the first 12 subjects. PK parameters will be dose normalized.

The PK of venetoclax will be summarized statistically as n, geometric mean, %CV, median, minimum and maximum for Cmax and AUC0-24h of venetoclax and M27 collected on Cycle 1 Day 8 (venetoclax + quizartinib) for the first 12 subjects. PK parameters will be dose normalized.

11.2 Phase II

The primary objective of the phase II is to evaluate the efficacy of the combination in patients with FLT3-ITD mutated AML (n=20). The primary endpoint is the rate of CRc (CRc=CR/CRp/CRi) at any time during the first three cycles of therapy. The CRc will be monitored with a time window of 3 months, and toxicity will be monitored as DLT within 1 cycle of the treatment. CRc and toxicity will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998).

Of note, recent FDA approval of midostaurin in combination with 7+3 induction chemotherapy in newly diagnosed FLT3-mutant AML signifies that essentially all relapsed FLT3-mutated AML patient will likely have been exposed to at least one FLT3 targeting TKI. In this setting, the marrow response (CRc) rates with second generation FLT3 inhibitors such as crenolanib, gilteritinib and quizartinib have been reported to be lower than in prior FLT3 TKI naïve patients and are in the range of 20-25% (26, 48, 49) and Daiichi Sankyo unpublished communication).

Thus, the historical data suggested a CRc rate of 25% for this population with quizartinib alone and the target CRc with the quizartinib and venetoclax combination is 50%. The treatment will be considered worthy of further investigation if it elicits an increase in CRc to 50% or higher with acceptable toxicity. A >30% DLT rate is considered unacceptable. Given this, we will stop enrollment into this cohort if the observed patients' data suggest that:

1) $Pr(CRc_E > CRc_H + 0.25 | data) < 0.025$ or
2) $Pr(TOX_E > 0.30 | data) > 0.90$

Here CRc_E and CRc_H are the CRc rate for quizartinib in combination with venetoclax and the historical treatment, respectively. TOX_E is the toxicity rate for quizartinib in combination with venetoclax, where the toxicity is defined as the DLTs. That is, if at any time during the study we determine that there is a less than 2.5% chance that the average CRc rate improves over historical CRc rate by more than 25% we will stop enrollment to this cohort. The second condition will stop the study early if there is more than 90% chance that the toxicity rate is more than 30%. The CRc_E and CRc_H are assumed to follow a prior of Beta (0.5, 1.5) and a constant of 25%, respectively. The stopping boundaries for CRc, based on these assumptions and monitoring conditions are found in **Table 4.** We will apply these stopping boundaries continuously starting from the tenth patient in a cohort size of 5 patients. For example, accrual will cease if less than or equal to 2 patients experience CRc among the first 10 patients treated.

Table 4. Stopping boundaries for CRc rate.

Stop accrual if the number patients with CRc among the number of patients evaluated			
Number of patients evaluated for CRc	10	15	20
Number of patients with CRc (i.e., CR, CRp, or CRi) is less than or equal to	0-2	0-4	Always stop with this many patients

Similarly, for monitoring the toxicity, a beta (0.6, 1.4) prior and a constant 30% toxicity rate were assumed for the historical treatment and the experimental combination, respectively. Based on these assumptions and monitoring conditions, the stopping boundaries for toxicity were generated and summarized in **Table 5**. For toxicity monitoring, we will apply these stopping boundaries continuously starting from the fifth patient in a cohort size of 5 patients. For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients.

For accrual between cohorts, if there are enough evidence indicating that the number of patients with CRc will be greater than that of the stopping boundaries (i.e., 2/10 or 4/15), it will continue; while will be held for evaluations of all patients if this cannot yet be determined with currently available data. Same strategy will be also applied to the toxicity monitoring.

Table 5. Stopping boundaries for Toxicity

Stop accrual if the number of patients with DLTs among the number of patients evaluated				
# patients evaluated	5	10	15	20
# patients with toxicities	4-5	6-10	8-15	Always stop with this many patients

The operating characteristics are summarized in Table 6. The probability of stopping the study early if the true CRc of the combination treatment was 50% and the true toxicity rate was 30% was 16.1%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 59.5% when the true CRc was 50% and 56.2% when true CRc rate was 65%.

Table 6. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment

True Toxicity Rate	True CRc	Prob(stop the trial early)
0.10	0.25	0.7188
	0.35	0.3976
	0.50	0.0837
	0.60	0.0177
	0.65	0.0069
0.20	0.25	0.7223
	0.35	0.4052
	0.50	0.0952
	0.60	0.0301

Table 6. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with combination treatment

True Toxicity Rate	True CRc	Prob(stop the trial early)
	0.65	0.0194
0.30	0.25	0.7424
	0.35	0.4481
	0.50	**0.1605**
	0.60	0.1001
	0.65	0.0902
0.40	0.25	0.7956
	0.35	0.5621
	0.50	0.3340
	0.60	0.2860
	0.65	0.2782
0.50	0.25	0.8758
	0.35	0.7340
	0.50	0.5955
	0.60	0.5663
	0.65	0.5616

If the study is not stopped early and 20 patients have been treated and evaluated in the study, a 95% credible interval around the CRc under the combination treatment will be no wider than 41%. The in-house Multc Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries, and the Parameter Solver (version 3.0.0) was used to construct the credible intervals.

11.3 Statistical Analysis Plan

All patients who receive any dose of the study agent will be included in the analysis for efficacy and safety. We will follow standard reporting guidelines for adverse events, and summarize safety data by category, severity and frequency. For the primary efficacy analysis, we will estimate the CRc rate for the combination treatment, along with the 95% credible interval. Patients who drop out of the study before completing all the cycles will be treated as “failures” for the primary analysis.

Patients’ demographic and clinical characteristics will be summarized using descriptive statistics. Specifically, categorical covariates will be summarized by frequencies and percentages and their associations with responses will be assessed using Fisher’s exact test or its generalization. Continuous covariates will be summarized by means, standard deviations, medians and ranges, and the difference between responses groups will be assessed using the Wilcoxon rank sum test. Paired t-tests or Wilcoxon signed-rank tests will be used to determine the immunological and molecular changes in the peripheral blood and bone marrow from baseline to the time of response, and to the time of disease progression.

We will estimate the rates of partial response and bone marrow blast reduction ≥ 50% within 3 months, along with 95% confidence intervals. For each subject, duration of response (DOR), event-free survival time and overall survival time will be calculated. DOR is defined as the time period from the first documentation of CRc to disease

recurrence, disease progression, or death whichever occurs first. Event-free survival time is defined as the time period from the date of treatment initiation to the date of documented treatment failure, relapses from CRc, or death from any cause, whichever occurs first. The observed DOR/EFS will be censored at the last follow-up if the patient is alive and no events observed. The overall survival time is defined as the time duration from treatment start till death or last follow-up if the patient is alive. The distributions of time-to-event endpoints including OS and DOR will be estimated using the Kaplan-Meier method. Comparisons of time-to-event endpoints by important covariate subgroups will be made using the log-rank tests. Progressive disease will be determined using ELN (2017) recommendations and is defined as any one or more of the following:

- 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 × 109/L [500/mL], and/or platelet count to > 50 × 109/L [50 000/mL] non-transfused);
- 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 109/L (> 25 000/μL);
- New extramedullary disease

The Investigator is responsible for completing Safety/Efficacy summary reports and submitting them to the IND office Medical Monitor for review, as follows:

Phase Ib Portion:
Submit a Toxicity Summary after the first six evaluable patients complete the first 28 days of study treatment, and every 6 patients thereafter, and before any dose modification or dose expansion.

Phase 2 Portion:
Submit an Efficacy/Toxicity Summary after the first five evaluable patients, per cohort, complete the first 28 days of study treatment and every 5 evaluable patients per cohort, thereafter. On every report submission, the information from previous reported patients will need to be updated to include toxicity assessment by the end of the first 28 days of treatment, and efficacy assessment by the end of cycle 3.

12.0 REFERENCES

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